Optimal estimation of coarse structural nested mean models with application to initiating ART in HIV infected patients

Judith J. Lok
Department of Mathematics and Statistics, Boston University
111 Cummington Mall, Boston, Massachusetts 02215, U.S.A.
Email: jjlok@bu.edu
June 25, 2021

Abstract

Coarse structural nested mean models are used to estimate treatment effects from longitudinal observational data. Coarse structural nested mean models lead to a large class of estimators. It turns out that estimates and standard errors may differ considerably within this class. We prove that, under additional assumptions, there exists an explicit solution for the optimal estimator within the class of coarse structural nested mean models. Moreover, we show that even if the additional assumptions do not hold, this optimal estimator is doubly-robust: it is consistent and asymptotically normal not only if the model for treatment initiation is correct, but also if a certain outcome-regression model is correct. We compare the optimal estimator to some naive choices within the class of coarse structural nested mean models in a simulation study. Furthermore, we apply the optimal and naive estimators to study how the CD4 count increase due to one year of antiretroviral treatment (ART) depends on the time between HIV infection and ART initiation in recently infected HIV infected patients. Both in the simulation study and in the application, the use of optimal estimators leads to substantial increases in precision.

Keywords: Causal inference; Doubly robust estimation; HIV/AIDS; Longitudinal data; Observational studies; Structural nested models
1 Introduction

The effect of time-dependent treatments is often estimated from observational data, since clinical trials where treatment is repeatedly randomized are not common. Estimating treatment effects from observational data is more difficult than from clinical trials. Since treatment was not randomized, patients receiving treatment typically have different pre-treatment characteristics than patients not receiving treatment, leading to confounding by indication. If patients with a worse prognosis were treated more often, a naive analysis would lead to underestimation of the treatment effect. It could even reverse the sign of the treatment effect, as illustrated for time-dependent treatments in an HIV example in Lok and DeGruttola (2012).

Several approaches exist to estimate treatment effects from longitudinal observational data. Time-dependent coarse structural nested mean models (coarse SNMMs) describe the effect of time-dependent treatments, conditional on patient characteristics at the time of treatment initiation. Coarse SNMMs model the mean difference between the outcome with treatment initiated at time $m$, versus never, on the outcome measured at a later time $k$, given a patient was not treated until time $m$, and given a patient’s covariate history at time $m$ (Lok and DeGruttola 2012). Previously, Robins (1998a) introduced coarse SNMMs for outcomes measured at the end of a study, for trials with noncompliance. Earlier SNMMs studied in Robins et al. (1992), Mark and Robins (1993), Lok et al. (2004), and Robins (1994) describe the effect of one treatment dosage conditional on patient characteristics just prior to this dosage. Estimating the effect of a longer duration of treatment from these quantities requires modeling the distribution of covariates given past treatment and covariate history, possibly leading to bias (Robins 1986, 1987, 1989, 1994), or even incompatibility of the different assumptions (Robins 1994). Coarse structural nested mean models are thus useful to estimate the effect of a treatment that is initiated once and then never stopped, since they directly estimate the effect of multiple treatment dosages.

Marginal structural models (Robins et al. 2000, Hernán et al. 2000) are another class of models to estimate the effect of time-dependent treatments from observational data. Marginal structural models estimate how treatment effects depend on baseline, but not time-dependent, covariates. Robins (2000) provides a detailed comparison of marginal structural models and structural nested models. Q-learning (Chakraborty and Murphy 2014, Nahum-Shani et al. 2012) also estimates treatment effects from time-
dependent observational data (and SMART trials, where treatments are repeatedly randomized). Q-learning builds on classical dynamic programming: 1. estimate the optimal last treatment strategy; 2., with backwards induction, the optimal treatment strategy at each time point given the optimal treatment strategy will be followed onwards. Q-learning is thus aimed at estimating optimal treatment regimes, and does not focus on the effect of a fixed duration of treatment, or of treatment initiation at different time points. As traditional SNMMs, Almirall et al. (2013) estimate the effect of a last blip of treatment conditional on a covariate and treatment history, and how this effect depends on potential effect modifiers, while allowing for confounders one might not want to estimate the effect modification of. They do not cover optimal estimation.

SMART trials (Chakraborty and Murphy 2014, Almirall et al. 2014) determine the best time-dependent treatment strategies using randomized trials. In SMART trials, baseline and subsequent treatment decisions are randomized, with randomization options determined by prior outcomes. Liu et al. (2018) combine outcome weighted learning with Q-learning to solve the optimal treatment strategy from SMART trials. They use support vector machines after a reformulation of the expected utility under any treatment strategy that leads to a convex optimization problem.

Various methods have been proposed to efficiently estimate the effect of point treatments. Newey (1993) describes efficient estimation under conditional moment restrictions. Our identifying assumption leads to a conditional mean being independent of a time-dependent treatment variable, which cannot be written in terms of such a conditional moment restriction, so the theory from Newey (1993) cannot be applied to derive efficient estimators of coarse structural nested models. There are similarities between our work and Newey (1993) in that we are deriving an optimal “instrumental variable” in the sense of the econometrics literature: a function of the covariates which leads to the smallest asymptotic variance. Targeted maximum likelihood estimation (TMLE: Van der Laan and Rubin 2006) is a method for doubly robust and efficient estimation of parameters in several semiparametric and nonparametric settings. Later targeted maximum likelihood estimation theory (Van der Laan and Gruber 2012, Schnitzer et al. 2014, Petersen et al. 2014) builds on theory from Bang and Robins (2005). Targeted maximum likelihood estimation has not been developed for structural nested models. Tsiatis (2006) covers semiparametric efficient estimation, but not of structural nested models. Tsiatis (2006) focuses on missing data problems, which could potentially be adapted easier to marginal structural models (Robins et al. 2000, Hernán et al. 2000), which use inverse prob-
ability of treatment weighting. Inverse probability of treatment weighting methods are also advocated in Chakraborty and Murphy (2014). Matching (Imbens 2004, Rosenbaum 2017) has been restricted to baseline treatments, not time-dependent treatments, and the most commonly used version with a fixed number of matches per individual is not efficient (Abadie and Imbens 2006). Gutman and Rubin (2013) describe the effect of a point treatment on a binary outcome $Y$ in the presence of one continuous confounder $X$. They use $EY = E[E[Y|X]]$ for $Y$ the outcome under no treatment and for $Y$ the outcome under treatment (see also Bang and Robins 2005 Section 2.1). Gutman and Rubin (2013) estimate the conditional expectations separately for treatment and control with splines, and use multiple imputation instead of the estimated conditional means. This method is not doubly robust or efficient (Bang and Robins 2005). Hahn (1998) proposed efficient methods to estimate the effect of point treatments from observational data. His proposed imputation methods are hard to generalize to time-dependent treatments, where if there are $K$ potential treatment times, the number of missing potential outcomes per patient is $2^K - 1$. In addition, it seems easier to specify the treatment initiation models than the models for the conditional expectations of the outcomes. The theory of Chernozhukov et al. (2015) Section 3 on optimal variance does not apply to coarse structural nested mean models, since, as we will show, coarse structural nested mean models lead to a continuum of (orthogonal) unbiased estimating equations for the causal parameter of interest.

In contrast to most of the literature on efficient estimation of treatment effects from observational data (Imbens 2004 provides an overview), this article focuses on optimal estimation of the effect of a time-dependent treatment. In addition, coarse structural nested mean models can estimate how the treatment effect depends on time-dependent pre-treatment characteristics, which is not the focus of most of the literature on efficient estimation of treatment effects.

We provide a description of the estimation methods and the assumptions needed to consistently estimate coarse structural nested mean models (coarse SNMMs) with an outcome measured over time. Detailed proofs are in Lok and DeGruttola (2012), Robins (1994), and Robins et al. (1999). The main focuses of this article however are double robustness and optimal estimation. Robins (1998a) and, for time-dependent outcomes, Lok and DeGruttola (2012) derived a large class of estimating equations for coarse SNMMs, all leading to consistent, asymptotically normal estimators for the treatment effect. It turns out that both estimates and standard errors may depend considerably on the choice of estimating equations within this large class.
This motivates the current article, which derives, under extra conditions, an optimal choice of estimators within a class that includes the estimators from Lok and DeGruttola [2012]. This optimal estimator leads to the smallest possible asymptotic variance. It is also doubly robust: it is consistent and asymptotically normal not only if the model for treatment initiation is correctly specified, but also if a certain outcome-regression model is correctly specified. The optimal estimator combines weighting and regression, and is therefore a mixed method (compare with mixed methods for point exposures described in Imbens [2004]).

Also without the extra conditions needed for optimality and in the presence of censoring, this optimal estimator is doubly robust; it just may not be optimal in such settings. As shown in Application Section 6, the optimal estimator may perform considerably better than arbitrarily choosing an estimator within the class of coarse SNMMs.

We implemented the proposed optimal estimator and compare it to other estimators for coarse SNMMs, both in a simulation study and in an HIV application. We estimate how the effect of one year of ART, the current standard of care for HIV infected patients, depends on the time between the estimated date of HIV infection and ART initiation. The application includes correction for informative censoring, and bootstrap confidence intervals. Consistency of the bootstrap for all our estimators is proven in Web-appendix A under regularity conditions.

Optimality for coarse SNMMs is simpler than optimality for more traditional SNMMs (see Robins [1994], Van der Laan and Robins [2003]), because coarse SNMMs avoid the need for accumulating the effects over time. This article therefore includes an accessible illustration of the steps involved in calculating optimal estimators. Our Web-Appendix explicitly proves all our results for time-dependent coarse SNMMs, thus providing a self-contained example.

2 Setting and notation

Initially, all patients are assumed to be followed at the same times 0, 1, ..., K + 1, with 0 indicating the baseline visit. The assumption that there is no censoring due to loss-to-follow-up is relaxed in Section 7. \( Y_k \) is the outcome at time \( k \). \( Y_k = (Y_0, Y_1, ..., Y_k) \) is the outcome history until time \( k \). \( A_k \) is the treatment at time \( k \). We investigate the effect of a binary treatment \( A_k \), which is either given \( (A_k = 1) \) or not \( (A_k = 0) \) at each time \( k \). \( \bar{A}_k \) is the treatment history until time \( k \). We only consider the impact of ini-
tiating treatment, and do not consider issues of treatment interruption or compliance: our analysis follows the intention-to-treat principle common in randomized trials. Thus, $A_k = 0$ until treatment is initiated, and $A_k = 1$ thereafter. $T$ is the time treatment was actually initiated, with $T = K + 1$ if treatment was never initiated. Similarly, $L_k$ are the covariates at time $k$, including the outcome $Y_k$ at time $k$, and $\mathcal{T}_k$ is the covariate history until time $k$. $\mathcal{T}_k$ is the space in which $\mathcal{T}_k$ takes its values. We assume that at each visit time $k$, treatment decisions $A_k$ are made after $L_k$ is measured and known. We suppress patient-level notation (such as the subscript $i$ often used to indicate individual $i$).

$Y_k^{(0)}$ and $Y_k^{(\emptyset)}$ are the counterfactual, not always measured, outcome and outcome history at time $k$ under the treatment regime “no treatment”. $L_k^{(0)}$ and $\mathcal{T}_k^{(0)}$ are the covariates and covariate history at time $k$ under the treatment regime “no treatment”. $Y_k^{(m)}$ is the outcome at time $k$ under the treatment regime “start treatment at time $m$”. We assume that observations and counterfactuals of the different patients are independent and identically distributed (Rubin 1978).

3 Time-dependent coarse structural nested mean models

Our model for treatment effect is similar to that in Robins (1998a), but differs in that we allow a time-dependent outcome, as in Lok and DeGruttola (2012):

Definition 3.1 (TIME-DEPENDENT COARSE SNMMS).
For $k = m, \ldots, K + 1$,

$$\gamma_k^{m} (\hat{I}_m) = E \left[ Y_k^{(m)} - Y_k^{(0)} \mid \mathcal{T}_k^{(0)} = \hat{I}_m, T = m \right].$$

$\gamma_k^{m} (\hat{I}_m)$ is the expected difference, for patients whose treatment started at time $m$ with covariates $\hat{I}_m$, of the outcome at time $k$ had the patient started treatment at time $m$, and the outcome at time $k$ had the patient never started treatment. It is the effect of treatment between times $m$ and $k$.

We assume a parametric model for the treatment effect $\gamma$, leading to a semiparametric setting. $\gamma$ models the expected difference between two counterfactual outcomes. How any of these outcomes depends on a patient’s covariates at time $m$ is not specified. For example, it could be that, for $k > m$
and with $g_k(T_m)$ any function of $T_m$,

$$Y_k^{(m)} = g_k(T_m) + \epsilon_k^{(m)}, \quad Y_k^{(0)} = g_k(T_m) + (\psi_1 + \psi_2m + \psi_3m^2) (k-m) + \epsilon_k^{(0)}$$

(note that $k - m$ is the treatment duration until time $k$), with

$E[\epsilon_k^{(m)} | T_m, T = m] = 0$ and $E[\epsilon_k^{(0)} | T_m, T = m] = 0$. In this example, $g_k(T_m)$ is left completely unspecified, and

$$\gamma_{k,\psi}^m(T_m) = (\psi_1 + \psi_2m + \psi_3m^2) (k-m)1_{\{k>m\}}.$$

So-called rank preservation holds if $Y_k^{(m)} - Y_k^{(0)} = \gamma_k^m(T_m)$, but rank preservation has been argued to not hold in many practical applications (Robins 1998b, Lok 2017). A coarse SNMM is a model for the effect of the treatment on the treated, as discussed in e.g. Imbens (2004). If $T$ contains enough information to make those treated and those untreated at time $m$ comparable given $T_m$, a structural nested mean model is also a model for the effect of the treatment on all patients with given covariates $T_m$. The lack of distinction between the effect of the treatment on the treated and the effect of the treatment is due to the fact that structural nested models condition on pre-treatment covariates.

**Assumption 3.2** (Parameterization of coarse structural nested mean model). $\gamma_{k,\psi}^m(T_m)$ is a correctly specified model for $\gamma_k^m(T_m)$, with $\psi$ a parameter in $\mathbb{R}^p$ and $\psi_*$ the true parameter.

The following example (Lok and DeGruttola 2012) motivated this work on optimal estimation:

**Example 3.3** (Effect of antiretroviral treatment (ART) depending on the time between estimated date of HIV infection and treatment initiation in HIV infected patients). We initially assume that

$$\gamma_{k,\psi}^m(T_m) = (\psi_1 + \psi_2m + \psi_3m^2) (k-m)1_{\{k>m\}}, \quad (1)$$

with $(k-m)$ the treatment duration from month $m$ to month $k$, is a correctly specified parametric model. Possibly, the mean treatment effect also depends non-linearly on the treatment duration. In that case, one could add non-linear terms such as $\psi_4(k-m)^21_{\{k>m\}}$, or additionally include a non-linear term depending on time since infection, such as $(\psi_1 + \psi_5m)(k-m)^21_{\{k>m\}}$.

The treatment effect $\gamma$ may also depend on pre-treatment covariates, such as log$_{10}$ HIV viral load in the blood (lvl), resistance mutations, and the CD4
count. To incorporate pre-treatment covariates such as log_{10} HIV viral load, one can extend the model by including terms such as $\psi_4 lvl_m (k - m) 1_{\{k > m\}}$. We chose some function of $(k - m)$ because the treatment duration may be predictive of its effect. If, for example, the treatment effect depends only on the viral load at treatment initiation for the first month of treatment, one might add terms such as $\psi_4 lvl_m 1_{\{k > m\}}$.

Following Robins et al. (1992) and Robins (1994), we use the propensity score (Rosenbaum and Rubin 1983), the prediction of treatment given the past, $p(m) = pr (A_m = 1 | A_{m-1} = 0, L_m)$, to estimate the treatment effect $\gamma$. Henceforth, we assume that $p_\theta(m)$ is a correctly specified model for $p(m)$, with $p(m) = p_\theta (m)$. We typically estimate $\theta_*$ by maximum partial likelihood.

4 No unmeasured confounding and consistency

As in Robins et al. (1992), Robins (1998b), Robins et al. (2000), Lok et al. (2004), Robins (1998a), and Lok and DeGruttola (2012), to distinguish between treatment effect and confounding by indication, we require the assumption of no unmeasured confounding. It states that information is available on all factors that both: (1) influence treatment decisions and (2) possibly predict a patient’s prognosis with respect to the outcome of interest. $Y_k$, the outcome at time $k$ without treatment, reflects a patient’s prognosis with respect to the outcome of interest. If there is no unmeasured confounding, treatment decisions at time $m$ ($A_m$) are independent of this (not always measured) prognosis $Y_k^{(0)}$ ($k > m$), given past treatment and covariate history $A_{m-1}$ and $L_m$:

**Assumption 4.1** (No unmeasured confounding - formalization). $A_m \perp \perp Y_k^{(0)} | L_m, A_{m-1}$ for $k > m$, where $\perp \perp$ means: is independent of (Dawid, 1979).

If a patient is not treated until time $k$, there is no difference in treatment between $Y_k$ and $Y_k^{(0)}$. In this and similar cases, it is reasonable to assume that until time $k$, the observed outcomes and the outcomes without treatment would have been the same:

**Assumption 4.2** (Consistency). If $T \geq k$, $Y_k = Y_k^{(0)}$ and $L_k = L_k^{(0)}$. $Y^{(T)} = Y$. 

8
5 Estimation: unbiased estimating equations

This section describes the estimation methods from Robins (1998a) and Lok and DeGruttola (2012). Proofs can be found in Lok and DeGruttola (2012).

Definition 5.1 On \( k > T \), define \( H(k) = Y_k - \gamma_k L_T \). On \( k \leq T \), define \( H(k) = Y_k \).

Example 5.2 (Effect of antiretroviral treatment (ART) depending on the time between estimated date of HIV infection and treatment initiation in HIV infected patients). In the setting of Example 3.3, on \( k > T \), \( H(k) = Y_k - (\psi_1 + \psi_2 T + \psi_3 T^2) (k-T) \).

For the true \( \psi^* \), \( H_{\psi^*}(k) = Y_k - \gamma_{k,\psi^*} L_T = H(k) \). This so-called blipping off of the treatment effect generates a random variable \( H(k) \) that mimics a counterfactual outcome:

Theorem 5.3 (MIMICKING COUNTERFACTUAL OUTCOMES). Under consistency assumption 4.2, for \( m \leq K \) and \( k \geq m \),

\[
E\left[ H(k) \mid \mathcal{L}_m, \mathcal{A}_{m-1} = \emptyset, A_m \right] = E\left[ Y_{k}^{(0)} \mid \mathcal{L}_m, \mathcal{A}_{m-1} = \emptyset, A_m \right].
\]

The idea behind estimation, similar to for example Robins et al. (1992) or Lok et al. (2004), is that under assumption of no unmeasured confounding 4.1, given past treatment and covariate history, \( Y_{k}^{(0)} \) does not help to predict treatment changes. In other words, in the model for treatment changes, that is, the propensity score (Rosenbaum and Rubin 1983), \( Y_{k}^{(0)} \) does not contribute. Lok and DeGruttola (2012) proved that because of Theorem 5.3, the same holds for \( H_{\psi^*}(k) \), and that similar to Lok (2008, 2007), this leads to the following theorem:

Theorem 5.4 (UNBIASED ESTIMATING EQUATIONS). Suppose that consistency assumption 4.2 and assumption of no unmeasured confounding 4.1 hold. Consider any \( \tilde{q}_m^k: \mathcal{L}_m \rightarrow \mathbb{R}^p \), \( m = 0, \ldots, K, k > m \), which are measurable, bounded, and vector-valued. Then

\[
E\left( \sum_{m=0}^{K} \sum_{k>m} \tilde{q}_m^k \mathcal{L}_m \right) H(k) 1_{\mathcal{A}_{m-1} = \emptyset} \{ A_m - p(m) \} = 0.
\]

If furthermore \( \gamma_\psi \) is correctly specified (Assumption 3.2) and \( p_\theta (m) \) correctly specifies \( p (m) \), then

\[
P_n \left( \sum_{m=0}^{K} \sum_{k>m} \tilde{q}_m^k \mathcal{L}_m \right) H_\psi(k) 1_{\mathcal{A}_{m-1} = \emptyset} \{ A_m - p_\theta(m) \} = 0,
\]
stacked with the estimating equations for \( \theta_* \), with \( P_n \) the empirical measure 
\[ P_n(X) = \frac{1}{n} \sum_{i=1}^{n} X_i, \]
are unbiased estimation equations for \((\psi, \theta)\). The \( \tilde{q}^k_m \) here are allowed to depend on \((\psi, \theta)\), as long as they are measurable and bounded for \((\psi, \theta)\).

For identifiability of the estimator, one needs as many estimating equations as parameters, in this case by choosing the dimension of \( \tilde{q} \). Including \( k \leq m \) does not help in these estimating equations, since for those \( k \), on \( \mathcal{A}_{m-1} = \emptyset \), 
\[ H_\psi(k) = Y_k(0) = Y_k, \]
which is part of \( \mathcal{L}_m \) and therefore generates a term with expectation 0 regardless of \( \psi \).

If \( \gamma \) is linear in \( \psi \), this approach leads to a linear restriction on \( \psi \) once the parameter \( \theta \) has been estimated, and thus to a closed form expression for \( \hat{\psi} \).

6 Optimal estimating equations

6.1 Assumptions and restrictions on the estimating equations

The vast literature on unbiased estimating equations, see e.g. Van der Vaart (1998) Chapter 5, indicates that under regularity conditions, \( \hat{\psi} \) is consistent and asymptotically normal for any choice of \( \tilde{q} \) with the same dimension as \( \psi \). Under those regularity conditions, the asymptotic variance of an estimator \( \hat{\psi} \) that is a zero of \( P_n G_\psi \), with \( E G_{\psi_*} = 0 \), is equal to

\[
\left\{ E \left( \frac{\partial}{\partial \psi} \mid \psi_* G_\psi \right) \right\}^{-1} E \left( G_{\psi_*} G_\psi^\top \right) \left\{ E \left( \frac{\partial}{\partial \psi} \mid \psi_* G_\psi \right) \right\}^{-1\top},
\]

(2)

because

\[
n^{1/2}(\hat{\psi} - \psi_*) = \left\{ E \left( \frac{\partial}{\partial \psi} \mid \psi_* G_\psi \right) \right\}^{-1} n^{1/2} P_n(G_{\psi_*}) + o_P(1).
\]

(3)

In the following we restrict to estimators that satisfy the regularity conditions needed for (3) and thus (2) to hold. Among such estimators, this article derives the optimal choice of \( \tilde{q} \). The remainder of this article also assumes assumption of no unmeasured confounding [4,1] consistency assumption [4,2] and correct specification of coarse structural nested mean model assumption [3,2]. Web-Appendix A provides proofs of all theorems and lemmas. Web-Appendix A shows, under regularity conditions, consistency of the bootstrap for all estimators considered.
6.2 Doubly robust estimators lead to increased precision

Definition 6.1 Let

\[ G(\psi, \theta, q) = \sum_{m=0}^{K} \sum_{k>m} \bar{q}_m^k (T_m) H_\psi(k) 1_{A_{m-1}=0} \{ A_m - p_\theta(m) \}, \]

\[ G^*(\psi, \theta, q) = \sum_{m=0}^{K} \sum_{k>m} \bar{q}_m^k (T_m) \left\{ H_\psi(k) - E \left[ H_\psi(k) \mid T_m, A_{m-1}=0 \right] \right\} 1_{A_{m-1}=0} \{ A_m - p_\theta(m) \}. \]

First, we consider estimating equations for \( \psi \) when \( \theta^* \) and thus the propensity score is known:

Theorem 6.2 (REPLACEMENT OF ESTIMATING EQUATIONS BY MORE EFFICIENT ONES). Under no unmeasured confounding assumption 4.1, consistency assumption 4.2 and the usual regularity conditions for the sandwich estimator for the variance, based on equation (2), to hold, \( P_n(G^*(\psi, \theta^*, q)) = 0 \) are unbiased estimating equations which, for given \( \bar{q} \), lead to a smaller asymptotic variance of \( \hat{\psi} \) than the estimating equations \( P_n(G(\psi, \theta^*, q)) = 0 \).

The equations with \( G^* \) are not true estimating equations, because their specification depends on the parameter \( \psi \) of interest, through the conditional expectation of \( H_\psi \). We will return to this issue later. Theorem 5.3 facilitates specifying the model for the conditional expectation of \( H \).

In practice, \( \theta^* \) will usually be unknown and has to be estimated. For the more efficient estimators based on \( G^* \) of Theorem 6.2, estimating \( \theta^* \) does not change the asymptotic variance of \( \hat{\psi} \). This result is similar to Proposition 1 in Rotnitzky and Robins (1995) for a missing data problem:

Theorem 6.3 Replacement of \( \theta^* \) by \( \hat{\theta} \) from a correctly specified pooled logistic regression model fitted by maximum partial likelihood, leading to \( \hat{\psi} \) that solves \( P_n(G^*(\psi, \hat{\theta}, q)) = 0 \), leads to the same asymptotic variance for \( \hat{\psi} \) as the estimator for \( \psi^* \) that solves \( P_n(G^*(\psi, \theta^*, q)) = 0 \).

For the estimators solving \( P_n(G(\psi, \theta^*, q)) = 0 \), estimating \( \theta^* \) may change the asymptotic variance. It usually reduces the asymptotic variance, as was also seen in Robins (2004) and Lok (2008) for different structural nested models. However, the resulting estimator is never more efficient than its doubly robust counterpart:
Theorem 6.4 For \( q \) fixed, replacement of \( \theta_\ast \) by \( \hat{\theta} \) from a correctly specified pooled logistic regression model fitted by maximum partial likelihood does not make the estimator for \( \psi_\ast \) which solves \( P_n(G(\psi, \hat{\theta}, q)) = 0 \) more efficient than the estimator which solves \( P_n(G^*(\psi, \hat{\theta}, q)) = 0 \).

As for SNMMs (Robins 2004, 3.10 page 23), estimators resulting from \( G^* \) are also doubly robust:

Theorem 6.5 (DOUBLE ROBUSTNESS). The estimator \( \hat{\psi} \) which solves \( P_n(G^*(\psi, \hat{\theta}, q)) = 0 \) is doubly robust: stacked with the estimating equations for \( \theta \), these estimating equations are unbiased for \( \psi \) if either \( p_\theta \) or \( E[H_\psi(k) \mid L_m, A_{m-1} = 0] \) is correctly specified. Thus, \( \hat{\psi} \) is consistent and asymptotically normal if either of these models is correctly specified.

It follows that both for robustness and for efficiency, the estimators with \( G^* \) are preferred.

6.3 A theorem that guarantees optimality of estimators

The following theorem, a consequence of Theorem 5.3 from Newey and McFadden (1994), gives a sufficient criterion under which \( \vec{q}_{\text{opt}} \) is optimal within our two classes of estimating equations, described by \( G \) and \( G^* \):

Theorem 6.6 (SUFFICIENT OPTIMALITY CRITERION WITH \( \theta_\ast \) KNOWN). For both \( G \) and \( G^* \): if \( \vec{q}_{\text{opt}} \) satisfies

\[
E \left( \frac{\partial}{\partial \psi} |_{\psi_\ast} G(\psi, \theta_\ast, q) \right) = E \left( G(\psi_\ast, \theta_\ast, q) G(\psi_\ast, \theta_\ast, \vec{q}_{\text{opt}})^\top \right), \tag{4}
\]

then no other \( \vec{q} \) satisfying our regularity conditions within this class leads to an estimator for \( \psi_\ast \) with a smaller asymptotic variance than \( \vec{q}_{\text{opt}} \). The estimator resulting from \( \vec{q}_{\text{opt}} \) has asymptotic variance equal to the inverse of \( E(G(\psi_\ast, \theta_\ast, \vec{q}_{\text{opt}}) G(\psi_\ast, \theta_\ast, \vec{q}_{\text{opt}})^\top) \). There is a unique (in \( L_2(P) \)-sense) optimal solution to equation (4) within this class of estimating equations.

6.4 Explicit expression for optimal estimating equations for coarse SNMMs with a time-varying outcome

This section finds the optimal \( \vec{q} \) under the following condition:

Assumption 6.7 (Homoscedasticity). For \( 0 \leq m \leq K \) and \( k, s > m \), \( \text{cov} [H(k), H(s) \mid L_m, A_{m-1} = 0, A_m] \) does not depend on \( A_m \).
Assumption 6.7 is a homoscedasticity assumption, because it states that a conditional covariance does not depend on $A_m$. Because of Theorem 5.3 and no unmeasured confounding assumption 4.1, homoscedasticity assumption 6.7 is equivalent to

$$E \left[ H(k)H(s) \mid \mathcal{L}_m, \mathcal{A}_{m-1} = \emptyset, A_m \right] = E \left[ H(k)H(s) \mid \mathcal{L}_m, \mathcal{A}_{m-1} = \emptyset \right]. \quad (5)$$

Assumption (5) is not far-fetched: under assumption of no unmeasured confounding 4.1, because of Theorem 5.3, the conditional expectation given $\mathcal{L}_m, A_m - 1 = 0, A_m$ of the two factors $H(k)$ and $H(s)$ does not depend on $A_m$. Assumption 6.7 can be checked empirically by using a preliminary estimator $\tilde{\psi}$ for $\psi^*$, regressing the product $H(\tilde{\psi}(k))H(\tilde{\psi}(s))$ on $\mathcal{L}_m, \mathcal{A}_m$, and investigating whether parameter(s) describing the dependence on $A_m$ are equal to 0.

Rank preservation holds if $H(k)$ does not just mimic $Y_k^{(0)}$ as described in Theorem 5.3, but $H(k)$ is equal to $Y_k^{(0)}$. Assumption of no unmeasured confounding 4.1 could be extended, without loss of meaning, to $(Y_k^{(0)}, Y_s^{(0)}) \perp \perp A_m \mid \mathcal{L}_m, \mathcal{A}_{m-1} = \emptyset$. Under this formulation of no unmeasured confounding and rank preservation, equation (5) and thus Assumption 6.7 are immediate.

Unfortunately, rank preservation is a very strong assumption, which we do not wish to make. For a discussion see e.g. Robins (1998b) or Lok (2017).

The following theorem describes the optimal estimator in an example:

**Theorem 6.8 (OPTIMAL ESTIMATOR).** Suppose that

$$\gamma_{k,\psi}^m(\mathcal{L}_m) = (\psi_1 + \psi_2m + \psi_3m^2 + \psi_4k) \ (k-m)$$

$$+ (\psi_5k^2 + \psi_6(k-m) + \psi_7lvl_m) \ (k-m) + \psi_8lvl_m$$

(compare with Example 3.3). Suppose that Assumption 6.7 holds. For $k > m$, define

$$\Delta_m(k) = \left( \begin{array}{c}
     k - m - E \left[ Tr(m, k) \mid \mathcal{A}_m = \emptyset, \mathcal{L}_m \right] \\
     m (k - m) - E \left[ TTr(m, k) \mid \mathcal{A}_m = \emptyset, \mathcal{L}_m \right] \\
     m^2 (k - m) - E \left[ T^2Tr(m, k) \mid \mathcal{A}_m = \emptyset, \mathcal{L}_m \right] \\
     k (k - m - E \left[ Tr(m, k) \mid \mathcal{A}_m = \emptyset, \mathcal{L}_m \right]) \\
     k^2 (k - m - E \left[ Tr(m, k) \mid \mathcal{A}_m = \emptyset, \mathcal{L}_m \right]) \\
     (k - m)^2 - E \left[ Tr^2(m, k) \mid \mathcal{A}_m = \emptyset, \mathcal{L}_m \right] \\
     lvl_m (k-m) - E \left[ lvlTTr(m, k) \mid \mathcal{A}_m = \emptyset, \mathcal{L}_m \right] \\
     lvl_m - E \left[ lvlTA_{k-1} \mid \mathcal{A}_m = \emptyset, \mathcal{L}_m \right]
\end{array} \right) \quad (6)$$
with \( \text{Tr}(m,k) \) the number of treated times between time \( m \) and time \( k \), and

\[
cov_m \left[ HI_8 \mid \mathcal{T}_m, \overline{A}_{m-1} = \overline{0} \right] = \begin{pmatrix}
\Gamma_{\min,\min}^m I_8 & \Gamma_{\min,\min+1}^m I_8 & \Gamma_{\min,\max}^m I_8 \\
\Gamma_{\min+1,\min}^m I_8 & \Gamma_{\max,\min}^m I_8 & \Gamma_{\max,\max}^m I_8 \\
\Gamma_{\max,\min}^m I_8 & \Gamma_{\max,\max}^m I_8 & \Gamma_{\max,\max}^m I_8
\end{pmatrix}
\]

(\( I_8 \) the \( 8 \times 8 \) identity matrix), with \( \Gamma_{k,s}^m = \text{cov} \left[ H(k), H(s) \mid \mathcal{T}_m, \overline{A}_{m-1} = \overline{0} \right] \).

If \( \tilde{q}^{\text{opt}} \) satisfies

\[
\begin{pmatrix}
\tilde{\Delta}_m^{(\min)} \\
\tilde{\Delta}_m^{(\min+1)} \\
\tilde{\Delta}_m^{(\max)}
\end{pmatrix} = cov_m \left[ HI_8 \mid \mathcal{T}_m, \overline{A}_{m-1} = \overline{0} \right] \begin{pmatrix}
\tilde{q}_m^{\text{opt,\min}} (\mathcal{T}_m) \\
\tilde{q}_m^{\text{opt,\min+1}} (\mathcal{T}_m) \\
\tilde{q}_m^{\text{opt,\max}} (\mathcal{T}_m)
\end{pmatrix},
\]

then \( P_n(G^*(\psi, \hat{\theta}, \tilde{q}^{\text{opt}})) = 0 \) leads to an optimal estimator \( \hat{\psi} \): any other estimator in our class, solving \( P_n(G^*(\psi, \hat{\theta}, \tilde{q})) = 0 \) for some \( \tilde{q} \), leads to an asymptotic variance that is at least as large as the asymptotic variance of \( \hat{\psi} \).

The class of estimators solving estimating equations of the form

\( P_n(G^*(\psi, \hat{\theta}, \tilde{q})) = 0 \)

leads to the smallest asymptotic variance of all estimators considered in this article (Theorems 6.2 and 6.4), and estimating \( \theta^* \) with pooled logistic regression does not change the asymptotic variance (Theorem 6.3). \( \tilde{q}^{\text{opt}} \) from Theorem 6.8 therefore leads to the smallest possible asymptotic variance.

**Theorem 6.9 (OPTIMAL ESTIMATOR).** Extending Theorem 6.8 to different treatment effect models \( \gamma \) can be done as follows. When choosing simpler models for \( \gamma^* \), delete the corresponding rows in equation (6) for \( \tilde{\Delta}_m(k) \) and replace the \( 8 \) in \( I_8 \) by the number of remaining parameters. For more complicated or different models, notice that the first entry in each row of \( \tilde{\Delta}_m(k) \) corresponds to the second entry in each row but with \( A_m = 0 \) replaced by \( A_m = 1 \). In addition, the model for \( \gamma^* \) of Theorem 6.8 can easily be generalized to contain similar terms depending on other covariates; the optimal estimator then follows similar to Theorem 6.8.

The term \( \Gamma_{k,s}^m \) and the double robustness term \( E \left[ H_\psi(k) \mid \mathcal{T}_m, \overline{A}_{m-1} = \overline{0} \right] \) are fixed functions of \( \mathcal{T}_m \), but they may depend on \( \psi \). We will use an
initial estimate \( \tilde{\psi} \), doubly robust but not optimal, in place of \( \psi \) in \( \Gamma^m_{k,s} \) and \( E \left[ H_{\psi}(k) \mid T_m, \bar{A}_{m-1} = 0 \right] \). If the treatment initiation model \( p_\theta \) is correctly specified, the estimating equations are unbiased for any fixed value of \( \tilde{\psi} \). In our application (Section 9), a candidate for \( \tilde{\psi} \) is motivated by the estimator which is optimal among those with \( \vec{q}^k_m \) only non-zero for \( k = m + 12 \). This can be shown to lead to \( q \) satisfying
\[
\begin{align*}
\tilde{\Delta}_m(m + 12) &= \text{Var} \left[ H(m + 12) \mid T_m, \bar{A}_{m-1} = 0 \right] q^{m+12} (T_m).
\end{align*}
\]
Additionally, replacing the conditional variance of \( H(m + 12) \) by a working identity covariance matrix gives \( \tilde{q}^{m+12}_m = \tilde{\Delta}_m(m + 12) \). This leads to valid estimates \( \tilde{\psi} \): stacking the estimating equations with this \( \tilde{q} \) with estimating equations for the parameters in \( \tilde{\Delta}_m \), results in unbiased estimating equations (Theorem 5.4).

The (generalized) inverse of \( \text{cov}_m \left[ H I_8 \mid T_m, \bar{A}_{m-1} = 0 \right] \) equals the (generalized) inverse of the conditional covariance matrix of \( H \) with each entry replaced by the entry times \( I_8 \).

The optimal estimator requires estimating conditional expectations. In small samples this may be an issue, but as for many efficient estimators (see e.g. Newey 1993, 1990, Hahn 1998, or Tsiatis 2006), it does not lead to a larger asymptotic variance if all models are correctly specified:

**Theorem 6.10** Suppose \( \tilde{\psi}_2 \) is a preliminary estimator of \( \psi \) which is the result of unbiased estimating equations \( P_n \tilde{G}(\psi_2) = 0 \), \( \hat{\theta} \) is an estimator of \( \theta \) from a correctly specified pooled logistic regression model with estimating equations \( P_n U(\theta) = 0 \), and \( E_{\xi} \left[ H_{\psi}(k) \mid T_m, \bar{A}_{m-1} = 0 \right] \) and \( \vec{q}^{\text{opt}}_{\psi,\xi} \) are parameterized by \( \xi \), with \( \xi^* \) the true \( \xi \) when \( \psi = \psi^* \), which can be estimated using estimating equations \( P_n J(\xi, \psi) = 0 \) with \( E J(\xi^*, \psi^*) = 0 \). Then, under regularity conditions, solving \( \tilde{\psi} \) from the unbiased estimating equations
\[
P_n \left( G^*(\psi, \hat{\theta}, \vec{q}^{\text{opt}}_{m,\psi_2,\xi}) \quad \tilde{G}(\psi_2) \quad J(\xi, \psi_2) \quad U(\theta) \right) = 0,
\]
results in the same asymptotic variance for \( \tilde{\psi} \) as using the true (but unknown) \( \vec{q}^{\text{opt}} \) from Theorem 6.8 in the estimating equations \( P_n(G^*(\psi, \hat{\theta}, \vec{q}^{\text{opt}})) = 0 \).

Solving these estimating equations simultaneously leads to the same estimator \( \hat{\psi} \) as plugging in \( (\tilde{\psi}_2, \hat{\theta}, \tilde{\xi}) \) into the estimating equations for \( \psi \), and then solving for \( \tilde{\psi} \). Theorem 6.10 implies that, if all models are correctly specified, the resulting \( \tilde{\psi} \) is optimal within the classes studied here.
In practice, instead of estimating \( \Gamma^{m}_{k,s} = \text{cov} \left[ H(k), H(s) \mid \mathcal{L}_{m}, \mathcal{A}_{m-1} = \emptyset \right] \), one may choose to use a so-called working covariance matrix, and replace \( \Gamma^{m} \) by, for example, the identity matrix. This can be compared with working correlation matrices in generalized linear models as in Zeger et al. (1988). As for generalized linear models, the resulting estimator is not optimal, but consistency, asymptotic normality and double robustness are not affected.

**Theorem 6.11** (CONSISTENCY OF THE BOOTSTRAP). Under regularity conditions, the bootstrap for all estimators above is consistent under the conditions already adopted for consistency and asymptotic normality.

### 7 Applying these methods: estimation steps

#### 7.1 Implementation: general remarks

Section 7 details the implementation of the estimators proposed in this article. The model for \( \gamma \) here is Example 3.3 model (1), but the methods can easily be adapted to other treatment effect models. Models that are linear in \( \psi \) are especially attractive because they lead to estimating equations that are linear in \( \psi \) and that are therefore easy to solve. SAS 9.1.3 (SAS Institute Inc., Cary, North Carolina, USA) was used for all analyses. The SAS code is available from the author.

As in Lok and DeGruttola (2012), we adopt a pooled logistic regression model for the treatment prediction model, \( p_{\theta}(m) \). As the outcome \( Y_{k} \) one could choose either the CD4 count itself or the CD4 count increase between month \( m \) and month \( k \). From Definition 3.1 of the treatment effect, the same quantity is estimated whether \( Y_{k} \) is the CD4 count or the CD4 count increase: subtracting CD4\(_{m}\) from the outcome CD4\(_{k}\) affects both \( Y_{k}^{(m)} \) and \( Y_{k}^{(\emptyset)} \) the same way, so the CD4\(_{m}\) terms in \( \gamma \) cancel. The CD4 count increase between month \( m \) and month \( k \) likely reflects more than the CD4 count at month \( k \) the effect of treatment taken between month \( m \) and month \( k \), i.e. less noise is expected. Thus, the CD4 count increase between month \( m \) and month \( k \) was used as the outcome for all estimators that are not doubly robust. For doubly robust estimators, subtracting CD4\(_{m}\) from the outcome CD4\(_{k}\) does not affect the point estimates, since the same covariate is included in \( \mathcal{L}_{m} \); subtracting CD4\(_{m}\) from CD4\(_{k}\) would affect both \( Y_{k} \) and \( E \left[ H(k) \mid \mathcal{L}_{m}, \mathcal{A}_{m-1} = \emptyset \right] \) in the same way, so the CD4\(_{m}\) terms in the estimating equations cancel.
7.2 A preliminary estimator \( \tilde{\psi} \)

As a preliminary estimator \( \tilde{\psi} \), necessary to implement the optimal estimator, we used a doubly robust version of the estimator from Lok and De-Gruttola (2012). This choice of \( \tilde{q}^k_m \) is the same as in Theorem 6.9, but with \( q^k_m = 0 \) for \( k \neq m + 12 \), and with the \( \text{cov}_m \left[ HI_3 \mid L_m, \overline{A}_m - 1 = 0 \right] \) replaced by identity matrices. Under a homoscedasticity condition, this choice of \( q \) is optimal within the class of estimating equations with \( q^k_m = 0 \) for \( k \neq m + 12 \).

In the models for \( q \), we first estimated \( \text{pr}(\text{Tr}(m,m+12) \mid L_m, \overline{A}_m - 1 = 0) \) using logistic regression, and then, conditional on \( \text{Tr}(m,m+12) \neq 0 \) and \( \overline{A}_m = 0 \), regressed \( \text{Tr}(m,m+12) \) on the covariates \( L_m \). In the presence of censoring, we restricted the regressions to patients still in follow-up at month \( m + 12 \). Misspecification of \( q \) of the preliminary estimator does not affect asymptotic optimality or double robustness of the optimal estimator that makes use of it. In finite samples it may affect the variance.

With this treatment effect model, \( H(m+12) = Y_{m+12} - (\psi_1 + \psi_2 T + \psi_3 T^2)\text{Tr}(m,m+12) \), and to estimate \( E[H(m+12) \mid L_m, \overline{A}_m - 1 = 0] \), we considered each term in this expression separately, leaving in \( \psi \).

For \( E[\text{Tr}(m,m+12) \mid L_m, \overline{A}_m - 1 = 0] \), we used the same approach as for \( E[\text{Tr}(m,m+12) \mid L_m, \overline{A}_m = 0] \). In the presence of censoring, we used Inverse Probability of Censoring Weighting (IPCW, see e.g. Robins et al. 1995) starting at month \( m \). With \( C_p = 0 \) indicating a patient was uncensored at month \( p \), these weights are

\[
W_{m,k} = \left\{ \prod_{p=m+1}^k \text{pr}(C_p = 0 \mid \overline{L}_{p-1}, \overline{A}_{p-1}, \overline{C}_{p-1} = 0) \right\}^{-1}.
\]

This procedure leads to estimating equations that are linear in \( \psi \) and thus easy to solve.

7.3 The optimal estimator

The mimicking outcome \( H(k) \) was first estimated by \( H_{\tilde{\psi}}(k) \). Theorem 5.3 facilitates specification of a model for \( E[H(k) \mid L_m, \overline{A}_m - 1 = 0] \). Linear regression was used to estimate \( E[H(k) \mid L_m, \overline{A}_m - 1 = 0] \). In the presence of censoring, we used IPCW, as for the preliminary estimator. This leads to an estimate \( \hat{E}[H(k) \mid L_m, \overline{A}_m - 1 = 0] \) based on estimating equations. Optimality depends on correct specification of \( E[H(k) \mid L_m, \overline{A}_m - 1 = 0] \), but if the treatment initiation model \( p_\theta \) is correctly specified, consistency
and asymptotic normality do not (because of double robustness). In the model for $\Delta$, $E[Tr(m, k) \mid L_m, A_m = 0]$ etcetera, the same approach as in Section 7.2 was used: first $pr(Tr(m, k) \neq 0 \mid L_m, A_m = 0)$ was estimated using logistic regression; then, conditional on $Tr(m, k) \neq 0$ and $A_m = 0$, $Tr(m, k)$ was regressed on the covariates $L_m$. In the presence of censoring, the regression was restricted to patients still in follow-up at month $k$. In the simulations, $\tilde{cov}_m [H_{I3} \mid L_m, A_{m-1} = 0]$ (Theorem 6.9) does not depend on $L_m$. In the application, a working model not depending on $L_m$ was used for $\tilde{cov}_m [H_{I3} \mid L_m, A_{m-1} = 0]$, similar to a working covariance matrix. $\Gamma_{k,s}^m$ was estimated by the empirical average over all patients of $\{H_{\tilde{\psi}}(k) - \tilde{E}[H(k) \mid L_m, A_{m-1} = 0]\} \{H_{\tilde{\psi}}(s) - \tilde{E}[H(s) \mid L_m, A_{m-1} = 0]\}$.

Alternatively, also after plugging in $\tilde{\psi}$, we could have used techniques similar to GEE to estimate a working covariance matrix. In the presence of censoring, we added $C_{\text{max}(k,s)} = 0$ to the conditioning event. Misspecification of $q$ (through $\Delta$ or $\tilde{cov}_m [H_{I3} \mid L_m, A_{m-1} = 0]$) leads to a suboptimal estimator, but (Theorem 6.10) does not affect double robustness, because all specifications leading to $q$ only depend on $L_m$ and parameters solving estimating equations.

This procedure leads to estimating equations that are linear in $\psi$ and thus easy to solve.

### 7.4 For comparison, a naive choice

For comparison, we implemented two non-doubly-robust estimators, based on Theorem 5.4 and not using the optimality theory developed here. For these Theorem 2-based estimators, since in our application (Section 9) interest lies in the effect of one year of treatment, $\tilde{q}_m^k = 0$ for $k \neq m + 12$, and the $\tilde{q}_m^{m+12}$ were as follows, with $CD4_m$, the CD4 count at month $m$, $\text{injdrug}$ an indicator of whether the patient ever injected drugs at or before the first visit, $\text{lvl}_m$ the log$_{10}$ viral load at month $m$, and $\text{firstvisit}_m$ an indicator for whether month $m$ was the month of the first visit. In the simulations, we chose

$$\tilde{q}_m^{m+12} = (CD4_m \hspace{0.2cm} m \hspace{0.2cm} \text{injdrug})^T \tag{7}$$

and

$$\tilde{q}_m^{m+12} = (CD4_m \hspace{0.2cm} \text{injdrug} \hspace{0.2cm} CD4_6)^T. \tag{8}$$

In the data application, we chose

$$\tilde{q}_m^{m+12} = (\sqrt{CD4_m} \hspace{0.2cm} m \hspace{0.2cm} \text{lvl}_m)^T \tag{9}$$

and

$$\tilde{q}_m^{m+12} = (\sqrt{CD4_m} \hspace{0.2cm} \text{lvl}_m \hspace{0.2cm} \text{firstvisit}_m)^T. \tag{10}$$
8 Simulations

We simulated data with monthly visits, and based choices for the simulated data on the AIEDRP data on HIV infected patients, described in Section 9. We used an auto-regressive model for the course of the CD4 count, which may be more realistic in months 6-30 than before month 6, given the different behavior of CD4 counts in the first 6 months since HIV infection (Web-Appendix C). Therefore, we simulated data in months 6-30, and estimated the effect of treatment initiation in months 6-18. Simulations are detailed in Web-Appendix C.

We simulated two scenarios: 1.: 1000 datasets with 1000 observations each, and 2.: 500 datasets with 5000 observations each. We fitted model (1) with 2 parameters, \((\psi_1, \psi_2)\), and 3 parameters, \((\psi_1, \psi_2, \psi_3)\). In these simulations, the true \(\psi_3\) equals 0. Since in our application interest focused on the effect of one year of treatment, we restricted the estimating equations to \(k = m + 1, \ldots, m + 12\) so as to rely less on model specification. Table 1 shows the root mean squared errors of the different estimators described in Sections 6 and 7. Web-Appendix C.2 describes the models fitted for the nuisance parameters.

Table 1 shows great improvements from applying our theory in comparison with a naive choice of estimating equations (Table 1 estimators 1a. and 1b., described in Section 7.4). Choosing \(q\) without using optimality theory can lead to useless inference. Making the estimator doubly robust (estimator 3.) results in improvements of the mean squared errors in the 3-parameter model. Not restricting the analysis to \(k = m + 12\) (estimators 4. and 5.) results in improvements overall, and our estimator with optimal asymptotic properties (estimator 5.) performs best in the simulations.

We also calculated the 2.5% and 97.5% quantiles (over the datasets) of the estimated parameters for estimators 2., 3., 4., and 5. For all parameters, the truth was in between these quantiles.

For \(n = 1000\), we also investigated choosing sparser models (Web-Appendix C.2) in the expressions for the prediction of treatment duration (for \(q\) and for the doubly robust term). Choosing sparser models made little difference for estimators 3., 4., and 5 in Table 1. For estimator 2. in Table 1, sparser models for \(q\) led to substantially larger mean squared errors (results not shown).

Figure 1 shows the results for the datasets with 1000 observations. Figure 1 compares the performance of estimators of the effect of treatment on the 1-year increase in the CD4s count due to treatment initiated at the different months. For example, for month 11, this is the root mean squared
error for the expected difference in CD4 count at month 23=12+11 between 1. initiating ART at month 11 versus 2. never initiating ART. Figure 1 does not include the naive estimators (1a. and 1b. in Table 1), since those perform much worse and incorporating them makes a comparison of the other estimators impossible. The same pattern appears as in Table 1, with the optimal estimator performing best.

9 The effect of ART in HIV infected patients during acute and early HIV infection

ART is the standard of care for HIV infection. Guidelines regarding ART initiation have been changing, with patients initiating ART earlier (Thompson et al. 2010, Panel on Antiretroviral Guidelines for Adults and Adolescents 2016, World Health Organization 2016), often even at the time of diagnosis, especially in the developed world.

The effect of ART in the early and acute stages of HIV infection was studied in Lok and DeGruttola (2012) using a preliminary version of our article; we aim to estimate the effect of ART with more robustness and precision. Given the limited data on early HIV infection, this is a timely question in HIV research. We estimate how the effect on immune reconstitution of initiating one year of ART depends on the time between the estimated date of HIV infection and ART initiation. The effect on immune reconstitution of one year of ART initiated \( m \) months after infection, is measured as the CD4 count at month \( m+12 \) with ART initiated at month \( m \) versus the CD4 count at month \( m+12 \) without ART. Of particular interest is the effect of one year of treatment initiated at month \( m \), given past covariate history \( l_m \); that is, \( \gamma_{m+12}^m (l_m) \).

The results of our investigation are important, since ART initiation soon after infection may not only improve a patient’s own outcomes, but also reduces the risk that a patient’s HIV infection is spread to others (Cohen et al. 2011, Granich et al. 2009, DeGruttola et al. 2008). Furthermore, the CDC is encouraging HIV testing (Satcher-Johnson et al. 2010), leading to earlier HIV diagnoses, so more treatment initiation decisions need to be made during early and acute infection. There is not a lot of evidence of clinical benefit for initiating ART this early, with likely a relatively small number of patients in the START trial (The INSIGHT START Study Group 2015) in acute or early infection at baseline. Our investigations shed light on the effect of efforts to diagnose HIV early, if early diagnosis is combined with immediate ART initiation as currently recommended.
We apply our estimators to the observational AIEDRP (Acute Infection and Early Disease Research Program) Core01 data, using data on 1762 HIV infected patients diagnosed during acute and early infection (Hecht et al. 2006). Dates of infection are estimated using an algorithm that incorporates clinical and laboratory data (Hecht et al. 2006; Smith et al. 2006). Lok and DeGruttola (2012) showed that in the AIEDRP, ART use depends on covariates such as the current CD4 count that are prognostic for the outcome CD4 count; and that this leads to substantial confounding by indication.

In this HIV application, $K + 1$ is 24 months. 0 is the estimated date of HIV infection, although visits may be missed during follow-up and particularly in the earliest months of infection. To account for missed visits, we include the visit pattern (in which months a visit took place) as a measured covariate. $Y$, $A$, and $L$ are measured at multiple time points that vary across patients. For $L$ we use the average measurement within the given month; if this is missing at month $m$, $L_m$ is coded as missing, a possible covariate value. $A_m$ cannot be missing because we assume that treatment can only start at visits and then it is always recorded. We impute missing data on the outcomes $Y_k$, after the first visit and until censoring, by interpolation, except for visits just prior to onset of treatment, for which we carry the last observation forward, in order to avoid using post-treatment information to impute outcomes prior to treatment. We assumed:

**Assumption 9.1** (Parameterization of coarse structural nested mean model). For $k = (m + 1) \lor 12, \ldots, (m + 12) \land (K + 1)$, suppose that

$$
\gamma^m_{k, \psi} (I_m) = (\psi_{*1} + \psi_{*2} m + \psi_{*3} m^2) (k - m) 1_{\{k > m\}},
$$

with $(k - m)$ the treatment duration from month $m$ to month $k$.

Since interest in this HIV application lies in the effect of 1 year of treatment, $\gamma^m_{m+12} (I_m)$, Assumption 9.1 suffices. Specifying $\gamma^m_k$ for $k < 12$ and $k > m + 12$ might lead to greater precision, but increases the risk of model misspecification. The restriction to these values of $k$ implies that in assumption of no unmeasured confounding $k$ can be similarly restricted. For estimation, every sum over $k$ is then also restricted to $k = (m + 1) \lor 12, \ldots, (m + 12) \land (K + 1)$.

Because treatment is assumed to only change at visit times, the estimating equations include $1_{\text{visit}}(m)$, an indicator of whether a visit took place at time $m$. For loss to follow-up, we assumed missing at random (Rubin 1976) and applied inverse probability of censoring weighting (Robins et al. 1995). Web-Appendix D describes the nuisance parameter models.
Table 2 provides estimates and bootstrap 95% confidence intervals based on the AIEDRP data, for the same estimators as described in Section 8. Table 2 shows that importantly, all estimators based on the optimality theory of the current article lead to much narrower 95% confidence intervals than the estimators based on Theorem 5.4 with \( q \) chosen in a naive way as described in Section 7.4. Both naive estimators lead to irrelevant estimators in the 3-parameter model, due to extremely wide confidence intervals. The same is true for the second naive estimator in the 2-parameter model. Double robustness does not lead to narrower confidence intervals in the AIEDRP data (compare estimators 2. and 3.). Estimator 5., which would be optimal without censoring and under homoscedasticity assumption 6.7 leads to much wider confidence intervals than Estimator 4. For the AIEDRP data, Estimator 4., which is similar to the optimal estimator but with working identity covariance matrices, leads to the narrowest confidence intervals.

Figure 2 compares the performance of estimators of the effect of ART treatment on the one-year increase in the CD4 count due to ART initiated at the different months since the estimated date of HIV infection. For example, for month 11, the quantity in Figure 2 is the estimated expected difference in the CD4 count at month 23=11+12, comparing initiating ART at month 11 versus never initiating ART. To facilitate the comparison of the other estimators, Figure 2 does not include the naive estimators of Section 7.4, which performed much worse. As in Table 2, Estimator 4., with a working identity covariance matrix, leads to the best precision.

Table 2 also describes the results of a sensitivity analysis (details in Web-Appendix D). In this sensitivity analysis, treatment initiation and dropout are modeled using model selection techniques. While model selection in principle invalidates the confidence intervals, this sensitivity analysis indicates that the results are somewhat sensitive to model specification.

The estimated effect of one year of ART initiated during acute and early HIV infection is substantial and significant. It decreases somewhat when the time between the estimated date of infection and ART initiation increases, but this trend is insignificant.

10 Discussion

Causal inference methods to analyze observational data require untestable assumptions, so it is important to analyze longitudinal observational data using different methods and compare the results. This requires a variety of methods, and the further development of structural nested models, as an
addition to the wider applied class of weighting methods.

Both in the simulation study and in the HIV application, most of the naive coarse structural nested mean model (coarse SNMM) estimators led to useless inference. This could realistically happen in practice if the nuisance function $\tilde{q}$ is chosen without knowledge of optimality theory, and motivated this article. In the HIV application, the naive estimators were so imprecise that it was important to not use a naive preliminary estimator in the first step for the optimal estimator.

Our theory resulted in substantially improved precision of coarse SNMMs. In the simulation study, the optimal doubly robust estimator resulted in useful inference, and performed best. In the HIV application, our methods also substantially improved precision. In the HIV application, the best performance was by a doubly robust estimator related to the optimal estimator, but using working identity covariance matrices, similar to the identity working covariance matrices approach in Generalized Estimating Equations (Tsiatis 2006, Section 4.6). The suboptimal behavior of the optimal estimator may have several causes. It could be due to the combination of limited sample size and censoring. It could also be due to model misspecification of the nuisance parameter models, especially of $\operatorname{cov}_m[H1|L_m, A_{m-1} = 0]$. We focused on coarse SNMMs with a time-varying outcome; Web-appendix B shows how the calculations simplify considerably with an outcome measured at the end of the study.

Inverse probability of treatment weighting of marginal structural models (Robins et al. 2000, Hernán et al. 2000) can only be used to estimate how a treatment effect depends on baseline covariates. It would be interesting to know whether coarse SNMMs provide more precise estimators than marginal structural models when interest lies in this scenario. Efficiency gains of coarse SNMMs could be expected, because SNMMs use all observed data, whereas if a saturated outcome model is used, marginal structural models use only the data that is consistent with the specific treatment regime. Our investigation is the first step in the comparison between coarse SNMMs and marginal structural models: we optimized of the performance of coarse SNMMs.

A promising area for future research are estimation methods when the number of potential confounders is large. Regularization methods such as LASSO are then the obvious candidates to estimate the propensity scores and the conditional expectation of $H$, assuming e.g. that only a limited number of confounders truly contribute. Since our proposed estimators are doubly robust, the estimating equations satisfy the orthogonality or immunization condition of Chernozhukov et al. (2015). This can be seen since, as
a function of one of the two nuisance parameter models, say $\xi$, the estimating function has expectation $0$ for all $\xi$ when the other parameter, say $\theta$, is held at its true value. Thus, provided that a high-quality regularization method is used, it can be expected that if both nuisance parameter models are correctly specified, asymptotically correct inference can be obtained by using the methods proposed in Chernozhukov et al. (2015). Correct specification of nuisance parameter models will be more likely for reasonable sample sizes if regularization is used, allowing for more elaborate candidate models. In addition, Yang and Lok are investigating semiparametric efficiency in the presence of censoring; this will involve investigating semiparametric efficient estimation as in e.g. Tsiatis (2006) and Hahn (1998), but adapted to treatment effects that depend on time-dependent pre-treatment covariates. Targeted maximum likelihood estimation could be another option to investigate semiparametric efficiency.

This article has limitations. As in traditional structural nested mean models, we have assumed that all confounders are measured. This assumption cannot be tested using the available data. Subject matter experts have to judge whether the data analyst included all covariates that are predictive of both treatment initiation and outcome. Moreover, in our HIV application we have assumed that a simple treatment effect model is correctly specified. Yang and Lok (2016) tested this assumption, and concluded that the AIEDRP data do not provide evidence that this assumption is violated; however, this may be due to a limited sample size. Investigating the properties of the proposed estimator when the treatment effect model is misspecified is an interesting topic for future research. In addition, our calculations for optimality are restricted to linear treatment effect models. Future research may involve nonlinear treatment effect models; for this Newey (1990), although mainly aimed at estimating the effect of point exposures, may be useful. Moreover, our estimators are likely not optimal in the presence of censoring. They do remain doubly robust if censoring is missing at random (Rubin 1976) and the model for censoring is correctly specified. In our HIV application, which includes censoring, our methods still led to remarkable variance reductions. In addition, one or more of the models for the nuisance parameters may be misspecified. Only the treatment initiation model and the outcome regression model affect consistency and asymptotic normality, and double robustness implies that misspecification of one of these two models preserves consistency and asymptotic normality.

We conclude that the precision of estimators for coarse structural nested mean models depends substantially on the estimating equations chosen. The substantial improvement we found by choosing optimal estimating equations
suggests that the use of optimal estimators may encourage more widespread use of coarse structural nested mean models.

Acknowledgements

This work was supported by the Milton Fund, the Career Incubator Fund from the Harvard School of Public Health, NSF DMS 1854934, and the National Institutes of Health [grant numbers NIAID R01 AI100762, R37 51164 AI43638, AI074621, AI106039 and AI036214]. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health or the National Science Foundation.

I am grateful to the patients who volunteered for AIEDRP, to the AIEDRP study team, and to Susan Little, Davey Smith, and Christy Anderson for their help and advice in interpreting the AIEDRP database. I would like to thank Ray Griner for extensive help with the programming in SAS, and Shu Yang for programming the estimators additionally in R. I would like to thank James Robins and Victor DeGruttola for insightful and fruitful discussions.

Supplementary material

The appendix includes proofs, outcomes measured at the end of the study, further details of the simulation study, and a description of the nuisance parameter models used in the HIV application.

References

Abadie, A. and G. W. Imbens (2006). Large sample properties of matching estimators for average treatment effects. *Econometrica* 74(1), 235–267.

Almirall, D., B. A. Griffin, D. F. McCaffrey, R. Ramchand, R. A. Yen, and S. A. Murphy (2013). Time-varying effect moderation using the structural nested mean model: estimation using inverse-weighted regression with residuals. *Statistics in Medicine* 33, 3466–3487.

Almirall, D., I. Nahum-Shari, N. E. Sherwood, and S. A. Murphy (2014). Introduction to SMART designs for the development of adaptive interventions: with application to weight loss research. *TBM* 4, 260–274.

25
Bang, H. and J. M. Robins (2005). Doubly robust estimation in missing data and causal inference models. *Biometrics* 61(4), 962–973.

Chakraborty, B. and S. A. Murphy (2014). Dynamic treatment regimes. *Annual review of statistics and its application* 1, 447–464.

Chernozhukov, V., C. Hansen, and M. Spindler (2015). Valid post-selection and post-regularization inference: An elementary, general approach. *Annual Review of Economics* 7(1), 649–688.

Cohen, M. S., Y. Q. Chen, M. McCauley, T. Gamble, M. C. Hosseinipour, N. Kumarasamy, and et al (2011). Prevention of HIV-1 Infection with Early Antiretroviral Therapy. *New England Journal of Medicine* 365, 493–505.

Dawid, A. P. (1979). Conditional independence in statistical theory (with discussion). *Journal of the Royal Statistical Society B* 41, 1–31.

DeGruttola, V., S. Little, and R. Schooley (2008). Controlling the HIV epidemic, without a vaccine! *AIDS* 22, 2554–2555.

Granich, R., C. Gilks, C. Dye, K. D. Cock, and B. Williams (2009). Universal voluntary HIV testing with immediate antiretroviral therapy as a strategy for elimination of HIV transmission: a mathematical model. *The Lancet* 373(9657), 48–57.

Gutman, R. and D. B. Rubin (2013). Robust estimation of causal effects of binary treatments in unconfounded studies with dichotomous outcomes. *Statistics in medicine* 32(11), 1795–1814.

Hahn, J. (1998). On the Role of the Propensity Score in Efficient Semiparametric Estimation of Average Treatment Effects. *Econometrica* 66(2), 315–331.

Hecht, F. M., L. Wang, A. Collier, S. Little, M. Markowitz, J. Margolick, J. M. Kilby, E. Daar, B. Conway, S. Holte, and AIEDRP Network (2006). A multicenter observational study of the potential benefits of initiating combination antiretroviral therapy during acute HIV infection. *Journal of Infectious Disease* 194, 725–733.

Hernán, M. A., B. Brumback, and J. M. Robins (2000). Marginal structural models to estimate the causal effect of zidovudine on the survival of HIV-positive men. *Epidemiology* 11(5), 561–570.
Imbens, G. W. (2004). Nonparametric estimation of average treatment effects under exogeneity: a review. *The Review of Economics and Statistics* 86(1), 4–29.

Liu, Y., Y. Wang, M. R. Kosorok, Y. Zhao, and D. Zeng (2018). Augmented outcome-weighted learning for estimating optimal dynamic treatment regimens. *Statistics in medicine* 37(26), 3776–3788.

Lok, J. J. (2007). Structural nested models and standard software: a mathematical foundation through partial likelihood. *Scandinavian Journal of Statistics* 34(1), 186–206.

Lok, J. J. (2008). Statistical modelling of causal effects in continuous time. *Annals of Statistics* 36(3), 1464–1507. arXiv: math.ST/0410271 at http://arXiv.org.

Lok, J. J. (2017). Mimicking counterfactual outcomes to estimate causal effects. *The Annals of Statistics* 45(2), 461–499.

Lok, J. J. and V. DeGruttola (2012). Impact of time to start treatment following infection with application to initiating HAART in HIV-positive patients. *Biometrics* 68, 745–754.

Lok, J. J., R. D. Gill, A. W. V. der Vaart, and J. M. Robins (2004). Estimating the causal effect of a time–varying treatment on time-to-event using structural nested failure time models. *Statistica Neerlandica* 58(3), 271–295.

Mark, S. D. and J. M. Robins (1993). Estimating the causal effect of smoking cessation in the presence of confounding factors using a rank preserving structural failure time model. *Statistics in Medicine* 12, 1605–1628.

Nahum-Shani, I., M. Qian, D. Almirall, W. E. Pelham, B. Gnagy, G. A. Fabiano, J. G. Waxmonskey, J. Yu, and S. A. Murphy (2012). Q-learning: A data analysis method for constructing adaptive interventions. *Psychological methods* 17(4), 478–494.

Newey, W. K. (1990). Efficient instrumental variables estimation of nonlinear models. *Econometrica* 58(4), 809–837.

Newey, W. K. (1993). Efficient estimation of models with conditional moment restrictions. In G. S. Maddala, C. R. Rao, and H. D. Vinod (Eds.), *Handbook of Statistics*, Volume 11, pp. 419–454. Elsevier Science Publishers B.V.
Newey, W. K. and D. McFadden (1994). Large Sample Estimation and Hypothesis Testing. In R. F. Engle and D. L. McFadden (Eds.), *Handbook of Econometrics*, Volume 4, pp. 2111–2245. Elsevier. Edition 1, chapter 36.

Panel on Antiretroviral Guidelines for Adults and Adolescents (2016). *Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents*. National Institutes of Health (NIH). July 14. Accessed 04/30/2017. (Available at https://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-treatment-guidelines/0/).

Petersen, M., J. Schwab, S. Gruber, N. Blaser, M. Schomaker, and M. Van der Laan (2014). Targeted maximum likelihood estimation for dynamic and static longitudinal marginal structural working models. *Journal of causal inference* 2(2), 147–185.

Robins, J. M. (1986). A new approach to causal inference in mortality studies with a sustained exposure period – Applications to control of the healthy worker survivor effect. *Mathematical Modelling* 7, 1393–1512.

Robins, J. M. (1987). Addendum to “A new approach to causal inference in mortality studies with a sustained exposure period – Application to control of the healthy worker survivor effect. *Computers and Mathematics with Applications* 14, 923–945.

Robins, J. M. (1989). The analysis of randomized and non-randomized AIDS treatment trials using a new approach to causal inference in longitudinal studies. In L. Sechrest, H. Freeman, and A. Bailey (Eds.), *Health service research methodology: a focus on AIDS*, pp. 113–159. Washington, D.C.: NCHSR, U.S. Public Health Service.

Robins, J. M. (1994). Correcting for non-compliance in randomized trials using structural nested mean models. *Communications in Statistics* 23, 2379–2412.

Robins, J. M. (1998a). Correction for non-compliance in equivalence trials. *Statistics in Medicine* 17, 269–302.

Robins, J. M. (1998b). Structural Nested Failure Time Models. In P. Armitage and T. Colton (Eds.), *Survival analysis*, Volume 6 of *Encyclopedia of Biostatistics*, pp. 4372–4389. Chichester, UK: John Wiley and Sons. Section Eds: P. K. Andersen and N. Keiding.
Robins, J. M. (2000). Marginal Structural Models versus Structural Nested Models as tools for causal inference. In M. E. Halloran and D. Berry (Eds.), Statistical Models in Epidemiology: The Environment and Clinical Trials, Volume 116, pp. 95–133. New York: Springer-Verlag.

Robins, J. M. (2004). Optimal Structural Nested Models for Optimal Sequential Decisions. In D. Y. Lin and P. Heagerty (Eds.), Proceedings of the Second Seattle Symposium on Biostatistics. New York: Springer.

Robins, J. M., D. Blevins, G. Ritter, and M. Wulfsohn (1992). G-estimation of the effect of prophylaxis therapy for pneumocystis carinii pneumonia on the survival of AIDS patients. Epidemiology 3(4), 319–336.

Robins, J. M., M. A. Hernán, and B. Brumback (2000). Marginal structural models and causal inference in epidemiology. Epidemiology 11(5), 550–560.

Robins, J. M., A. Rotnitzky, and D. O. Scharfstein (1999). Sensitivity analysis for selection bias and unmeasured confounding in missing data and causal inference models. In M. E. Halloran and D. Berry (Eds.), Statistical models in epidemiology: the environment and clinical trials, Volume 116, pp. 1–92. New York: Springer-Verlag.

Robins, J. M., A. Rotnitzky, and L. P. Zhao (1995). Analysis of semiparametric regression models for repeated outcomes in the presence of missing data. Journal of the American Statistical Association 90(429), 106–121.

Rosenbaum, P. R. (2017). Observation and experiment: an introduction to causal inference. Harvard University Press.

Rosenbaum, P. R. and D. B. Rubin (1983). The central role of the propensity score in observational studies for causal effects. Biometrika 70(1), 41–55.

Rotnitzky, A. and J. M. Robins (1995). Semiparametric Regression Estimation in the Presence of Dependent Censoring. Biometrika 82(4), 805–820.

Rubin, D. B. (1976). Inference and missing data. Biometrika 63, 581–592.

Rubin, D. B. (1978). Bayesian inference for causal effects: the role of randomization. Annals of Statistics 6, 34–58.

Satcher-Johnson, A., J. Heitgerd, L. J. Koenig, M. VanHandel, B. M. Branson, E. Connelly, H. I. Hall, and L. A. Valleroy (2010). Vital Signs: HIV
Testing and Diagnosis Among Adults – United States, 2001–2009. Technical Report 47, Centers for Disease Control and Prevention. MMWR December 3.

Schnitzer, M. E., M. J. Van der Laan, E. E. M. Moodie, and R. W. Platt (2014). Effect of breastfeeding on gastrointestinal infection in infants: a targeted maximum likelihood approach for clustered longitudinal data. The Annals of Applied Statistics 8(2), 703–725.

Smith, D. M., M. C. Strain, S. D. W. Frost, S. K. Pillai, J. K. Wong, T. Wrin, Y. Liu, C. J. Petropolous, E. S. Daar, S. J. Little, and D. D. Richman (2006). Lack of neutralizing antibody response to HIV-1 predisposes to superinfection. Virology. 355, 1–5.

The INSIGHT START Study Group (2015). Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection. New England Journal of Medicine 373(9), 795–807. PMID: 26192873.

Thompson, M. A., J. A. Aberg, P. Cahn, J. S. G. Montaner, G. Rizzardini, A. Telenti, J. M. Gatell, H. F. Guenthard, S. M. Hammer, M. S. Hirsch, D. M. Jacobsen, P. Reiss, D. D. Richman, P. A. Volberding, P. Yeni, and R. T. Schooley (2010). Antiretroviral Treatment of Adult HIV Infection 2010 Recommendations of the International AIDS Society–USA Panel. Journal of the American Medical Association 304(3), 321–333.

Tsiatis, A. A. (2006). Semiparametric theory and missing data. New York: Springer.

Van der Laan, M. J. and S. Gruber (2012). Targeted minimum loss based estimation of causal effects of multiple time point interventions. The international journal of biostatistics 8(1).

Van der Laan, M. J. and J. M. Robins (2003). Unified methods for censored longitudinal data and causality. New York: Springer Verlag.

Van der Laan, M. J. and D. Rubin (2006). Targeted maximum likelihood learning. The International Journal of Biostatistics 2(1).

Van der Vaart, A. W. (1998). Asymptotic statistics. Cambridge series in statistical and probabilistic mathematics. Cambridge: Cambridge University Press.
World Health Organization (2016). *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection.* http://www.who.int/hiv/pub/arv/arv-2016/en/.

Yang, S. and J. J. Lok (2016). A goodness-of-fit test for Structural Nested Mean Models. *Biometrika 103*(3), 734–741.

Zeger, S. L., K. Liang, and P. S. Albert (1988). Models for longitudinal data: a generalized estimating equation approach. *Biometrics*, 1049–1060.
Table 1: Simulations: Comparison of root mean squared error rMSE (bias) for the various estimators

| Model                                           | Two parameters | Three parameters |
|-------------------------------------------------|----------------|-----------------|
|                                                 | $\psi_1$       | $\psi_2$       | $\psi_1$       | $\psi_2$       | $\psi_3$       |
|                                                 | rMSE (bias)    | rMSE (bias)    | rMSE (bias)    | rMSE (bias)    | rMSE (bias)    |
| 1000 patients in 1000 datasets                  |                |                |                |                |                |
| 1a. $q$ as in (9), not DR                       | 3.5 (0.07)     | 0.29 (-0.007)  | 3570 (107)     | 784 (-24)      | 38 (1)         |
| 1b. $q$ as in (10), not DR                       | 1019 (-28)     | 94 (2)         | 736 (-14)      | 163 (2)        | 8.0 (-0.06)    |
| 2. restricted approx. optimal, not DR           | 2.1 (-0.05)    | 0.17 (0.003)   | 10.3 (1.4)     | 1.9 (-0.3)     | 0.084 (0.01)   |
| 3. restricted approx. optimal, DR               | 2.1 (-0.04)    | 0.17 (0.003)   | 6.6 (0.1)      | 1.2 (-0.03)    | 0.049 (0.001)  |
| 4. working identity covariances, DR             | 1.6 (-0.06)    | 0.10 (0.003)   | 3.9 (0.04)     | 0.53 (-0.01)   | 0.017 (0.0005) |
| 5. approximately optimal, DR                    | 1.3 (-0.04)    | 0.079 (0.002)  | 3.1 (-0.05)    | 0.41 (0.004)   | 0.013 (-0.00005) |
| 5000 patients in 500 datasets                   |                |                |                |                |                |
| 1a. $q$ as in (9), not DR                       | 1.6 (0.05)     | 0.13 (-0.006)  | 285 (8)        | 58 (-2)        | 2.7 (0.07)     |
| 1b. $q$ as in (10), not DR                       | 187 (-8)       | 18 (0.8)       | 529 (10)       | 112 (-2)       | 5.4 (0.1)      |
| 2. restricted approx. optimal, not DR           | 0.94 (0.003)   | 0.073 (-0.002) | 4.2 (0.2)      | 0.78 (-0.04)   | 0.034 (0.002)  |
| 3. restricted approx. optimal, DR               | 0.94 (0.005)   | 0.073 (-0.002) | 2.9 (0.04)     | 0.51 (-0.009)  | 0.022 (0.0003) |
| 4. working identity covariances, DR             | 0.75 (-0.03)   | 0.047 (0.0009) | 1.7 (0.06)     | 0.23 (-0.01)   | 0.0075 (0.0005) |
| 5. approximately optimal, DR                    | 0.59 (-0.02)   | 0.035 (0.0007) | 1.4 (-0.01)    | 0.18 (-0.0004) | 0.0056 (0.00003) |

rMSE: root mean squared error. DR: doubly robust.
1a. and 1b. Naive choices of estimators within class (Section 7.4). Not doubly robust.
2. $q$ approximately optimal within the class with $q^m_k = 0$ for $k \neq m + 12$ (Section 7.2). Not doubly robust.
3. $q$ approximately optimal within the class with $q^m_k = 0$ for $k \neq m + 12$ (Section 7.2). Doubly robust.
4. Like the optimal estimator, but with working identity covariance matrices (Sections 6 and 7.3). Doubly robust.
5. Optimal under correct specification of all models (Sections 6 and 7.3). Doubly robust.
Table 2: The AIEDRP data: Various estimators and their bootstrap 95% confidence intervals (CIs)

| Model                              | \( \hat{\psi}_1 \) (95% CI) | (width CI) | \( \hat{\psi}_2 \) (95% CI) | (width CI) | \( \hat{\psi}_3 \) (95% CI) | (width CI) |
|-----------------------------------|------------------------------|------------|------------------------------|------------|------------------------------|------------|
| 2-parameter model                 |                              |            |                              |            |                              |            |
| 1a. \( q \) as in (11), not DR   | 22.4 (18.9,25.8)             | (6.9)      | 0.16 (-0.59,1.0)             | (1.58)     | -                            | -          |
| 1b. \( q \) as in (12), not DR   | 43 (-128,209)                | (338)      | -9 (-89,68)                  | (157)      | -                            | -          |
| 2. restricted approx. optimal, not DR | 22.3 (19.1,25.3)             | (6.1)      | 0.18 (-0.53,1.00)            | (1.53)     | -                            | -          |
| 3. restricted approx. optimal, DR | 24.1 (20.8,27.2)             | (6.4)      | -0.72 (-1.39,-0.02)          | (1.37)     | -                            | -          |
| 4. working identity covariances, DR | 25.3 (22.2,28.5)             | (6.3)      | -0.23 (-0.71,0.28)           | (0.99)     | -                            | -          |
| 5. approximately optimal, DR      | 24.8 (20.2,29.0)             | (8.7)      | -0.44 (-2.1,1.3)             | (3.44)     | -                            | -          |
| 2b. as 2., sensitivity analysis   | 24.0 (20.6,27.6)             | (7.0)      | -0.24 (-1.09,0.62)           | (1.71)     | -                            | -          |
| 3b. as 3., sensitivity analysis   | 26.0 (22.7,29.3)             | (6.6)      | -0.88 (-1.62,0.17)           | (1.45)     | -                            | -          |
| 4b. as 4, sensitivity analysis    | 25.7 (22.4,29.0)             | (6.5)      | -0.33 (-0.83,0.18)           | (1.01)     | -                            | -          |
| 5b. as 5, sensitivity analysis    | 25.4 (20.1,30.0)             | (9.9)      | -0.60 (-2.2,1.3)             | (3.48)     | -                            | -          |
| 3-parameter model                 |                              |            |                              |            |                              |            |
| \( \xi \)                         |                              |            |                              |            |                              |            |
| 1a. \( q \) as in (11), not DR   | 39 (-27.175)                 | (203)      | -11 (-99,33)                 | (131)      | 1.2 (-4.1,12)                | (16.2)     |
| 1b. \( q \) as in (12), not DR   | 38 (-126,208)                | (334)      | -11 (-132,107)               | (239)      | 1.6 (-15,19)                 | (34)       |
| 2. restricted approx. optimal, not DR | 19.5 (14.8,24.1)             | (9.3)      | 2.0 (-0.3,4.4)               | (4.7)      | -0.20 (-0.43,0.02)           | (0.45)     |
| 3. restricted approx. optimal, DR | 23.4 (18.5,28.0)             | (9.5)      | -0.2 (-2.6,2.3)              | (4.9)      | -0.06 (-0.32,0.19)           | (0.51)     |
| 4. working identity covariances, DR | 25.6 (21.7,29.5)             | (7.8)      | -0.35 (-1.8,1.2)             | (3.0)      | 0.0095 (-0.09,0.11)          | (0.20)     |
| 5. approximately optimal, DR      | 25.9 (19.0,31.8)             | (12.8)     | -0.87 (-3.8,2.7)             | (6.5)      | 0.025 (-0.21,0.23)           | (0.44)     |
| 2b. as 2., sensitivity analysis   | 24.8 (19.7,31.0)             | (11.3)     | -0.7 (-4.0,1.9)              | (5.8)      | 0.06 (-0.23,0.51)            | (0.74)     |
| 3b. as 3., sensitivity analysis   | 25.9 (21.2,30.6)             | (9.5)      | -0.8 (-2.9,1.3)              | (4.3)      | -0.004 (-0.22,0.21)          | (0.43)     |
| 4b. as 4, sensitivity analysis    | 27.3 (23.2,31.4)             | (8.2)      | -1.1 (-2.5,0.4)              | (2.9)      | 0.06 (-0.04,0.15)            | (0.19)     |
| 5b. as 5, sensitivity analysis    | 30.4 (20.7,33.6)             | (12.8)     | -3.2 (-4.4,1.6)              | (5.9)      | 0.22 (-0.13,0.30)            | (0.43)     |

DR: doubly robust.
95% CI: 95% confidence interval based on bootstrap, Efron’s percentile method.
1a. and 1b. Naive choices of estimators within class (Section 7·4). Not doubly robust.
2. \( q \) approximately optimal within the class with \( q^m_k = 0 \) for \( k \neq m+12 \) (Section 7·2). Not doubly robust.
3. \( q \) approximately optimal within the class with \( q^m_k = 0 \) for \( k \neq m+12 \) (Section 7·2). Doubly robust.
4. Like the optimal estimator, but with working identity covariance matrices (Sections 6 and 7·3). Doubly robust.
5. Optimal under correct specification of all models (Sections 6 and 7·3). Doubly robust.
Figure 1: Square root MSE of estimators 2.-5. in the simulation study. For example, for month 11, the quantity in the figure is the estimate for the square root MSE for the expected difference in the CD4 count at month $23=11+12$ between starting ART at month 11 versus never starting ART.
Figure 2: Estimates of the effect of one year of ART: AIEDRP data. For example, for month 11, the quantity in the figure is the estimate for the expected difference in the CD4 count at month 23=11+12 between starting ART at month 11 versus never starting ART.