Chapter 24
Case Study: Longitudinal HIV Cohort Data

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In this chapter, we introduce a case study based on the treatment of HIV infection. A series of scientific questions concerning how best to detect and manage antiretroviral treatment failure in resource-limited settings are used to illustrate the general road map for targeted learning. We emphasize the translation of background knowledge into a formal causal and statistical model and the translation of scientific questions into target causal parameters and corresponding statistical parameters of the distribution of the observed data. Readers may be interested in first reading the longitudinal sections of Appendix A for a rigorous treatment of longitudinal TMLE and related topics.

HIV is a virus that damages the human immune system, resulting in a decline in CD4+ T lymphocytes and increased susceptibility to opportunistic infections. Antiretroviral drugs used in combination can suppress HIV replication to the point that HIV becomes undetectable in the blood stream, allowing CD4+ T-cell counts and immunologic function to recover. Unfortunately, HIV may develop resistance to the initial combination antiretroviral regimen used, allowing viral replication to rebound despite ongoing treatment. Failure to modify antiretroviral regimens once resistance and viral failure have occurred results in the evolution of additional resistance mutations and can compromise future treatment options. Delayed modification can also increase morbidity and mortality as a result of both CD4+ T cell depletion and inflammation-associated immune damage (Petersen et al. 2008; Rodger et al. 2009). In order to prevent these complications, the standard of care in resource-rich settings is to measure plasma HIV RNA levels (viral loads) regularly and modify a patient's antiretroviral regimen as soon as viral failure is detected (Hammer et al. 2008).

The majority of HIV-infected individuals, however, live in settings where resource and infrastructure limitations currently preclude regular viral load monitoring (Stringer et al. 2006). As a result, patients in much of the world may remain for extended periods on regimens that permit ongoing viral replication at detectable levels. The consequences of this limited monitoring capacity and resulting delays in regimen modification remain incompletely understood. Further, less resource-

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intensive modes of effectively detecting treatment failure remain to be identified. With this motivation, this chapter focuses on the following public health questions: What impact does delayed regimen modification following emergence of resistance have on long-term mortality? To what extent will use of less resource-intensive modification strategies, such as those based on CD4+ T cell measurements rather than viral loads, result in worse patient outcomes? How can CD4+ T cell measurements best be used to guide regimen modification? We illustrate how these questions can be approached using a formal causal inference framework and answers estimated using data drawn from observational HIV cohorts.

24.1 Data

Let baseline time $t = 0$ denote time of failing first-line antiretroviral therapy, where first-line therapy is defined as a combination antiretroviral (cART) regimen containing two nucleoside reverse transcriptase inhibitors (NRTIs) and one nonnucleoside reverse transcriptase inhibitor (NNRTI), and failure is defined as the second of two consecutive plasma HIV RNA levels greater than 500 copies/ml, measured at least 6 months after starting cART. We use a discrete time scale, with $t = 0, ..., \tau$. For simplicity, we refer to the time scale as days for the remainder of the chapter; however, time increments could also represent months, quarters, or longer intervals. The appropriate time scale will depend on the frequency with which treatment decisions and measurements are made. The target population is defined as adults who are antiretroviral-naive prior to initiating cART and who fail first-line cART a minimum of τ days prior to the calendar date at which the database is administratively closed.

We consider two types of treatment variables; $A_1(t)$ is defined as an indicator that jumps to zero if a subject interrupts first-line therapy, and $A_2(t)$ is defined as an indicator that jumps to zero if a subject modifies first-line therapy (or in other words, starts second-line therapy). Modification is defined as initiation of a protease inhibitor drug plus two new NRTIs. Interruption is defined as stopping all drugs for at least 2 weeks. All other changes to the antiretroviral regimen are assumed to represent substitutions due to patient preference, availability, or adverse effects and are not coded as treatment changes.

Subjects may also leave the cohort or be "lost to follow-up." We define a censoring time C as the time point at which a subject leaves the cohort and define $C(t) \equiv I(C \leq t)$ as the indicator that a subject is no longer in follow-up at time t. We treat censoring as an additional intervention variable because we are interested in the effect of treatment if all subjects remained in the cohort (and thus under observation) until time τ. All intervention variables by definition jump only once; changes in antiretroviral regimen after interruption or modification are not considered part of the treatment of interest, and a subject does not return to the cohort once he or she has been censored. Time-varying covariates can be considered under the following categories: laboratory measurements, diagnoses of new comorbidities, clinic visit dates,

and vital status. The latter three categories, as well as the days on which laboratory measurements are updated, can be coded as counting processes.

The most recent laboratory covariate values at a given time t are coded as $W(t) = (W_1(t), ..., W_J(t))$. In clinical cohort data from resource-rich settings, $W(t)$ often includes the following J time-varying covariates: CD4+ T cell count, CD8+ T cell count, viral load, hepatitis C virus antibody, and hepatitis B virus surface antigen. In resource-limited settings such as Africa, $W(t)$ may be limited to CD4+ T cell count, complete blood count, or body mass index. Each time-dependent covariate may be measured at different and possibly irregular time points. We denote the process tracking when new laboratory measurements are made as $\Delta(t) = (\Delta_1(t), ..., \Delta_J(t))$, where $\Delta_j(t)$ denotes an indicator that covariate j is measured at time t. A covariate $W_j(t)$ is missing until $\Delta_j(t)$ first jumps; subsequently $W_j(t)$ is coded as the covariate's most recent value. New diagnoses made at time t are coded using a vector of counting processes $D(t) = (D_1(t), ..., D_K(t))$. These K counting processes include diagnosis of AIDS-defining illnesses and, in data from resource-rich settings, diagnosis of major non-AIDS comorbidities.

Clinic visits are coded as a separate counting process $M(t)$. Note that only when $dM(t) = 1$ (i.e., a patient visits the clinic) are any of the counting processes in $D(t)$ or the treatment process $A_2(t)$ at risk of jumping. In contrast, $\Delta(t)$, corresponding to updates of the laboratory covariates, can jump on any date, as can losses to follow-up and treatment interruptions. Finally, data are collected on vital status. Let T denote time of death and $\tilde{T} = \min(T, C, \tau)$ be the follow-up time. In addition, let $Y(t) = I(T \leq t)$ indicate whether a subject has died by time t, a counting process that can jump on any day.

In addition to the time-varying covariates above, the data include the following non-time varying-covariates: age at baseline, calendar year at baseline, sex, ethnicity, HIV risk group, nadir CD4 count prior to baseline, and peak viral load prior to baseline. We denote these non-time-varying covariates with B.

24.2 Causal Model

We separate variables into intervention variables $A(t) = (A_1(t), A_2(t), C(t))$, nonintervention variables $L(t) \equiv (M(t), D(t), \Delta(t), W(t))$, and the outcome $Y(t)$ and assume the following time ordering, as shown more explicitly below: $(Y(t), L(t), A(t))$. Baseline variables $L(0)$ include non-time-varying covariates and the baseline values of time-varying covariates $L(0) \equiv (B, M(0), D(0), \Delta(0), W(0))$. We use $\bar{X}(t) = (X(0), X(1), ..., X(t))$ to denote the history of any covariate X through time t. We define covariate values after death deterministically as their last observed value $L(t) \equiv L(T-1)$ and $A(t) \equiv A(T-1)$ for $t \geq T$. We also specify the following set of structural equations ($t = 1, ..., \tau$):

$$
\begin{aligned}
&L(0) = f_{L(0)}(U_0),\\
&Y(t) = f_{Y(t)}(Y(t-1), \bar{L}(t-1), \bar{A}(t-1), U_{Y(t)}),\\
&M(t) = f_{M(t)}(Y(t), \bar{L}(t-1), \bar{A}(t-1), U_{M(t)}),\\
&D_k(t) = f_{D_k(t)}(M(t), Y(t), \bar{L}(t-1), \bar{A}(t-1), U_{D_k(t)}); k = 1, ..., K,\\
&\Delta_j(t) = f_{\Delta_j(t)}(D(t), M(t), Y(t), \bar{L}(t-1), \bar{A}(t-1), U_{\Delta_j(t)}); j = 1, ..., J,\\
&W_j(t) = f_{W_j(t)}(\Delta(t), D(t), M(t), Y(t), \bar{L}(t-1), \bar{A}(t-1), U_{W_j(t)}); j = 1, ..., J,\\
&A_1(t) = f_{A_1(t)}(Y(t), \bar{L}(t), \bar{A}(t-1), U_{A_1(t)}),\\
&A_2(t) = f_{A_2(t)}(Y(t), A_1(t), \bar{L}(t), \bar{A}(t-1), U_{A_2(t)}),\\
&C(t) = f_{C(t)}(Y(t), A_1(t), A_2(t), \bar{L}(t), \bar{A}(t-1), U_{A_1(t)}).
\end{aligned}
$$

All subjects are assumed alive, on first-line therapy, and uncensored at baseline ($A_1(0) = A_2(0) = 1$, $Y(0) = C(0) = 0$). Specification of the causal model also involves specification of the joint distribution of the background factors or errors U:

$$
\begin{aligned}
&U_0 = (U_B, U_{M(0)}, U_{D(0)}, U_{W(0)}, U_{\Delta(0)}),\\
&U = (U_0, U_{Y(t)}, U_{M(t)}, U_{D_k(t)}, U_{\Delta_j(t)}, U_{W_j(t)}, U_{A_1(t)}, U_{A_2(t)}, U_{C(t)} : t, k, j),\\
&U \sim P_U.
\end{aligned}
$$

If it were known, for example, that the decision to modify therapy (among subjects who were alive and still on first-line therapy) was randomly assigned and perfectly complied with, this knowledge would justify an assumption that $U_{A_2(t)}$ is independent of all other errors [as well as an exclusion restriction on the structural equation model such that $A_2(t) = f_{A_2(t)}(Y(t), A_1(t), \bar{A}(t-1), U_{A_2(t)})$]. However, given the observational nature of the data, we avoid making any assumptions at this stage regarding the joint distribution P_U.

We denote the observed history of a covariate X as $\bar{X} \equiv \bar{X}(\tilde{T})$. The observed data consist of n i.i.d. copies of $O = \bar{O}(\tilde{T}) = (\bar{Y}, \bar{L}, \bar{A})$. These data are observed for a given individual until he or she either leaves the cohort (is lost to follow-up), dies, or time τ. We denote the distribution of O as P_0 and corresponding density p_0. We assume that the observed data correspond to n repeated draws from the SCM. In other words, for $i = 1, ..., n$, O_i is drawn by first drawing U_i from the distribution of background factors P_U (e.g., this might correspond to drawing a subject from a population), then generating each component of O sequentially for either τ time points or until $C(t)$ jumps to one. If $Y(t)$ jumps to one, covariate values for all subsequent time points are set equal to their last observed values.

24.3 Target Causal Parameters

In this section, we introduce a range of target causal parameters. For each, we begin with a scientific question and describe a hypothetical randomized trial that could be used to answer it. Each of these trials targets a distinct causal parameter. We illus-

trate how each target parameter in turn can be expressed in terms of counterfactuals, where the relevant counterfactuals are defined in terms of an intervention on the causal model.

24.3.1 Standard Marginal Structural Models

In assessing how changes in the availability of viral load monitoring will impact patient outcomes, the first question is whether delayed regimen modification following viral failure increases patient mortality, and if so, by how much. Previous analyses documented an increased risk of mortality with delayed modification of virologically failing NNRTI-based regimens; however, these analyses were based on subjects treated in resource-rich settings and included patients exposed to antiretroviral therapy prior to initiating cART (Petersen et al. 2008). Understanding how mortality varies as a function of cumulative delay until modification, and whether any increased risk of mortality resulting from delayed modification persists after second-line therapy has been initiated, could further inform the design of alternative monitoring strategies. For example, if most of the harm of delayed modification accrues during the first 3 months of failure, use of a semiannual vs. annual viral load testing strategy may have a smaller benefit than if mortality increases linearly with cumulative time spent on failing therapy. In theory, these questions could be addressed by enrolling subjects at the time of viral failure and randomly assigning each subject to remain on first-line failing therapy until a fixed switching time, ranging from immediate switch to switch after some maximum delay. In such an ideal trial, subjects would be prevented from interrupting therapy or leaving the cohort. Survival could then be compared between subjects randomized to different modification times.

In order to translate this ideal trial into a target causal parameter, we define counterfactuals indexed by interventions on interruptions and modifications of first-line therapy and on losses to follow-up. We denote counterfactual covariate and outcome values (the values that covariates and outcome would have taken under a specific treatment history $\bar{a}$) as $\bar{L}_{\bar{a}}$ and $\bar{Y}_{\bar{a}}$. These counterfactuals are defined as the solutions to the corresponding structural equations under an intervention on the SCM in which the structural equations $f_{A(t)}$, for $t = 1, ..., \tau$, are replaced with the constant values implied by $\bar{a}$. Our outcome of interest is counterfactual survival $\bar{Y}_{\bar{a}}(\tau)$. We focus on counterfactuals indexed by interventions under which first-line therapy is not interrupted and is modified at a fixed time (ranging from immediate switch to no switch during follow-up) and where no loss to follow-up occurs. The set of counterfactual interventions of interest is thus

$$\mathcal{A} \equiv \left\{ \bar{c} = 0, \bar{a}_1 = 1, \bar{a}_2 : \sum_{t=1}^{\tau} a_2(t) \in \{0, \tau\} \right\}. \tag{24.1}$$

Let

$$X_{SM} = \left(\bar{Y}_{\bar{a}}(\tau) : \bar{a} \in \mathcal{A}\right)$$

denote the collection of counterfactual survival times under each possible treatment regimen and let $X_{SM} \sim F_{X_{SM}}$. If we believe that the SCM accurately represents the processes that generated our observed data, this distribution represents the distribution of survival times that would have been observed if we had intervened on the data-generating system to change the mechanism by which treatment decisions were made (i.e., by forcing all subjects, rather than a self-selected subgroup, to follow each regimen $\bar{a} \in \mathcal{A}$), without altering any of the remaining data-generating processes.

Multiple target parameters can be defined using the counterfactual outcomes $(\bar{Y}_{\bar{a}}(\tau) : \bar{a} \in \mathcal{A})$ and corresponding counterfactual survival times. For example, if the counterfactual (discrete) hazard under every possible delay time is of interest, one option is to smooth across time points and delay times using a marginal structural model (Robins 2000, 1998, 1999b), such as

$$\text{logit}\left(P(T_{\bar{a}} = t \mid T_{\bar{a}} \geq t)\right) = m_{SM}(t, \bar{a} \mid \beta)\,.$$

For example, one might specify the following model to investigate a linear summary of the relationship between counterfactual hazard at time t and and cumulative time spent on failing therapy up till time t:

$$m_{SM}(t, \bar{a} \mid \beta) = \beta_0 + \beta_1 \sum_{j=1}^{t-1} a_2(j) + \beta_2 t + \beta_3 \sum_{j=1}^{t-1} a_2(j) \times t. \tag{24.2}$$

For this particular specification, $\exp(\beta_1 + \beta_3 t)$ is the relative (discrete) odds of death at time t for each additional day spent on failing therapy. Alternatively, more flexible model specifications could be used, such as models in which splines allow for nonlinear changes in baseline hazard over time and nonlinear effects of delayed modification. We refer to model (24.2), indexed by an intervention beginning at a single time point and applied uniformly to all subjects in the population, as a "standard" marginal structural model, to contrast it with the history-adjusted and dynamic marginal structural models described in the following sections.

At this stage in the road map, we are aiming purely to define our target parameter and wish to avoid introducing new model assumptions. We thus define our target causal parameter as a projection of true counterfactual hazard under different possible values for $\bar{a}$ onto the model $m_{SM}(t, \bar{a} \mid \beta)$ using a marginal structural working model (Neugebauer and van der Laan 2007). For model (24.2), the target causal parameter is defined as

$$\beta_{SM} = \arg\max_{\beta} E_{F_{X_{SM}}}\left[\sum_{\bar{a}} \sum_{t} \log\left((\lambda_{SM,\beta})^{I(T_{\bar{a}}=t)}(1 - \lambda_{SM,\beta})^{I(T_{\bar{a}}>t)}\right)\right], \tag{24.3}$$

where to simplify notation we use $\lambda_{SM,\beta}$ to refer to $\text{expit}(m_{SM}(\bar{a}, t \mid \beta))$. In other words, β_{SM} is defined as the parameter value of β that minimizes the average of the

Kullback–Liebler divergence between the model $m_{SM}(t, \bar{a} \mid \beta)$ and the distribution $F_{X_{SM}}$ across time points and possible switching times. One way to understand this projection is to think of the target parameter as the parameter value that would have been obtained if the investigator had access to the true counterfactual survival times (or a perfectly executed randomized trial) for an infinite population under every possible modification time and regressed these counterfactual outcomes on modification time according to model $m(t, \bar{a} \mid \beta)$. In this manner, the causal parameter β_{SM} is explicitly defined as a function of the distribution of the counterfactual survival times:

$$\beta_{SM} = \Psi_{SM}(F_{X_{SM}}). \tag{24.4}$$

24.3.2 History-Adjusted Marginal Structural Models

Target parameters defined using standard marginal structural models can be used to estimate counterfactual survival if the entire population of patients failing antiretroviral therapy (or subgroups defined by baseline covariate values $V \subset L(0)$) were forced to delay regimen modification. In practice, however, such a uniform treatment pattern is unlikely to occur. When viral loads are not available, the World Health Organization (WHO) currently recommends the use of CD4+ T cell counts to guide regimen modification (World Health Organization 2006). Specifically, any of the following three immunologic criteria can be interpreted as evidence of regimen failure and used to trigger modification to second-line therapy: (1) decline of CD4+ T cell counts to pretherapy baseline or below, (2) $\geq$ 50% decline of CD4+ T cell counts from on-treatment peak value, or (3) persistent CD4+ T cell counts < 100 cells/μl. While requiring fewer resources to implement than viral-load-based monitoring, however, CD4-based monitoring of antiretroviral treatment is complicated by the fact that in some patients CD4 counts remain stable for weeks or months despite ongoing viral replication (Reynolds et al. 2009). As a result, immunologic criteria have poor sensitivity for detecting virologic failure, and if used exclusively to guide switching decisions would result in delayed regimen modification for many patients.

The findings that (1) delayed regimen modification enforced across the entire target population would result in lower expected survival and (2) use of CD4+ T cell counts would on average result in delayed regimen modification do not in themselves imply that use of CD4+ T cell counts to guide modification decisions would necessarily increase mortality. Specifically, if CD4+ T cell counts are used to trigger regimen modification, delays will be longest for those subjects who maintain elevated CD4 counts despite ongoing viral replication and will be shortest for those subjects whose CD4 counts are low at the time of or decline rapidly following viral failure. This suggests an additional scientific question: Among subjects with viral failure, is delayed modification less harmful for those subjects who maintain CD4 counts above WHO switching criteria than it is for subjects with low CD4 counts? A CD4-based monitoring strategy would have a substantially smaller impact on mor-

tality if delayed modification resulted in increased mortality primarily among those subjects with low CD4 counts on failing therapy.

In order to address whether CD4 count during virologic failure modifies the effect of additional delays in regimen modification, a clinical trial could enroll subjects who had remained on virologically failing first-line regimens for varying durations, stratify them on the basis of their current CD4+ T cell count, and within each CD4 count stratum randomly assign each subject an additional fixed delay time. Such a trial would allow the effect of additional delay time on survival to be compared between subjects who did vs. did not meet WHO CD4 switching criteria in the context of viral failure. Importantly, however, the effect of delayed modification within CD4 count strata would be estimated among a selected subpopulation: those who remained alive and on first-line therapy. Petersen et al. (2007a), Robins et al. (2007a), van der Laan et al. (2007a), van der Laan and Petersen (2007b), and Petersen et al. (2007b) provide further discussion of this issue.

We define counterfactual outcomes indexed by a series of baseline time points: $r = 1, ..., \tau - m$. For each baseline time point r, the counterfactual outcome is defined as the probability of survival for at least m additional time points under an intervention on treatment decisions beginning at time r. Treatment decisions from time 0 through time $r - 1$ are left random and treatment decisions from time r until the outcome is measured at $r + m$ are intervened on. More formally, the counterfactuals of interest are $Y_{\bar{A}(r-1)\underline{a}(r)}(r + m)$ for $r = 1, ..., \tau - m$, where $\underline{a}(r) \equiv (a(r), a(r + 1), ..., a(r + m - 1)) \in \mathcal{A}_r$. We consider $\mathcal{A}_r$ (the set of possible treatment regimens beginning at time r) such that for each $\underline{a}(r) \in \mathcal{A}_r$ we have $(\bar{A}(r - 1), \underline{a}(r)) \in \mathcal{A}$, where $\mathcal{A}$ (the set of possible treatments from $t = 1, ..., \tau$) is defined as in (24.1) to include all possible modification times and no losses to follow-up or interruptions. To simplify notation, we use $Y_{\underline{a}(r)}(r + m)$ to refer to $Y_{\bar{A}(r-1)\underline{a}(r)}(r + m)$ and $T_{\underline{a}(r)}$ to refer to $T_{\bar{A}(r-1)\underline{a}(r)}$. Let $F_{X_{HM}}$ denote the distribution of

$$X_{HM} = \left(\left\{\bar{A}(r - 1), Y(r), \text{CD4}(r), \left(Y_{\underline{a}(r)}(r + m) : \underline{a}(r) \in \mathcal{A}_r\right)\right\} : r = 1, ..., \tau - m\right).$$

Here $\text{CD4}(r) \in W(r)$ denotes the most recent CD4 measurement available at time r.

We aim to estimate how the effect of additional time spent on a failing regimen differs depending on a subject's most recent CD4+ T cell count among those subjects who remain alive, in follow-up, and on first-line therapy. In order to define a target parameter that addresses this question, we could estimate counterfactual survival probability m days in the future as a function of additional time spent on failing therapy and current CD4+ T cell count using a series of standard marginal structural working models and treating each time point $0, ..., \tau - m - 1$ in turn as baseline. Alternatively, the use of history-adjusted marginal structural models (van der Laan et al. 2005; Petersen et al. 2007a) allows us to use a common working model and smooth across baseline time points:

$$\begin{aligned}&\text{logit}\left(P\left(T_{\underline{a}(r)} \leq r + m \mid \bar{A}_1(r - 1) = \bar{A}_2(r - 1) = 1, C \geq r, T > r, \text{CD4}(r)\right)\right)\\ &\quad = m_{HM}(r, \underline{a}(r), \text{CD4}(r) \mid \beta),\end{aligned}$$

for $r = 1, ..., \tau - m$. For example, we might define our target parameter using the following working model:

$$m_{HM}\left(r, \underline{a}(r), \text{CD4}(r)|\beta\right) = \beta_0 + \beta_1 \sum_{t=r}^{r+m-1} a_2(t) + \beta_2 I(\text{CD4}(r) > w*) + \beta_3 \sum_{t=r}^{r+m-1} a_2(t) \times I(\text{CD4}(r) > w*), \quad (24.5)$$

where $w*$ is the CD4 modification threshold recommended by the WHO. Such a model provides a linear summary of the effect of additional delay until regimen modification ($\sum_{t=r}^{r+m-1} a_2(t)$) on probability of survival m time points in the future and allows this effect to differ depending on current CD4 count. An alternative model specification could also allow this effect to differ depending on duration of time already spent on failing therapy (r). For the particular working model specification (24.5), $\beta_3 = 0$ corresponds to the null hypothesis that the effect of additional delay until regimen modification is the same regardless of current CD4 count, and $\exp(\beta_1 + \beta_3)$ corresponds to the discrete hazard ratio associated with an incremental increase in delay until regimen modification for subjects with a CD4 count $> w*$. A finding that $\beta_1 > 0$ while $(\beta_3 + \beta_1) \leq 0$ would suggest that increased mortality resulting from delayed regimen modification was occurring primarily in those subjects with CD4 counts below the WHO-recommended modification threshold.

Again, rather than assuming that equality (24.5) holds for some value of β, the target parameter β_{HM} can be defined using a projection as

$$\beta_{HM} = \arg\max_{\beta} E_{F_{X_{HM}}} \left[\sum_{\underline{a}(r)} \sum_{r} \log\left((\lambda_{HM,\beta})^{I(T_{\underline{a}(r)} \leq r+m)} (1 - \lambda_{HM,\beta})^{I(T_{\underline{a}(r)} > r+m)} \right) \right], \quad (24.6)$$

where to simplify notation we use $\lambda_{HM,\beta}$ for $\text{expit}(m_{HM}(r, \underline{a}(r), \text{CD4}(r) \mid \beta))$. In this manner, the history-adjusted marginal structural model target causal parameter is explicitly defined as a function of the distribution of the counterfactual survival times indexed by interventions beginning at time r:

$$\beta_{HM} = \Psi_{HM}(F_{X_{HM}}). \quad (24.7)$$

24.3.3 Dynamic Marginal Structural Models

The target parameters defined using standard and history-adjusted marginal structural models address the scientific questions of whether delayed regimen modification following viral failure results in increased mortality, whether the effect of additional delay until regimen modification among subjects who remain on first-line therapy differs depending on current CD4+ T cell count, and whether delayed modification remains detrimental to those subjects with CD4 counts above the WHO-

recommended modification threshold. The target parameters defined thus far do not, however, address the following questions: (1) How would patient outcomes have differed if a CD4-based rule *vs.* a viral load-based rule had been used to decide when to modify therapy? (2) Which CD4 -based rule would have resulted, on average, in optimal patient outcomes?

A clinical trial to address the latter two questions would enroll subjects at the time of cART initiation and randomly assign them to a strategy for deciding when to modify therapy. Random assignment of subjects to remain on failing therapy until they met a CD4-based switching criterion *vs.* a viral-load-based switching criterion would allow patient outcomes to be compared under these two strategies, while random assignment of subjects to a range of different CD4-based switching criteria would provide insight into the best choice of CD4-based rule. The randomized exposure in such hypothetical trials can be contrasted with the exposure in the hypothetical trials described in Sects. 24.3.1 and 24.3.2, in which subjects were randomly assigned a fixed delay time until modification rather than assigned a strategy for deciding when to modify.

The target parameters defined in Sects. 24.3.1 and 24.3.2 focused on subjects who were virologically failing cART. In order to focus on the larger population of subjects starting cART, we redefine our baseline time point in the current section such that $t = 0$ corresponds to time of cART initiation rather than the time of cART failure. We define counterfactuals indexed by dynamic treatment regimens, or rules that assign treatment decisions at each time point in response to patient characteristics. Our focus is on dynamic rules that assign subjects to switch to second-line therapy as soon as (and no sooner than) their CD4+ T cell count reaches a specified threshold, and that do not allow subjects to either interrupt first-line therapy or to leave the cohort. A similar approach could be used to define counterfactuals under viral-load-based rules.

Let $d_\theta(t, \overline{\text{CD4}}(t), \bar{A}(t-1))$ denote a treatment rule that deterministically assigns values to the intervention variables $A(t) = (A_1(t), A_2(t), C(t))$ based on treatment history and CD4 count up till time t according to the following algorithm:

- Do not interrupt first-line therapy (set $A_1(t) = 1$ for all t).
- Remain in follow-up (set $C(t) = 0$ for all t).
- If most recent CD4+ T cell count is $< \theta$ and a subject is still on first-line therapy, switch to second-line therapy (set $A_2(t) = 0$ if $A_2(t-1) = 1$ and $\text{CD4}(t) < \theta$).
- If most recent CD4+ T cell count is $\geq \theta$ and a subject is still on first-line therapy, do not switch to second-line therapy (set $A_2(t) = 1$ if $A_2(t-1) = 1$ and $\text{CD4}(t) < \theta$).
- Once a subject has modified regimens, $A_2(t) = 0$ by definition.

We focus on counterfactual survival times $(\bar{Y}_{d_\theta}(\tau) : \theta \in \Theta)$ under an intervention on the SCM that assigns interruption, modification, and censoring according to the rule $d_\theta(t, \overline{\text{CD4}}(t), \bar{A}(t-1))$, $t = 1, .., \tau$, where Θ is a set of CD4 switching thresholds of interest. In other words, $Y_{d_\theta}(t)$ is defined as the solution to the structural equation $f_{Y(t)}$ under an intervention on the system of equations in which $f_{A_1(t)}$,$f_{A_2(t)}$, and $f_{C(t)}$ are replaced with the treatment rule $d_\theta(t, \overline{\text{CD4}}(t), \bar{A}(t-1))$. Let $F_{X_{DM}}$ denote the

distribution of

$$X_{DM} = \left(\bar{Y}_{d_\theta}(\tau) : \theta \in \Theta\right).$$

We are interested in how the counterfactual survival distribution differs as a function of the CD4+ T cell count (or viral load) threshold θ used to trigger regimen modification. A dynamic marginal structural model can be used to summarize this relationship, smoothing over possible values of the threshold θ (Hernan et al. 2006; van der Laan and Petersen 2007a; Robins et al. 2008). For example, one could specify a working model for the discrete counterfactual hazard as a function of θ:

$$\text{logit}\left(P(T_{d_\theta} = t \mid T_{d_\theta} \geq t)\right) = m_{DM}(\theta, t \mid \beta).$$

For example, one might specify the following working model:

$$m_{DM}(t, \theta \mid \beta) = \beta_0 + \beta_1\theta + \beta_2\theta^2 + h(t), \tag{24.8}$$

where $h(t)$ is some user-specified function of t. For example, if $h(t)$ corresponds to an indicator variable for each time point t, (24.8) approximates a Cox proportional hazards model for fine enough time scale t. Alternative model specifications could allow the effect of the threshold θ on the discrete hazard to vary by time (or, in other words, relax the proportional hazards assumption). As with β_{SM} and β_{HM}, rather than assuming that equality (24.8) holds for some value θ, we define β_{DM} using a projection:

$$\beta_{DM} = \arg\max_{\beta} E_{F_{X_{DM}}}\left[\sum_{\theta}\sum_{t} \log\left((\lambda_{DM,\beta})^{I(T_{d_\theta}=t)}(1-\lambda_{DM,\beta})^{I(T_{d_\theta}>t)}\right)\right], \tag{24.9}$$

where to simplify notation we use $\lambda_{DM,\beta}$ to refer to expit$(m_{DM}(t, \theta \mid \beta))$. The dynamic marginal structural model parameter is now defined a a function of the distribution of the counterfactual survival times indexed by rules d_θ:

$$\beta_{DM} = \Psi_{DM}(F_{X_{DM}}). \tag{24.10}$$

24.4 Statistical Model and Identifiability Results

Recall that the observed data consist of n i.i.d. copies of $O \sim P_0$, while the target parameters are functions of the counterfactual distributions $F_{X_{SM}}$, $F_{X_{HM}}$, and $F_{X_{DM}}$. In order to estimate these target causal parameters, we must thus first be able to express $\Psi_{SM}(F_{X_{SM}})$, $\Psi_{HM}(F_{X_{HM}})$, and $\Psi_{DM}(F_{X_{DM}})$ as parameters of the observed data distribution P_0. The sequential randomization assumption is one sufficient assumption for β_{SM} and β_{HM} to be identified as parameters of the observed data distribution (Robins 1986, 1987a,b):

$$
\begin{aligned}
&Y_{\bar{a}}(j) \perp\!\!\!\perp A_1(t) \mid \bar{L}(t) = \bar{l}(t), \bar{A}(t-1) = \bar{a}(t-1), \\
&Y_{\bar{a}}(j) \perp\!\!\!\perp A_2(t) \mid \bar{L}(t) = \bar{l}(t), \bar{A}(t-1) = \bar{a}(t-1), A_1(t) = a_1(t), \\
&Y_{\bar{a}}(j) \perp\!\!\!\perp C(t) \mid \bar{L}(t) = \bar{l}(t), \bar{A}(t-1) = \bar{a}(t-1), A_1(t) = a_1(t), A_2(t) = a_2(t), \\
&\text{for } t < j \leq \tau.
\end{aligned} \tag{24.11}
$$

For β_{DM} the corresponding assumption is

$$
\begin{aligned}
&Y_{d_\theta}(j) \perp\!\!\!\perp A_1(t) \mid \bar{L}(t) = \bar{l}(t), \bar{A}(t-1) = \bar{a}(t-1), \\
&Y_{d_\theta}(j) \perp\!\!\!\perp A_2(t) \mid \bar{L}(t) = \bar{l}(t), \bar{A}(t-1) = \bar{a}(t-1), A_1(t) = a_1(t), \\
&Y_{d_\theta}(j) \perp\!\!\!\perp C(t) \mid \bar{L}(t) = \bar{l}(t), \bar{A}(t-1) = \bar{a}(t-1), A_1(t) = a_1(t), A_2(t) = a_2(t), \\
&\text{for } t < j \leq \tau.
\end{aligned} \tag{24.12}
$$

In words, modification, interruption, and loss to follow-up at each time point are assumed to be independent of counterfactual survival, given the observed past up till that time point. In terms of the causal model, these identifiability assumptions impose restrictions on the allowable joint distribution of the error terms P_U. We refer to the resulting SCM, corresponding to the model in Sect. 24.2 augmented with the restrictions on the joint distribution of the errors needed for identifiability, as the working SCM. We use the term "working" to refer to the SCM under which the target causal parameter is identified, which might include assumptions not fully supported by background knowledge and thus not part of the original SCM. We pursue estimation under the working model, while emphasizing that any interpretation of resulting estimates as causal effects is based on the plausibility of these working model assumptions. In the current example, neither the original SCM nor the working SCM imposes restrictions on the allowable joint distributions of the observed data. Thus for the purpose of estimation we commit to a nonparametric statistical model for each of the target parameters.

24.4.1 Likelihood

Let $Q_{L(0),0}(l(0)) \equiv P_0(L(0) = l(0))$ denote the conditional distribution of the baseline covariates and

$$
Q_{L(t),0}(l(t) \mid Y(t), \bar{L}(t-1), \bar{A}(t-1)) \equiv P_0(L(t) = l(t) \mid Y(t), \bar{L}(t-1), \bar{A}(t-1))
$$

denote the conditional distribution at time t of the nonintervention covariates (other than vital status), given past covariates, vital status, and treatment. Let

$$
g_{A(t),0}(a(t) \mid Y(t), \bar{L}(t), \bar{A}(t-1)) \equiv P_0(A(t) = a(t) \mid Y(t), \bar{L}(t), \bar{A}(t-1))
$$

denote the conditional distribution at time t of treatment and censoring given the past. Let

$$Q_{Y(t),0}(y(t) \mid Y(t-1), \bar{L}(t-1), \bar{A}(t-1)) \equiv P_0(Y(t) = y(t) \mid Y(t-1), \bar{L}(t-1), \bar{A}(t-1))$$

denote the conditional distribution of vital status at time t given past covariates and treatment, and

$$\bar{Q}_{Y(t),0}(Y(t-1), \bar{L}(t-1), \bar{A}(t-1)) \equiv P_0(Y(t) = 1 \mid Y(t-1), \bar{L}(t-1), \bar{A}(t-1)).$$

The likelihood can be factorized as follows:

$$P_0(O) = Q_{L_0,0}(L(0)) \prod_{t=1}^{\tilde{T}} \left\{ \begin{array}{l} \bar{Q}_{Y(t),0}(Y(t-1), \bar{L}(t-1), \bar{A}(t-1))^{Y(t)} \\ (1 - \bar{Q}_{Y(t),0}(Y(t-1), \bar{L}(t-1), \bar{A}(t-1)))^{1-Y(t)} \\ Q_{L(t),0}(L(t) \mid Y(t), \bar{L}(t-1), \bar{A}(t-1)) \\ g_{A(t),0}(A(t) \mid Y(t), \bar{L}(t), \bar{A}(t-1)) \end{array} \right\}.$$

The components of this likelihood $Q_{L(t),0}$ and $g_{A(t),0}$, $t = 1, ..., \tilde{T}$ can be further factorized into their respective components, where each factor represents the conditional distribution of a variable given its parents, those covariates on the right-hand side of the corresponding structural equation in the SCM presented in Sect. 24.2. For example,

$$\begin{aligned} g_{A(t),0}(A(t) \mid Y(t), \bar{L}(t), \bar{A}(t-1)) \equiv\ & g_{A_1(t),0}(A_1(t) \mid Y(t), \bar{L}(t), \bar{A}(t-1)) \\ & \times g_{A_2(t),0}(A_2(t) \mid A_1(t), Y(t), \bar{L}(t), \bar{A}(t-1)) \\ & \times g_{C(t),0}(C(t) \mid A_1(t), A_2(t), Y(t), \bar{L}(t), \bar{A}(t-1)). \end{aligned}$$

$Q_{L(t),0}$ can similarly be factorized into a series of conditional distributions, corresponding to $Q_{M(t),0}$, $Q_{D(t),0}$, $Q_{\Delta(t),0}$, and $Q_{W(t),0}$. Finally, the likelihood for the multidimensional variables $D(t)$, $W(t)$, and $\Delta(t)$ can be further factorized according to some arbitrary ordering. The data can be organized in long format, with a subject contributing a new line of data each time at least one of the counting processes jumps.

24.4.2 Target Parameters $\Psi(P_0)$

When (24.11) (or its graphical counterpart) holds, the target counterfactual parameters $\Psi(F_X)$ defined in Sect. 24.3 are identified (with slight abuse of notation) as parameters $\Psi(P_0)$ of the observed data distribution by the longitudinal g-computation formula (Robins 1986, 1987a,b; Pearl 2009). The g-computation formula for the marginal distribution of the counterfactual survival time indexed by a given intervention is derived by (1) intervening on the likelihood to remove those factors that correspond to the structural equations for the intervention variables, (2) evaluating the resulting truncated likelihood at the value of the intervention variables used to

index the counterfactual, and (3) integrating with respect to the distribution of all nonintervention variables other than the outcome. The target parameters β_{SM} and β_{DM} are identified as the projections of these counterfactual survival times under each possible intervention ($\bar{a} \in \mathcal{A}$ and d_θ for $\theta \in \Theta$, respectively) onto the corresponding working model. The target parameter β_{HM} is identified as the projection of the joint distribution of the counterfactual survival times under each possible intervention $(Y_{\underline{a}}(r+m) : \underline{a}(r) \in \mathcal{A}_r)$ and $(\text{CD4}(r), Y(r), \bar{A}(r-1))$, for each baseline time point r, onto working model m_{HM}.

We provide the full identifiability result for the distribution of the counterfactual survival time $T_{\bar{a}}$ [and thus for $\beta_{SM} = \Psi_{SM}(F_{X_{SM}})$] as an illustration:

$$P(T_{\bar{a}} = t) \overset{24.11}{=} \sum_{\bar{l}(t-1)} \left\{ \begin{array}{l} \bar{Q}_{Y(t),0}(T \geq t, \bar{L}(t-1) = \bar{l}(t-1), \bar{A}(t-1) = \bar{a}(t-1)) \times \\ \prod_{j=1}^{t-1}(1 - \bar{Q}_{Y(j),0}(T \geq j, \bar{L}(j-1) = \bar{l}(j-1), \bar{A}(j-1) = \bar{a}(j-1)) \times \\ \prod_{j=1}^{t-1} Q_{L(j),0}(l(j) \mid Y(j) = 0, \bar{L}(j-1) = \bar{l}(j-1), \bar{A}(j-1) = \bar{a}(j-1)) \\ Q_{L(0),0}(l(0)) \end{array} \right\},$$

where the right-hand side of this equation is a parameter of the observed data distribution P_0.

This identifiability result implies that the target parameter β_{SM} can be evaluated by drawing repeatedly from the truncated likelihood to generate the distribution of $Y_{\bar{a}}(t)$ for $t = 0, ..., \min(T, \tau)$ and $\bar{a} \in \mathcal{A}$. In other words, β_{SM} is evaluated using the following algorithm:

1. Draw $L(0)$ from the distribution $Q_{L(0),0}$ and draw $Y(1)$ from the conditional distribution $Q_{Y(1),0}$ given the draw of $L(0)$. If $Y(1) = 1$, skip to step 6.
2. Draw $L(1)$ from the conditional distribution $Q_{L(1),0}$ given $L(0)$ (noting that $Q_{L(1),0}$ is itself is composed of multiple conditional distributions and thus requires multiple sequential draws).
3. Draw $Y(2)$ from the conditional distribution $Q_{Y(2),0}$ given $\bar{L}(1)$ and setting $A(1) = a(1)$. If $Y(2)$=1, skip to step 6.
4. Draw $L(2)$ from the conditional distribution $Q_{L(2),0}$ given $\bar{L}(1)$ and setting $A(1) = a(1)$.
5. Repeat steps 3 and 4 to draw $Y(t)$ and $L(t)$ until $Y(t) = 1$ or $t = \tau$, whichever happens first.
6. Repeat steps 1–5 an infinite number of times for each treatment regimen $\bar{a} \in \mathcal{A}$
7. Evaluate β_{SM} by regressing the counterfactuals $Y_{\bar{a}}(t)$ simulated in steps 1–6 on treatment history $\bar{a}$ and t using pooled logistic regression model $m_{SM}(t, \bar{a}|\beta)$.

The parameter β_{DM} can be evaluated using a similar process, with the modifications that $A(t)$ in steps 3–5 is set by evaluating the function $d_\theta(t, \overline{\text{CD4}}(t), \bar{A}(t-1))$, steps 1–5 are repeated for each $\theta \in \Theta$, and in step 7 the simulated counterfactuals $Y_{d_\theta}(t)$ are regressed on θ and t using pooled logistic regression model $m_{DM}(t, \theta \mid \beta)$.

Evaluation of β_{HM} requires a modification of the algorithm such that a draw for a given time point r involves drawing from the nontruncated likelihood up till r

and the truncated likelihood after r. In other words, β_{HM} can be evaluated using the following algorithm:

1. Draw $(Y(r), \bar{L}(r), \bar{A}(r-1))$ by first drawing $L(0)$ from $Q_{L(0),0}$, then drawing $Y(j)$ from $Q_{Y(j),0}$, $L(j)$ from $Q_{L(j),0}$, and $A(j)$ from $g_{A(j),0}$ for $j = 1, ..., r-1$, and finally drawing $Y(r)$ from $Q_{Y(r),0}$ and $L(r)$ from $Q_{L(r),0}$. If $Y(r) = 1$, $C(r-1) = 1$, $A_1(r-1) = 0$ or $A_2(r-1) = 0$, skip to step 5.
2. Draw $Y(r+1)$ from the conditional distribution $Q_{Y(r+1),0}$ given draw $(\bar{L}(r), \bar{A}(r-1))$ and setting $A(r) = a(r)$. If $Y(r+1) = 1$, skip to step 5.
3. Draw $L(r+1)$ from the conditional distribution $Q_{L(r+1),0}$ given draw $(\bar{L}(r), \bar{A}(r-1))$ and setting $A(r) = a(r)$.
4. Repeat steps 2 and 3 to draw $Y(t)$ and $L(t)$ until $Y(t) = 1$ or $t = r + m$, whichever happens first.
5. Repeat steps 1–4 an infinite number of times for each $\underline{a}(r) \in \mathcal{A}_r$ and each $r = 1, ..., \tau - m$.
6. Evaluate β_{HM} by regressing the counterfactuals $Y_{\underline{a}}(r+m)$ simulated in steps 2–5 in those draws for which $Y(r) = C(r-1) = 0$ and $A_1(r-1) = A_2(r-1) = 1$ on $\underline{a}(r)$, CD4(r), and r using pooled logistic regression model $m_{HM}(r, \underline{a}(r), \text{CD4}(r) \mid \beta)$.

Each of these parameters $\beta = \Psi(P_0)$ can now be targeted for estimation, under the additional assumption of positivity needed to ensure that the relevant conditional probabilities are well defined (Chap. 10).

24.5 Estimation

We provide a succinct summary of MLE, IPCW estimation, TMLE, and IPCW reduced-data TMLE. Inference can be based on the nonparametric bootstrap or the influence curve; details are not provided in this chapter. We use the shorthand

$$Q_{\bar{L}(t),0} \equiv \prod_{j=0}^{t} Q_{L(j),0}(L(j) \mid Y(j), \bar{L}(j-1), \bar{A}(j-1)), \tag{24.13}$$

$$Q_{\bar{Y}(t),0} \equiv \prod_{j=1}^{t} Q_{Y(j),0}(Y(j) \mid Y(j-1), \bar{L}(j-1), \bar{A}(j-1)), \tag{24.14}$$

and $Q_0 \equiv Q_{\bar{L}(\tilde{\tau}),0} \times Q_{\bar{Y}(\tilde{\tau}),0}$ to refer to the L and Y components of P_0. We use

$$g_{\bar{A}(t),0} \equiv \prod_{j=1}^{t} g_{A(j),0}(A(j) \mid Y(j), \bar{L}(j), \bar{A}(j-1)) \tag{24.15}$$

and $g_0 \equiv g_{\bar{A}(\tilde{\tau}),0}$ to refer to the conditional distributions of the A components in $P_0 = Q_0 g_0$.

24.5.1 MLE

Above, each target parameter was expressed as a function of P_0 and algorithms were provided that described how each parameter could be evaluated given knowledge of the true data-generating distribution. A substitution estimator for each parameter is provided by plugging in an estimator of the data-generating distribution to these algorithms. The parameters β_{SM} and β_{DM} are only functions of Q_0; thus a substitution estimator of these parameters only requires an estimator Q_n of Q_0. In order to implement such an estimator, the conditional distribution of $L(t)$ can be factorized in terms of conditional distributions of the components of $L(t)$, where many of these components are binary indicators. The continuous or ordered discrete components of $L(t)$, such as the biomarkers CD4 count and viral load, can be discretized and coded accordingly in terms of binary indicators as well. These different conditional distributions can then be estimated based on the log-likelihood of the data $O_1, \ldots, O_n$, where, for each type of conditional distribution, we only have to work with the relevant factor of the likelihood that represents the particular conditional distribution we wish to estimate.

In estimating the t-specific conditional distribution of a given variable, one option is to pool across time or across different levels of an ordered discrete variable. For example, we could estimate the probability of a clinic visit at time t given the past by pooling across time points and including some function of time t as a covariate in a corresponding regression model. MLE according to parametric models for these conditional distributions can be carried out with standard multivariate logistic regression software. In addition, we can utilize machine learning algorithms such as log-likelihood-based super learning to construct data-adaptive estimators that avoid reliance on a priori specified parametric forms of these conditional distributions. This results in an initial estimator Q_n^0 of Q_0 (where we use the 0 superscript to differentiate this initial estimator of Q_0 from targeted estimators of Q_0 created by updating this initial fit when implementing TMLE in Sect. 24.5.3). An estimator Q_n^0 defines the maximum-likelihood-based substitution estimators $\Psi_{SM}(Q_n^0)$ and $\Psi_{DM}(Q_n^0)$ of the target parameters β_{SM} and β_{DM}.

The target parameter β_{HM} is a function of both Q_0 and g_0 (its evaluation according to the algorithm defined in Sect. 24.4.2 requires $g_{\bar{A}(r-1),0}$ in addition to $Q_{\bar{Y}(r+m),0}$ and $Q_{\bar{L}(r+m-1),0}$ for each time point r). Thus implementation of an MLE of β_{HM} according to this algorithm requires an estimator g_n of g_0. As with Q_0, g_0 can be factorized into a series of conditional distributions of binary variables, and these conditional distributions can be estimated using either parametric logistic regression models or with data-adaptive estimators. Rather than simulating data using Q_n^0 and g_n beginning at time $t = 0$, step 1 of the algorithm can alternatively be implemented by drawing from the empirical distribution of the observed data at time r $(\bar{L}(r), Y(r), \bar{A}(r-1))$. Consistency of the MLEs of β_{SM} and β_{DM} requires consistency of the estimator Q_0^n, consistency of the MLE of β_{HM} also requires consistent estimation of either $g_{\bar{A},0}(r-1)$ or the distribution of $(\bar{L}(r), Y(r), \bar{A}(r-1))$ for each time point r (which will be achieved if estimation of this distribution is based on sampling from the empirical distribution of the data at time r).

24.5.2 Inverse-Probability-Weighted Estimation

An alternative approach is to define an inverse probability of treatment and censoring-weighted estimating function for each of our target parameters as described in previous chapters.The following estimating functions are unbiased estimating functions for the target parameters β_{SM} and β_{DM}:

$$D^{SM}_{IPCW}(g_0,\beta_{SM}) = \sum_{t\le\tilde{T}} \frac{I(A_1(t-1)=1)\frac{d}{d\beta}m_{SM}(t,\bar{A}(t-1)\mid\beta)}{g_{\bar{A}(t-1),0}}(Y(t)-\lambda_{SM,\beta}),$$

$$D^{DM}_{IPCW}(g_0,\beta_{DM}) = \sum_{\theta}\sum_{t\le\tilde{T}} \frac{I(\bar{A}(t-1)=d_\theta(\bar{L}))\frac{d}{d\beta}m_{DM}(t,\theta\mid\beta)}{g_{\bar{A}(t-1),0}}(Y(t)-\lambda_{DM,\beta}).$$

The estimating function for β_{HM} involves a sum over those baseline time points r for which $Y(r)=C(r-1)=0, A_1(r-1)=A_2(r-1)=1$, and $r\le\tau-m$. To facilitate definition of the estimating function, let $\mathcal{R}$ refer to this set. Further, let

$$\begin{aligned}&\mathcal{W}(C(r+m-1),A_1(r+m-1),m_{HM},g_0)\\ &\quad\equiv \frac{I(C(r+m-1)=0,A_1(r+m-1)=1)\frac{d}{d\beta}m_{HM}(r,\underline{A}(r),\mathrm{CD4}(r)\mid\beta)}{\prod_{j=r}^{r+m-1} g_{A(j),0}(A(j)\mid\bar{L}(j),\bar{A}(j-1))}.\end{aligned}$$

The following is now an unbiased estimating function for β_{HM}:

$$D^{HM}_{IPCW}(g_0,\beta_{HM}) = \sum_{r\in\mathcal{R}}\mathcal{W}(C(r+m-1),A_1(r+m-1),m_{HM},g_0)(Y(r+m)-\lambda_{HM,\beta}).$$

Given an estimator g_n of g_0, an estimate β_n is then defined as the solution of $0=\sum_{i=1}^n D_{IPCW}(g_n,\beta_n)(O_i)$. These estimators can be implemented with weighted logistic regression software. For example, β_{SM} can be implemented by fitting a pooled weighted logistic regression of the observed outcomes $Y(t)$ on the observed modification times implied by $\bar{A}_2(t-1)$ among subjects that remain alive and uncensored and who have not interrupted therapy by time $t-1$, with weights corresponding to the inverse of the product of $g_{A(j),0}$ taken up to time $t-1$. Consistency of the IPCW estimators relies on consistency of the estimator g_n.

24.5.3 TMLE

In the interest of space, we focus on estimation of $\beta_{SM}=\Psi_{SM}(Q_0)$, with brief comments regarding estimation of β_{DM} and β_{HM}. The MLE of the parameter β_{SM} is implemented based on an initial estimator of the conditional distributions of binary nonintervention variables, where this estimator, Q^0_n, was represented as a series of logistic regression fits. The TMLE of β_{SM} involves adding a clever covariate to

each of these logistic regression fits, using the current logistic regression fit as an offset, and fitting the coefficients ϵ in front of the clever covariate with parametric logistic regression (van der Laan 2010a,b). This TMLE corresponds with using the log-likelihood loss function $L(P) = -\log P$ and using these parametric logistic regression working models with parameter ϵ as the parametric submodel through the initial estimator that encodes the fluctuations of an initial estimator.

The clever covariate for the conditional distribution $Q_B(B \mid Pa(B))$ of a binary indicator B given its parents $Pa(B)$ (the variables on the right-hand side of the corresponding structural equation) is a function $H_B(Q_n^0, g_n)$ of the same dimension as the target parameter, and it can be evaluated for each observation O_i as a function of the parent set $Pa_i(B)$ for that observation. Specifically,

$$H_B(Q_n^0, g_n) = E_{Q_n^0, g_n}(D_{IPCW}^{SM}(g_n, \beta_n^0) \mid B = 1, Pa(B)) \\ -E_{Q_n^0, g_n}(D_{IPCW}^{SM}(g_n, \beta_n^0) \mid B = 0, Pa(B)),$$

where $D_{IPCW}^{SM}(g_n, \beta_n^0)$ is the inverse probability of treatment and censoring-weighted estimating function for the target parameter as presented above (formally, any gradient of the pathwise derivative of the target parameter can be selected). The resulting update of Q_n^0 is denoted by Q_n^1, and this process is iterated until convergence to Q_n^*, at which point the coefficients in front of the clever covariate (i.e., the fluctuation parameters ϵ) approximate zero. Current experience shows very fast convergence of this targeted maximum likelihood algorithm, with the majority of bias reduction achieved in the first step.

One can also use a separate ϵ for each factor of the likelihood, and carry out the updates Q_n^k of Q_n^0 sequentially, starting at the last factor of Q, each time using the clever covariate evaluated at the most recent update Q_n^k, and proceeding till the update of the first factor. The latter closed-form TMLE has been presented in van der Laan (2010a,b).

The TMLE for β_{SM} is defined as the substitution estimator $\Psi_{SM}(Q_n^*)$. Consistency of the TMLE relies on consistent estimation of Q_0 or consistent estimation of g_0 (as well as use of an estimator g_n that converges to a distribution that satisfies the positivity assumption). Efficiency of the TMLE requires the consistency of both estimators.

The TMLE for the target parameter $\beta_{DM} = \Psi_{DM}(Q_0)$ is implemented in the same fashion, with Q_n^* used to implement the substitution estimator $\Psi_{DM}(Q_n^*)$. A similar approach can be used for a history-adjusted target parameter that is defined by specifying a separate working model for each time point r. In this special case of history-adjusted parameters, the TMLE can be implemented using sequential applications of the TMLE standard marginal structural model algorithm to estimate the parameters of each r-specific working model, treating covariates up till time r (including $\bar{A}(r-1)$) as baseline nonintervention covariates. When the history-adjusted target parameter is defined by pooling over time points r, as with β_{HM}, the TMLE involves additional updates of g_n; however, details are beyond the scope of this chapter.

24.5.4 IPCW Reduced-Data TMLE

Implementation of the TMLE in Sect. 24.5.3 requires fitting all conditional distributions of the Q_0-factor of the likelihood and carrying out the TMLE update for each. The need to update the fit for each conditional distribution prior to simulating from Q_n^* can make the TMLE procedure quite computer intensive. Further, the initial estimation step requires estimation of a very high-dimensional Q_0-factor. Due to the curse of dimensionality, Q_n^0 may be a highly biased estimator of Q_0, resulting in a TMLE that is inefficient and relies heavily on the consistency of g_n for its consistency. We provide an overview of the IPCW reduced-data TMLE (IPCW-R-TMLE) as one response to these challenges (van der Laan 2008b). In order to simplify the discussion, we again focus on the target parameter β_{SM}, noting that a parallel approach could be used to estimate and β_{DM} while estimation of β_{HM} would require additional steps.

We motivate development of the estimator by considering a scenario in which the same SCM holds, but in which the observed data available to the analyst have been reduced such that the only time-varying covariates observed are the intervention variables (interruption, modification, and censoring), the outcome, and CD4+ T cell count. We denote the reduced covariate set by $L^r(t) \equiv \text{CD4}(t)$ and the corresponding reduced observed data $O^r \equiv \left(\bar{Y}, \bar{L}^r, \bar{A}\right)$. Parallel to the notation introduced for P_0, we use $P_0^r = Q_0^r g_0^r$ to denote the distribution of O^r, where $Q_{0L^r(t)}^r$, $Q_{0Y(t)}^r$ and $g_{0A(t)}^r$ are defined by replacing $L(t)$ with $L^r(t)$ in the conditional distributions (24.13), (24.14), and (24.15), and where $Q_0^r \equiv Q_{0\bar{L}^r(\tilde{T})}^r \times Q_{0\bar{Y}(\tilde{T})}^r$.

Identifiability of the target causal parameter based on this new reduced-data structure requires stronger assumptions; each conditional independence statement of (24.11) needs to hold conditional on $\bar{L}^r(t)$ rather than $\bar{L}(t)$. This stronger identifiability assumption would impose additional restrictions on the allowed distributions of the error terms P_U and thus imply a working SCM different from that defined in (24.4). We develop a TMLE for this reduced observed data structure, then consider how this reduced-data TMLE can be modified such that it remains a consistent estimator of the target causal parameter β_{SM} under the original SCM working model implied by the weaker identifiability assumption (24.11) (given consistency of g_n or Q_n^0 and convergence of g_n to an appropriate distribution).

Under the reduced-data identifiability assumption, the target causal parameter β_{SM} can be represented as a function of the distribution of the reduced observed data distribution $\Psi_{SM}^r(Q_0^r)$, where Q_0^r is much lower dimensional than Q_0. We can estimate this target parameter with TMLE as described in Sect. 24.5.3, now applied to the reduced-data structure O^r. Briefly, Q_0^r and g_0^r can be factorized into a series of conditional distributions of binary variables, and maximum likelihood methods, potentially combined with data-adaptive approaches, can be applied to provide an initial estimator Q_n^{r0} and an estimator g_n^r. Updating Q_n^{r0} until convergence provides an estimate Q_n^{r*} of Q_0^r.

The problem is that the stronger identifiability assumption with respect to the reduced-data structure O^r might not hold, and as a result the substitution estima-

tor $\Psi^r_{SM}(Q^{r*}_n)$ may be an inconsistent estimator of $\beta_{SM} = \Psi_{SM}(Q_0)$, even when $\Psi^r_{SM}(Q^{r*}_n)$ is a consistent (and efficient) estimator of $\Psi_{SM}(Q^r_0)$. That is, conditioning on time-varying covariates in addition to CD4 count may be required for the counterfactual outcome to be independent of censoring, treatment modifications, and interruptions and thus for the causal parameter to be identified as a parameter of the distribution of the observed data. The reduced-data TMLE can be modified to adjust for any such residual confounding by observed time-varying covariates other than CD4 count by using an estimator g_n of the true g_0 (the conditional distribution of the intervention variables in the nonreduced observed data), and applying inverse weights g^r_n/g_n to each of the estimation steps in the reduced-data TMLE procedure.

Specifically, for maximum-likelihood-based estimation of a conditional distribution $Q_B(B \mid Pa(B))$, where $Pa(B)$ only depends on $\bar{A}$ through $\bar{A}(t)$, we use weights $g^r_{n\bar{A}(t)}/g_{n\bar{A}(t)}$ to obtain an IPCW-R-ML-based initial estimator Q^{r0}_n of Q^r_0, and an IPCW-R-ML estimator of the fluctuation parameter ϵ in the TMLE step. The resulting IPCW-R-TMLE $\Psi_{SM}(Q^{r*}_n)$ is now a consistent estimator of $\Psi_{SM}(Q_0)$ if the true treatment and censoring mechanism g_0 is estimated consistently, and, in the case where g^r_n/g_n converges to 1, then this estimator is double robust with respect to misspecification of estimators of Q^r_0 and $g^r_0 = g_0$. For further details we refer the interested reader to Appendix A and van der Laan (2008b).

24.6 Discussion

An additional issue complicates the link between an SCM and the observed data. Ideally, the exact date at which censoring occurred would be known. For example, a subject transferring care to an alternative clinic would report the date of the transfer. In practice, however, censoring time C must often be approximated using an operational definition. Any algorithm used to define C should be based on past covariates in order to respect the temporal ordering in the underlying causal model. A common approach is to define censoring time based on a minimum duration during which no counting process for a subject has jumped. In order to maintain the link between the observed data and the underlying SCM, any data that do become available on a subject subsequent to C should not be used. Even when this approach is employed, however, the link between the observed data and the SCM will remain imperfect. For some subjects a period will exist during which a subject's follow-up status is incorrectly classified (e.g., a subject already died before our definition of censoring, but we do not know), resulting in time-updated observed covariates and outcomes that fail to reflect the true underlying processes.

In summary, SCMs are a useful tool for translating background knowledge and scientific questions into statistical models and target parameters, and for informing the interpretation of resulting parameter estimates by providing transparency regarding the assumptions needed in order for these estimates to approximate causal effects. As our discussion makes clear, however, the steps of specifying an SCM and its link to the observed data, defining a target causal parameter that adequately

addresses the scientific question of interest, and implementing estimators of this parameter can each increase dramatically in complexity when applied to real clinical cohort data. We have raised several examples of possible complications as illustrations, but many more remain. Issues not addressed include the fact that the subjects in a clinical cohort are rarely a random sample from a well-defined population, and that many covariates will have substantial measurement error and/or potentially informative reporting processes. Acknowledgement of these challenges is not intended as a disincentive to using observational data to target causal questions, but rather as encouragement to approach such analyses systematically, to use a road map that clearly delineates between true causal knowledge and working models, and to remain humble in the interpretation of resulting estimates.