In this chapter, TMLE is illustrated with a data analysis from a longitudinal observational study to investigate “when to start” antiretroviral therapy to reduce the incidence of AIDS-defining cancer (ADC), defined as Kaposi sarcoma, non-Hodgkin’s lymphoma, or invasive cervical cancer, in a population of HIV-infected patients. A key clinical question regarding the management of HIV/AIDS is when to start combination antiretroviral therapy (ART), defined in the Department of Health and Human Services (2004) guidelines as a regimen containing three or more individual antiretroviral medications. CD4+ T-cell count levels have been the primary marker used to determine treatment eligibility, although other factors have also been considered, such as HIV RNA levels, history of an AIDS-defining illness (Centers for Disease Control and Prevention 1992), and ability of the patient to adhere to therapy. The primary outcomes considered in ART treatment guidelines described above have always been reductions in HIV-related morbidity and mortality. Until recently, however, guidelines have not considered the effect of CD4 thresholds on the risk of specific comorbidities, such as ADC. In this analysis, we therefore evaluate how different CD4-based ART initiation strategies influence the burden of ADC. We are analyzing ADC here since it is well established that these malignancies are closely linked to immunodeficiency.

We compare the effectiveness in delaying onset of ADC of two clinical guidelines regarding when to start ART. Specifically, the following research question is addressed: Should ART be initiated when a patient’s CD4 count drops below 350 cells/μl (current guideline) or should ART initiation be instead delayed until his/her CD4 count drops below 200 cells/μl (official guideline for years 2001–2007)? The target population where this effect is of interest is composed of all patients who are HIV-infected, aged 18 years or older, ART-naive, never diagnosed with ADC and engaged in medical care as demonstrated by receipt of a CD4 test.
Addressing this research question involves the estimation of the effect of two personalized ART intervention rules (each based on the patients’ CD4 count profile over time) on the distribution of the resulting failure times defined as the patients’ times to cancer onset. A dynamic marginal structural model (dMSM) provides an adequate causal model for such an effect since dMSMs are models for the distribution of rule-specific counterfactual outcomes. More precisely, each of the two decision rules of interest for when to start ART are indexed by a CD4 count threshold denoted by $\theta$ (equal to 200 or 350) and can be described as follows: “Only initiate ART once the patient’s CD4 count drops below $\theta$ and continue treatment with ART without interruption thereafter.”

### 26.1 Longitudinal Data Structure

This analysis was conducted within Kaiser Permanente of Northern California (KPNC), a large integrated health care delivery system that provides comprehensive medical services to approx. 3.2 million members in a 14-county region in northern California, representing 30% of the surrounding population (N. Gordon, pers. comm.). KPNC maintains complete databases on hospitalizations, outpatient visits, laboratory tests, and prescriptions. Numerous disease registries are maintained at the KPNC Division of Research, including HIV and cancer. For additional details on KPNC’s registries and members we refer readers to Selby et al. (2005) and our accompanying technical report: Neugebauer et al. (2010).

KPNC’s databases were used to retrospectively identify a cohort of adult HIV-infected patients within KPNC followed between 1996 and 2007 who met the following eligibility criteria: HIV-infected, at least 18 years old, KPNC member during years 1996–2007, never previously treated with antiretrovirals, at least one CD4 count measurement available in the previous year, and never previously diagnosed with an ADC. Based on these eligibility criteria, a total of 6,250 HIV-infected patients were identified. The start of follow-up for patients was the first date at which they met all of the eligibility criteria defined above. Patients were then followed until they achieved the outcome of interest, i.e., incident ADC, or until right censored due to occurrence of a competing event: death, discontinuation of KPNC health insurance, or administrative censoring at the end of the study on December 31, 2007. Small gaps in KPNC health insurance of less than 3 months were ignored, which more likely represented administrative glitches as opposed to lack of health plan coverage. In addition, ART discontinuation lasting less than 6 months was also ignored.

The data for this analysis are viewed as realizations of 6250 i.i.d. copies of the following random longitudinal data structure:

$$O = (\tilde{T}, A, L(0), A(0), L(1), A(1), \ldots, L(t), A(t), \ldots, L(\tilde{T}), A(\tilde{T}), L(\tilde{T} + 1)),$$