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Observational Study and Individualized Antiretroviral Therapy Initiation Rules for Reducing Cancer Incidence in HIV-Infected Patients

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Abstract

Targeted Maximum Likelihood Learning (TMLL) has been proposed as a general estimation methodology that can, in particular, be applied to draw causal inferences based on marginal structural modeling with observational data using either a point treatment approach (all confounders are assumed not to be affected by the exposure(s) of interest) or a longitudinal data approach (some confounders may be affected by one of the exposures of interest). While formal development of TMLL has included road maps for applications in longitudinal data approaches, real-life implementations have been restricted to studies based on a point treatment approach. In this article, we illustrate the application of TMLL using a longitudinal approach to investigate the comparative effectiveness in delaying onset of AIDS-defining cancers of two clinical guidelines regarding "when to start" combination antiretroviral therapy based on a patient's evolving CD4 count level. The analysis is based on observational data from the Kaiser Permanente electronic medical record to fit a non-parametric dynamic marginal structural model with the so-called inverse probability of action weighted-reduced data-targeted minimum loss-based estimator (IPAW-R-TMLE). The estimator is developed using formal results from previous, theoretical articles on TMLL before providing details on its implementation for this analysis.

1 Introduction

In this article, targeted maximum likelihood learning (van der Laan and Rubin (2006)) is illustrated with a data analysis from a longitudinal observational study to investigate the question of "when to start" antiretroviral therapy to reduce the incidence of AIDS-defining cancer in a population of HIV-infected patients.

1.1 Combination antiretroviral therapy initiation

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 (DHHS) guidelines (DHHS (2010)) as a regimen containing three or more individual antiretroviral medications. Since the introduction of protease inhibitors in 1996, marking the beginning of the combination ART era, DHHS guidelines for the initiation of ART have undergone several revisions. 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 (CDC (1992)), and ability of the patient to adhere to therapy. Early in the ART era (i.e. prior to 2001) guidelines supported the notion of hit early, hit hard whereby all patients with AIDS or AIDS-free patients with CD4<500 cells/μl initiate ART. In 2001, however, guidelines strongly supported ART initiation only for patients with AIDS or AIDS-free patients with CD4<200 cells/μl, and indicated there was conflicting or lack of data to support initiation at higher CD4 levels. In 2007, guidelines began to see a shift back to the concept of hit early, hit hard with a strong recommendation for treatment initiation for AIDS-free patients with CD4<350. Current DHHS guidelines published in 2009 (DHHS (2010)) strongly support initiating ART for patients with CD4+ T-cell counts below 350 cells/μl based on clinical trial data. The guidelines also indicate a moderate to strong recommendation for initiating ART for patients with CD4+ T-cell counts between 350 to 500 cells/μl, based on data from observational studies. Finally, current guidelines provide some support for initiating therapy with CD4>500 cells/μl, although the guidelines indicated evidence for such early treatment is sparse.

1.2 HIV, immunodeficiency and cancer incidence

The primary outcome 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 cancer.

Since 1996, individuals with HIV infection in developed countries have seen a precipitous decline in mortality and a decreased incidence for AIDS-defining cancers (ADC), specifically Kaposi sarcoma (KS) and Non-Hodgkins lymphoma (NHL), as well as opportunistic infections. However, with increasing age in this population, there has been a rise in other chronic conditions associated with aging, including non-AIDS-defining cancers (NADC) such as lung and anal cancers, which are now more common than ADC (Crum-Cianflone et al. (2009), Engels et al. (2008), Silverberg et al. (2007)). Both ADC, and several NADC, particularly those with a known infectious cause, continue to pose a higher risk for HIV-infected persons than for the general population (Silverberg et al. (2009), Engels et al. (2008), Patel et al. (2008)). This increased risk in part may be due to higher prevalence of cancer risk factors in this group such as smoking (Clifford et al. (2005), Hessol et al. (2004), Phelps et al. (2001)), alcohol use (Hessol et al. (2004), Murillas et al. (2005)), and oncogenic virus coinfection, such as human papillomavirus (HPV) or hepatitis B and C (Evans and Kaslow (2006), Martin et al. (1998), Palefsky et al. (1999), Vallet-Pichard and Pol (2004)).

At the same time, HIV infection and associated immune deficiency may also contribute to the higher risk. It is possible, for example, that the impaired immune system may result in the general reduced immune surveillance for malignant cells (Burnet (1970)). Alternatively, an impaired ability of the immune system to suppress oncogenic viruses may also result in a higher risk of these cancers (Palefsky et al. (1999), Rauch et al. (2008)). This mechanism is further supported by a large meta-analysis by Grulich et al. (2007) who compared cancers elevated in persons with HIV infection and organ transplant recipients. These two very different populations have few shared risk factors for cancer except both populations have suppressed immune systems (Grulich et al. (2007), Serraino et al. (2007)). Most of the cancers seen with increased frequency in both populations compared

to general population rates had a known infectious cause including ADC, as well as several infection-related NADC. Others have demonstrated a higher risk of Hodgkins disease (Engels et al. (2008), Clifford et al. (2005), Frisch et al. (2001), Goedert et al. (1998), Grulich et al. (1999), Bedimo (2008)), oral/pharynx (Engels et al. (2008), Frisch et al. (2001)), anal (Bedimo (2008), Piketty et al. (2008)), liver (Serraino et al. (2007)) and penile (Frisch et al. (2001)) cancers with advanced immunosuppression measured mainly by closer proximity to an AIDS diagnosis (Engels et al. (2008), Frisch et al. (2001), Goedert et al. (1998), Grulich et al. (1999)) or low CD4+ T-cell counts (Patel et al. (2008), Clifford et al. (2005), Bedimo (2008), Piketty et al. (2008)). One study did indicate a higher risk of Hodgkins disease with less immunosuppression (Biggar et al. (2006)).

As described, there have been no studies that have directly evaluated whether earlier treatment in fact reduces the burden of cancer or other specific comorbidities. In this analysis, we therefore evaluate how two different CD4-based ART initiation strategies influence the burden of ADC.

1.3 The Kaiser Permanente electronic medical record

This analysis was conducted within Kaiser Permanente of Northern California (KPNC), a large integrated health care delivery system that provides comprehensive medical services to approximately 3.2 million members in a 14-county region in Northern California, representing 30% of the surrounding population (N. Gordon, personal communication). Based on comparison to 2000 U.S. Census data, KPNC members are similar to the general population with respect to age and race/ethnicity, but have slightly higher income and education levels (N. Gordon, personal communication). These data are consistent with earlier work that found the KPNC members to be similar to the underlying geographic population, but with some underrepresentation of the very poor (Krieger (1992)).

KPNC maintains complete databases on hospitalizations, outpatient visits, laboratory tests and prescriptions. Numerous disease registries are maintained at the KPNC Division of Research (DOR), including HIV and cancer, which have been used to conduct rigorous and cost-efficient research. Linkage across these databases is possible since members are assigned a unique lifetime medical record number. The source data are generated as part of routine clinical care, and therefore continuously collected based on the interaction of each patient with KPNC (i.e., no set visit schedule).

1.3.1 KPNC HIV Registry

The KPNC HIV Registry, developed initially in 1989, includes all known cases of HIV infection dating back to the early 1980s (>19,000 cumulative KPNC members). However, this analysis was limited to patients followed after 1996 corresponding to availability of combination ART. Health plan members are initially identified as possibly HIV-infected if they are found to have one or more of the following indicators identified from electronic databases: 1) positive HIV antibody test; 2) detectable HIV viral load; 3) CD4/CD8 ratio < 1.0; 4) prescription for any antiretroviral drug; 5) outpatient documentation of HIV infection; 6) HIV/AIDS discharge diagnosis; 7) pathology report for Kaposis sarcoma or Pneumocystis carinii pneumonia; and 8) CDC AIDS case report forms, infection control nurse notes, and internal physician reporting. Next, medical chart confirmation of potential cases is performed. The case ascertainment methodology is estimated to have >95% sensitivity and >99% specificity based on comparisons of the registry and clinician HIV case lists. Data elements maintained in the HIV registries include gender, race/ethnicity, HIV risk group, dates of known HIV and AIDS diagnoses and dates of death.

1.3.2 KPNC Cancer Registry

The KPNC cancer registry is a contributing site to the Surveillance, Epidemiology, and End Results (SEER) program registry. All medical facilities in California are required by law to report all newly diagnosed cases of cancer to the California Cancer Registry (CCR), through a network of 10 regional registries that together capture the cancer incidence experience of the entire state. All registries follow SEER practices in verifying and coding incident cancers. Therefore, the KPNC-maintained cancer registry is of comparable accuracy and completeness to that of SEER. SEER requirements include categorization of histopathology, invasiveness, tumor

size, extension, and lymph node involvement. The cancer registry maintained at DOR contains data on all members since 1988 and from selected medical centers since 1947.

1.3.3 Pharmacy Database

Comprehensive electronic outpatient pharmacy prescription data have been available since 1994. Over 95% of members have a drug benefit with minimal co-pay and fill their prescriptions at KPNC pharmacies located at each facility. Members without a drug benefit typically purchase their prescriptions at these same pharmacies because of convenience and often discounted cost. For HIV patients, pharmacy data are even more complete since KPNC pharmacies are approved AIDS Drug Assistance Program facilities that provide free HIV prescription drugs to qualifying HIV patients with no or limited prescription drug benefit. Prescription data available include brand/generic name, dose, formulation, drug class, # pills dispensed, and date and time filled. For HIV patients, the source pharmacy data is mapped to a monthly file with a flag for each and every antiretroviral medication a patient received during that month. Receipt of combination ART was guided by DHHS guidelines and defined as a regimen containing three or more antiretrovirals (DHHS (2010)).

1.3.4 Laboratory Tests

A region-wide laboratory database has been in place in KPNC since 1994. Typically, all laboratory tests (inpatient and outpatient) performed on KPNC members are captured in this database including specialized tests that are sent out to reference labs. CD4+ cell count test results have been captured electronically since 1989. Routine quality assurance checks are performed to comply with state and national standards.

1.3.5 Outpatient & Hospital-Based Care databases

Outpatient databases include all physician diagnoses associated with outpatient encounters at KPNC facilities since 1995. Hospital discharge diagnoses (ICD-9) and procedure codes (ICD-9 and CPT) have been available since 1984. Data regarding care at non-KPNC facilities are included in a billing claims database.

1.3.6 Administrative/Death

Date of birth, gender, membership dates and vital status are available on all members. Race/ethnicity is available in hospitalization databases and on all members included in the HIV registry (by medical chart review). Deaths are identified from hospitalization, health plan, death certificates, and Social Security Administration data sets.

1.4 A longitudinal observational study

1.4.1 Study population

The described databases were used to retrospectively identify a cohort of adult HIV-infected patients within KPNC followed between 1996-2007 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 is available in the previous year
- never previously diagnosed with an AIDS-defining cancer

Based on these eligibility criteria, a total of 6,250 HIV-infected patients were identified.

1.4.2 Follow-up

The start of follow-up for patients was the 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 three months were ignored which more likely represented administrative glitches as opposed to lack of health plan coverage. In addition, ART discontinuation lasting less than six months were also ignored.

1.5 Illustration of targeted maximum likelihood learning

1.5.1 Research question

The aim of this analysis is to 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 for whom this effect is of interest is composed of all patients who are HIV-infected, aged 18-years or older, ART-naive, never-diagnosed with AIDS-defining cancer and engaged in medical care as demonstrated by a receipt of a CD4 testing.

1.5.2 Dynamic marginal structural model

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 representation of such an effect since dMSMs are models for the distribution of rule-specific counterfactual outcomes (Murphy et al. (2001); van der Laan (2006); Orellana et al. (2006)). Specifically in this analysis, a dMSM is used to represent the distributions of counterfactual failure times had patients been treated according to a given treatment guideline which dynamically maps each patient's evolving CD4 count to the decisions to treat or not with ART over time (Hernan et al. (2006)). More precisely, each of the two decision rules of interest are indexed by a CD4 count threshold denoted by θ (equal to 200 or 350) and can be described as follows: "Only initiate ART once the patient's CD4 count drops below θ and continue treatment with ART without interruption thereafter."

2 Data structure

The data for this analysis are approached as realizations of n independent and identically distributed (i.i.d.) copies of the following random process:

$$O = (\tilde{T} = \min(T, C), \Delta = I(T \leq C), L(0), A(0), L(1), A(1), \ldots, L(t), A(t), \ldots, L(\tilde{T}), A(\tilde{T}), L(\tilde{T}+1)) \sim P_0.$$

where:

- $n = 6,250$ is the sample size, i.e. the number of patients in the cohort.
- t denotes a discrete time stamp that indexes the consecutive intervals of $\tau = 180$ days following a patient's study entry. Thus, τ denotes the number of days used to discretize the patient's follow-up time that is originally expressed on a finer time scale (days). The interval of days represented by t is denoted by $[t\tau, (t+1)\tau[$. In particular, $t = 0$ represents the first τ days of a patient's follow-up: $[0, \tau[$.
- O denotes the collection of random variables that represent measurements of subject-matter attributes characterizing one patient for the entire duration of follow-up (time-independent variables) or for a period of τ days (time-dependent variables). Each of these random variables is described below. The data set

for this analysis is thus composed of observations on n copies of such random processes that are assumed to be i.i.d..

- P_0 denotes the unknown joint distribution of the collection of random variables that compose the observed data process O.
- $\tilde{T}$ is the follow-up time expressed in units of τ days since study entry and is defined as the minimum between the time to cancer onset, T, and the time to right-censoring, C: $\tilde{T} \equiv \min(T, C)$. The right-censoring time is defined as the minimum between the time to the administrative end of the study (December 31$^{\text{st}}$ 2007) and the minimum time to a competing event (all expressed in units of τ days since study entry). Competing events are dis-enrollment from the Kaiser Permanente health plan and death. Note that the time to cancer onset, T, is the failure time of interest (i.e. outcome) in this analysis. Note also that unlike t for $t = 0, \ldots, \tilde{T} - 1$ which represents a monitoring interval of τ days $[t\tau, (t+1)\tau[$, the follow-up time $t = \tilde{T}$ typically represents a shorter monitoring interval: The actual follow-up time expressed in days typically falls within the interval of τ days: $[\tilde{T}\tau, (\tilde{T}+1)\tau[$.
- Δ is the binary indicator that cancer onset occurs prior to a competing event: $\Delta = 0$ represents right-censoring of the patient's data.
- $A(t)$ is referred to as the action at time t, i.e. the variables at time t on which hypothetical interventions are considered below for the purpose of explicitly defining a causal estimand that represents the causal effects for which statistical inference is of interest to answer the research question. In this analysis, the action at time t is the collection of the treatment and right-censoring status at time t, $A(t) \equiv (A_1(t), A_2(t))$ where:
  - $A_1(t)$ is a binary variable that represents treatment status at time t (a value of 1 indicates treatment with ART). Since time t represents an interval of τ days, $[t\tau, (t+1)\tau[$, the following protocol was devised to map the information available on daily ART status during this interval to the binary representation above: A patient was deemed to initiate ART on the first day of a sequence of at least two consecutive months during which the patient was treated with ART. The values for all treatment variables before ART initiation were set to 0, i.e. the value for each $A_1(t)$ such that t represents an interval of τ days that all precede ART initiation was set to 0. Values for all other treatment variables, $A_1(t)$, were mapped to 1 except for all time points t that include or follow the first day of a sequence of 6 consecutive months when the patient had discontinued ART (discontinuation of ART is defined as being treated with less than three antiretroviral medications). For such time points, treatment with ART was deemed interrupted and the value for $A_1(t)$ was set to 0 for t representing the interval of τ days when first discontinuation of ART was deemed to occur and was set to NA (i.e. considered missing) for all subsequent time points. Note that this missing treatment information could have been recovered but is irrelevant for the estimation of the causal estimand of interest in this analysis (see section 4.3) and was thus left indeterminate.
  - $A_2(t)$ is a binary variable that denotes the indicator of right-censoring at or before time t, i.e. $A_2(t) = I(C \leq t)$. It is entirely defined by both $\tilde{T}$ and Δ:
    - If $\Delta = 0$, $A_2(t) = 0$ for all $t = 0, \ldots, \tilde{T} - 1$ and $A_2(\tilde{T}) = 1$.
    - If $\Delta = 1$, $A_2(t) = 0$ for all $t = 0, \ldots, \tilde{T}$.

  In section 4, we describe interventions on the action process $(A(0), A(1), \ldots)$ which define the causal estimand whose estimation is the goal of this analysis.
- $L(t)$ is referred to as the covariate at time t. It is the collection of time-independent (e.g. age at study entry) and/or time-dependent random variables (e.g. CD4 count) other than the action at time t. Such variables typically represent subject-matter attributes that occur before the action at time t and otherwise are assumed not to be affected by the actions at time t or thereafter, $(A(t), A(t+1), \ldots)$. In particular, $L(0)$ is referred to as the baseline covariate and represents the collection of subject-matter attributes (e.g. age at study entry) which are not affected by any actions $(A(0), A(1), \ldots)$.

In particular, the covariate $L(t)$ contains information on the failure time through the outcome variable $Y(t) = I(T \leq t-1) \in L(t)$ which denotes the indicator of failure at or before time $t-1$ for $t > 0$ and $Y(0) \equiv 0$ by convention since all patients are cancer free at study entry. Note that failure time T is not observed if right-censoring, C, occurs first, i.e. the observation for the outcome variable $Y(\tilde{T}+1)$ is missing if $\Delta = 0$. More specifically, we have:

- If $\Delta = 0$, $Y(t) = 0$ for $t = 0, \ldots, \tilde{T}$ and $Y(\tilde{T}+1)$ is missing (NA).
- If $\Delta = 1$, $Y(t) = 0$ for $t = 0, \ldots, \tilde{T}$ and $Y(\tilde{T}+1) = 1$.

The outcome variable, $Y(\tilde{T}+1)$, is the only covariate relevant at time $\tilde{T}+1$ for this analysis and information on other attributes at that time is thus ignored, i.e. $L(\tilde{T}+1) \equiv Y(\tilde{T}+1)$.

A list and brief descriptions of the subject-matter attributes considered in this analysis are provided in Table 1. Except for the attribute 'ART', measurements of all other attributes in this table are represented by covariates in $L(t)$. Note that all such covariates are discrete since all attributes were measured on a discrete scale or, for clarity in the description of the approach, they were discretized from measurements obtained on a continuous scale.

The number of time-independent and time-dependent attributes are denoted by $p = 15$ and $q = 4$. The covariates in $L(t)$ that represent time-independent attributes are denoted by $L_j(t)$ for $j = 1, \ldots, p$ such that j represents an arbitrary order of the time-independent attributes in Table 1. The covariates in $L(t)$ that represent time-dependent attributes are denoted by $L_j(t)$ for $j = p+1, \ldots, p+q$ such that j represents an order of the time-dependent attributes in Table 1 where $L_{p+1}(t)$ and $L_{p+2}(t)$ represent the indicator of past failure (i.e. $L_{p+1}(t) \equiv Y(t)$) and the CD4 count variable respectively. We thus have:

$$(L_j(0))_{j=1,\ldots,p+q} \subset L(0),$$

where $L_j(0)$ for $j = 1, \ldots, p$ represent the time-independent covariates collected at baseline and $L_j(0)$ for $j = p+1, \ldots, p+q$ represent the time-dependent covariates collected at baseline. Similarly, we have

$$(L_j(t))_{j=p+1,\ldots,p+q} \subset L(t) \text{ for } t = 1, \ldots, \tilde{T},$$

where $L_j(t)$ for $j = p+1, \ldots, p+q$ represent the time-dependent covariates collected at time t. Finally, we have:

$$L(\tilde{T}+1) = L_{p+1}(\tilde{T}+1) = Y(\tilde{T}+1).$$

Table 2 summarizes the link between the measurements of the subject-matter attributes in Table 1 and the notation adopted above to represent these data with the covariates in $L(t)$ for $t = 0, \ldots, \tilde{T}+1$. Note that each measurement of these subject-matter attributes at any given time point t were derived from daily measurements of these attributes during follow-up for each patient. The following protocol was devised to map the initial data available on a fine time scale (measured in units of one day) to the data representation adopted in this analysis based on a coarsened time scale (measured in units of τ days).

To respect the so-called time-ordering assumption which imposes that covariates $L(t)$ be not affected by actions at time t and thereafter, $(A(t), A(t-1), \ldots)$, the daily data on time-dependent attributes during follow-up were mapped to an observation of $L_j(t)$ for $j \in \{p+1, \ldots, p+q\}$ as follows:

- For all time points t representing intervals $[t\tau, (t+1)\tau[$ that do not contain the day when ART is deemed to be initiated, $L_j(t)$ represents the last measurement for attribute j available 1) at time $t-1$ (i.e. the last measurement obtained during interval $[(t-1)\tau, t\tau[$) if $t > 0$ and 2) within the year preceding study entry if $t = 0$.
- For the time point t representing the interval $[t\tau, (t+1)\tau[$ that contains the day when ART is deemed to be initiated, $L_j(t)$ represents the last measurement for attribute j available 1) at time $t-1$ or time t but always prior to the actual day when ART was initiated if $t > 0$ and 2) within the year preceding study entry or at time point 0 but always prior to the actual day when ART was initiated if $t = 0$.

Once this mapping was implemented, observations for $p^{'} = 5$ time-independent attributes ('race', 'censusEdu', 'censusPov', 'censusInc', and 'riskHIV') were left missing. Similarly, observations for $q^{'} = 2$ time-dependent attributes ('CD4' and 'VL') were left missing. Such observations were imputed and indicators of imputation (named 'I.censusEdu', 'I.censusPov', 'I.censusInc', 'I.race', 'I.riskHIV', 'I.CD4', and 'I.VL' respectively) were created. Each of these indicators are denoted by $L_j(t)$ such that $L_j(t)$ for $j = p+q+1, \ldots, p+q+q^{'}$ represent the indicators of imputation for the time-dependent attributes ordered arbitrarily ('CD4' and 'VL') and $L_j(t)$ for $j = p+q+q^{'}+1, \ldots, p+q+q^{'}+p^{'}$ represent the indicators of imputation for the time-independent attributes ordered arbitrarily ('race', 'censusEdu', 'censusPov', 'censusInc', and 'riskHIV'). These covariates are included in the definition of $L(t)$ and the covariate process is thus defined as

$$L(0) \equiv (L_j(0))_{j=1,\ldots,p+q+q'+p'},\ L(t) \equiv (L_j(t))_{j=p+1,\ldots,p+q+q'} \text{ for } t = 1, \ldots, \tilde{T} \text{ and } L(\tilde{T}+1) = L_{p+1}(\tilde{T}+1).$$

Table 2 summarizes the mapping between the notation adopted above for all covariates in $L(t)$ and the measurements of the subject-matter attributes these covariates represent.

The following imputation method was used for missing observations of the time-independent ('race' and 'riskHIV') and time-dependent ('censusEdu', 'censusPov', 'censusInc', 'CD4', and 'VL') covariates at $t = 0$:

- If the underlying subject-matter attribute was measured on a discrete scale, the missing observations for the covariate were imputed with the mode of all non-missing observations of the covariate at $t = 0$.
- If the underlying subject-matter attribute was measured on a continuous scale, the missing observations for the covariate were imputed with the average of all non-missing observations of this attribute at time $t = 0$ before being recoded on the discrete scale (see Table 1).

In addition, for the covariates 'race' and 'riskHIV', the imputation above was implemented conditional on the covariate 'sex'.

The following forward imputation method was used for missing observations of time-dependent covariates at any time $t > 0$: The missing observation for $L_j(t)$ was imputed with the last non-missing and non-imputed observation of the covariates $(L_j(0), \ldots, L_j(t-1))$ if available and otherwise with the imputed observation for $L_j(0)$.

For conciseness, we adopt the following shorthand notation to represent the history of measurements on a given subject-matter attribute between time point 0 and t: $\bar{\cdot}(t) \equiv (\cdot(0), \ldots, \cdot(t))$ and by convention $\bar{\cdot}(t)$ is nil for $t < 0$. Using this notation, the observed data for one patient can be summarized as follows:

$$O = (\tilde{T} = \min(T, C), \Delta = I(T \leq C), \bar{L}(\tilde{T}+1), \bar{A}(\tilde{T})).$$

Tables 3 through 13 and Fig. 1 provide summaries of the distributions of the random variables that compose this longitudinal process O.

Table 1: Subject-matter attributes whose measurements for each patient are represented by the covariates, $L(t)$, and actions, $A(t)$, of the observed data process O.

Name	Description	Time-dependent	Coding
sex	Sex		0='male', 1='female'
race	Race/ethnicity		Other, White, Black, Hispanic
censusEdu	Percentage of persons aged 25 years or above with less than a 12th grade education in the patient's census block		1='[0; 6.8]', 2=']6.8; 13.6]', 3=']13.7; 25.2]', 4=']25.2; 100]'
censusPov	Percentage of persons below the federal poverty level in the patient's census block		1='[0; 5.5]', 2=']5.5; 9.9]', 3=']9.9; 17.5]', 4=']17.5; 100]'
censusInc	Median household income in the patient's census block		1='[0; 37,720]', 2=']37,720; 51,880]', 3=']51,880; 68,210]', 4='>68,210'
riskHIV	Primary risk factor for HIV infection		IDU='Intravenous drug user', OTH='Other risk factors', HET='Heterosexual', MSM='Men who have sex with men'
enrollYear	Year of enrollment in the study		1='1996', 2='1997', 3='1998',..., 12='2007'
yearsHIV	Number of years before study entry with known HIV positive status		1='0', 2=']0,5[', 3='[5,10[', 4='$\geq$ 10'
ageAtEntry	Age at the start of follow-up		1='<40', 2='[40,50[', 3='$\geq$ 50'
everSmoke	Smoking status at the start of follow-up		0='not a smoker', 1='smoker'
everAlcohol	Alcohol abuse status at the start of follow-up		0='no alcohol abuse', 1='alcohol abuse'
everDrug	Drug abuse status at the start of follow-up		0='no drug abuse', 1='drug abuse'
everHepatitisB	Hepatitis B status at the start of follow-up		0='not diagnosed with Hepatitis B', 1='diagnosed with Hepatitis B'
everHepatitisC	Hepatitis C status at the start of follow-up		0='not diagnosed with Hepatitis C', 1='diagnosed with Hepatitis C'
everObese	Overweight or obese status at the start of follow-up		0='not overweight', 1='overweight'
CD4	CD4 count in cells per μl	✓	1='<200', 2='[200; 350[', 3='[350; 500[', 4='$\geq$ 500'
VL	Viral load in copies per ml	✓	1='<500', 2='[500; 10,000[', 3='[10,000; 100,000[', 4='$\geq$100,000'
clinicalAIDS	Indicator of past clinical AIDS-defining events (excluding the CD4<200 criterion) (CDC (1992))	✓	0='no past clinical AIDS', 1='past clinical AIDS'
ART	ART status	✓	0='no ART use', 1='ART use', NA='indeterminate'
Y	Indicator of a past diagnosis of AIDS-defining cancer	✓	0='not diagnosed with AIDS-defining cancer', 1='diagnosed with AIDS-defining cancer', NA='missing due to right-censoring'

Table 2: Mapping of the subject-matter attribute measurements into the covariates, $L(t)$, and actions, $A(t)$, of the observed data process O.

Attribute	Variable representation	Number of levels
sex	$L_1(0)$	2
race	$L_2(0)$	4
censusEdu	$L_3(0)$	4
censusPov	$L_4(0)$	4
censusInc	$L_5(0)$	4
riskHIV	$L_6(0)$	4
enrollYear	$L_7(0)$	12
yearsHIV	$L_8(0)$	4
ageAtEntry	$L_9(0)$	3
everSmoke	$L_{10}(0)$	2
everAlcohol	$L_{11}(0)$	2
everDrug	$L_{12}(0)$	2
everHepatitisB	$L_{13}(0)$	2
everHepatitisC	$L_{14}(0)$	2
everObese	$L_{15}(0)$	2
Y	$L_{16}(t)$ for $t = 0, \ldots, \tilde{T} + 1$	$n(t, 16) \equiv 2$
CD4	$L_{17}(t)$ for $t = 0, \ldots, \tilde{T}$	$n(t, 17) \equiv 4$
VL	$L_{18}(t)$ for $t = 0, \ldots, \tilde{T}$	$n(t, 18) \equiv 4$
clinicalAIDS	$L_{19}(t)$ for $t = 0, \ldots, \tilde{T}$	$n(t, 19) \equiv 2$
I.CD4	$L_{20}(t)$ for $t = 0, \ldots, \tilde{T}$	$n(t, 20) \equiv 2$
I.VL	$L_{21}(t)$ for $t = 0, \ldots, \tilde{T}$	$n(t, 21) \equiv 2$
I.race	$L_{22}(0)$	2
I.censusEdu	$L_{23}(0)$	2
I.censusPov	$L_{24}(0)$	2
I.censusInc	$L_{25}(0)$	2
I.riskHIV	$L_{26}(0)$	2
ART	$A_1(t)$ for $t = 0, \ldots, \tilde{T}$	2

Table 3: Distribution (counts and percentages) of the indicator of observed failure (Δ).

0	1
6073	177
97.2	2.8

Table 4: Distribution (counts and percentages) of the race covariate in $L(0)$. A missing observation for a female patient was imputed with 'Black' and a missing observation for a male patient was imputed with 'White'.

NA	Other	White	Black	Hispanic
433	367	3350	1233	867
6.9	5.9	53.6	19.7	13.9

Table 5: Distribution (counts and percentages) of the riskHIV covariate in $L(0)$. A missing observation for a female patient was imputed with 'HET' and a missing observation for a male patient was imputed with 'MSM'.

NA	HET	IDU	MSM	OTH
826	1002	493	3849	80
13.2	16	7.9	61.6	1.3

Table 6: Distribution (counts and percentages) of the binary covariates in L(0).

L(0)	0	1
sex	5590	660
	89.4	10.6
everSmoke	3553	2697
	56.8	43.2
everAlcohol	5361	889
	85.8	14.2
everDrug	5227	1023
	83.6	16.4
everHepatitisB	6005	245
	96.1	3.9
everHepatitisC	5752	498
	92	8
everObese	3528	2722
	56.4	43.6
clinicalAIDS	5623	1129
	83.3	16.7

Table 7: Distribution (counts and percentages) of the ordinal covariates in L(0). The missing observations for censusEdu, censusPov, and censusInc were imputed with the values 3, 3, and 3 respectively.

L(0)	NA	1	2	3	4	5	6	7	8	9	10	11	12
censusEdu	13	1575	1548	1567	1547								
	0.2	25.2	24.8	25.1	24.8								
censusPov	13	1580	1560	1545	1552								
	0.2	25.3	25	24.7	24.8								
censusInc	13	1586	1535	1553	1563								
	0.2	25.4	24.6	24.8	25								
enrollYear	0	1795	571	500	453	430	420	371	365	361	359	352	273
	0	28.7	9.1	8	7.2	6.9	6.7	5.9	5.8	5.8	5.7	5.6	4.4
yearsHIV	0	2167	2616	968	499								
	0	34.7	41.9	15.5	8								
ageAtEntry	0	3514	1869	867									
	0	56.2	29.9	13.9									
CD4	0	1902	1303	1301	1744								
	0	30.4	20.8	20.8	27.9								
VL	0	509	944	3627	1170								
	0	8.1	15.1	58	18.7								

Table 8: Distribution (counts and percentages) of the maximum time for which a patient contributes an observation, i.e. the follow-up time ($\tilde{T}$).

0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
836	597	500	469	350	310	273	255	212	188	182	192	145	156	139	119	113	130	112	106	123	112	107	114	410
13.4	9.6	8	7.5	5.6	5	4.4	4.1	3.4	3	2.9	3.1	2.3	2.5	2.2	1.9	1.8	2.1	1.8	1.7	2	1.8	1.7	1.8	6.6

Table 9: Distribution (counts and percentages) of the times to cancer onset (i.e. $T = \tilde{T}$ such that $Y(\tilde{T}+1) = 1$) for the 177 patients that were not right-censored (i.e. Δ=1).

0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
70	24	15	9	1	5	6	4	4	6	6	6	4	4	1	0	1	4	3	0	2	2	0	0	0
39.5	13.6	8.5	5.1	0.6	2.8	3.4	2.3	2.3	3.4	3.4	3.4	2.3	2.3	0.6	0	0.6	2.3	1.7	0	1.1	1.1	0	0	0

Table 10: Distribution (counts and percentages) of the times to right-censoring (i.e. $C = \tilde{T}$ such that $A_2(\tilde{T}) = 1$) for the 6073 patients that were right-censored (i.e. Δ=0).

0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
766	573	485	460	349	305	267	251	208	182	176	186	141	152	138	119	112	126	109	106	121	110	107	114	410
12.6	9.4	8	7.6	5.7	5	4.4	4.1	3.4	3	2.9	3.1	2.3	2.5	2.3	2	1.8	2.1	1.8	1.7	2	1.8	1.8	1.9	6.8

Table 11: Distribution (counts and percentages) of the time to the first use of ART for the patients who experienced ART at least once during follow-up (i.e. $\min(\{t : A_1(t) = 1\})$).

0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
2473	375	272	213	164	109	84	75	68	31	36	32	19	23	15	16	12	8	8	8	5	7	5	9	1
60.8	9.2	6.7	5.2	4	2.7	2.1	1.8	1.7	0.8	0.9	0.8	0.5	0.6	0.4	0.4	0.3	0.2	0.2	0.2	0.1	0.2	0.1	0.2	0

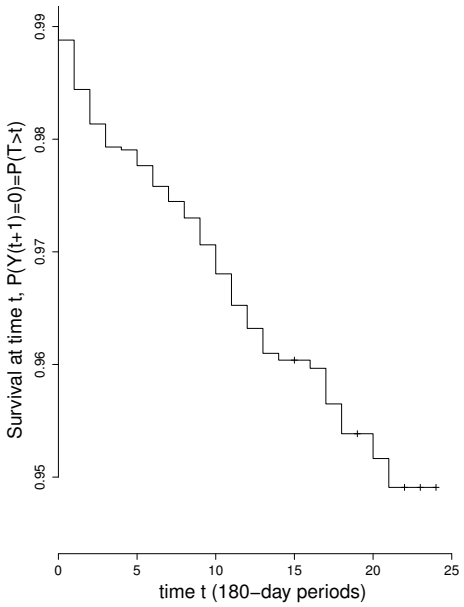

Figure 1: Kaplan-Meier curve associated with time to cancer onset (reminder: t=0 represents the first 180 days of follow-up and $Y(t+1) = I(T \leq t)$).

Table 12: Distribution (counts and percentages) of the indicator variable that the patient experienced ART at least once during follow-up (i.e. $I(\sum_{t=0}^{\tilde{T}} A_1(t) > 0)$).

never experienced ART	experienced ART
2182.0	4068.0
34.9	65.1

Table 13: Distribution (counts and percentages) of the CD4 levels prior ART initiation for the patients who experienced ART at least once during follow-up (i.e. $L_{p+1}(\min(\{t : A_1(t) = 1\}))$).

1	2	3	4
1731	1178	659	500
42.6	29	16.2	12.3

3 Likelihood of the data

Following the time ordering of actions and covariates encoded in the directed acyclic graph implied by Fig. 2 (Pearl (2009)), the likelihood of the observed data can be factorized as

$$P(O) = \prod_{t=0}^{\tilde{T}+\Delta} P(L(t) \mid \bar{L}(t-1), \bar{A}(t-1)) \prod_{t=0}^{\tilde{T}} P(A(t) \mid \bar{A}(t-1), \bar{L}(t)).$$

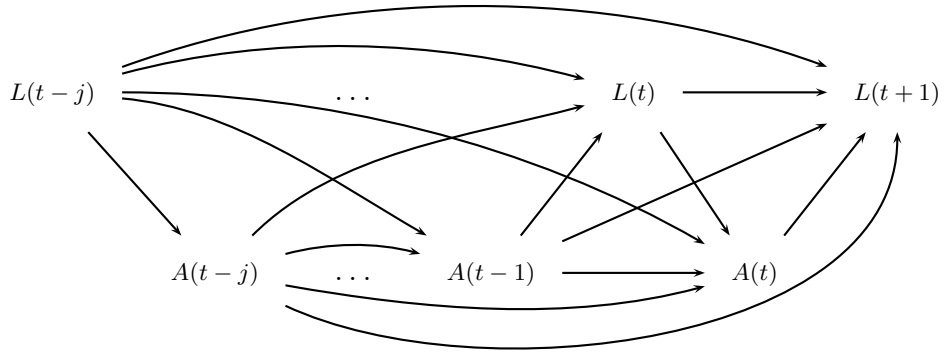

Figure 2: Template of the directed acyclic graph that encodes the time ordering of all variables of the observed data process O. The complete graph can be derived by sequentially drawing the nodes and arcs implied by this template for $t = 0, \ldots, \tilde{T}$ and $j \leq t$.

Note that the the first product of conditional probabilities ends with the conditional probability of $L(\tilde{T})$ given all past actions, $\bar{A}(\tilde{T}-1)$, and past covariates, $\bar{L}(\tilde{T}-1)$, when the patient's data are right-censored, i.e. $\Delta = 0$, since $L(\tilde{T}+1) \equiv Y(\tilde{T}+1)$ is then missing with probability one. Otherwise, the first product ends with the conditional probability of $L(\tilde{T}+1)$ given past actions, $\bar{A}(\tilde{T})$, and past covariates, $\bar{L}(\tilde{T})$ when the patient's cancer onset is observed, i.e. $\Delta = 1$.

The two products of the likelihood above are referred to as the Q part and g part of the likelihood. The Q part of the likelihood is composed of the product of the conditional probabilities of covariates given past covariates and actions whereas the g part of the likelihood is composed of the product of the conditional probabilities of actions given past actions and covariates. The g part of the likelihood is also referred to as the 'action mechanism'. Following this terminology, the notation for the likelihood of the observed data can be summarized as

$$P = \prod_{t=0}^{\tilde{T}+\Delta} Q_{L(t)} \prod_{t=0}^{\tilde{T}} g_{A(t)}, \tag{1}$$

where the factors $P(L(t) \mid \bar{L}(t-1), \bar{A}(t-1))$ are denoted by $Q_{L(t)}$ and the factors $P(A(t) \mid \bar{A}(t-1), \bar{L}(t))$ are denoted by $g_{A(t)}$.

At each time point t, the covariate $L(t)$ is composed of a collection of discrete covariates denoted by $L_j(t)$:

$$L(0) \equiv (L_j(0))_{j=1,\ldots,p+q+q'+p'}$$

$$L(t) \equiv (L_j(t))_{j=p+1,\ldots,p+q+q'} \text{ for } t = 1, \ldots, \tilde{T}$$

$$L(\tilde{T}+1) \equiv L_{p+1}(\tilde{T}+1),$$

where, as described in Table 2, for $p = 15$, $q = 4$, $q^{'} = 2$, and $p^{'} = 5$:

- $j = 1, \ldots, p$ indexes the covariates that represent the time-independent attributes listed in Table 1,
- $j = p+1, \ldots, p+q$ indexes the covariates that represent the time-dependent attributes listed in Table 1 such that $p+1$ represents 'Y' and $p+2$ represents 'CD4',
- $j = p+q+1, \ldots, p+q+q^{'}$ indexes the indicators of imputations for the $q^{'}$ time-dependent attributes that have missing observations,

- $j = p + q + q^{'} + 1, \ldots, p + q + q^{'} + p^{'}$ indexes the indicators of imputations for the $p^{'}$ time-independent attributes that have missing observations.

The factors $Q_{L(t)}$ of the likelihood for $t = 1, \ldots, \tilde{T} + \Delta$ can thus be factorized as

$$Q_{L(t)} = \prod_{j=1}^{n_{\tilde{T}}(t)} Q_{L_{p+j}(t)} \tag{2}$$

where $n_{\tilde{T}}(t) \equiv q + q^{'}$ for $t = 1, \ldots, \tilde{T}$, $n_{\tilde{T}}(\tilde{T}+1) \equiv 1$, and $Q_{L_{p+j}(t)} \equiv P(L_{p+j}(t) \mid Pa(L_{p+j}(t)))$ with $Pa(L_{p+j}(t)) \equiv (\bar{L}(t-1), L_{p+1}(t), \ldots, L_{p+j-1}(t), \bar{A}(t-1))$. Note that the notation above makes implicit use of the convention that $(L_j(t), \ldots, L_{j'}(t))$ for $j^{'} < j$ is nil.

Similarly, at each time point t, the action $A(t)$ is composed of a treatment, $A_1(t)$, and an indicator of right-censoring, $A_2(t)$: The factors $g_{\bar{A}(t)}$ of the likelihood can thus be factorized as

$$g_{A(t)} = g_{A_1(t)} g_{A_2(t)}, \tag{3}$$

where $g_{A_1(t)} \equiv P(A_1(t) \mid \bar{A}(t-1), \bar{L}(t), A_2(t))$ and $g_{A_2(t)} \equiv P(A_2(t) \mid \bar{A}(t-1), \bar{L}(t))$.

Based on equations (2) and (3), the likelihood (1) can be further factorized as

$$P = Q_{L(0)} \prod_{t=1}^{\tilde{T}+\Delta} \prod_{j=1}^{n_{\tilde{T}}(t)} Q_{L_{p+j}(t)} \prod_{t=0}^{\tilde{T}} g_{A_1(t)} g_{A_2(t)}. \tag{4}$$

Since each covariate $L_{p+j}(t)$ for $t = 1, \ldots, \tilde{T} + \Delta$ and $j = 1, \ldots, n_{\tilde{T}}(t)$ is discrete with $n(t, p+j)$ categories (see Table 2), it can be recoded with $n(t, p+j) - 1$ binary variables: $L_{p+j,m}(t) \equiv I(L_{p+j}(t) = m)$ for $m = 1, \ldots, n(t, p+j) - 1$, i.e. $L_{p+j}(t) = (L_{p+j,m}(t))_{m=1,\ldots,n(t,p+j)-1}$. This recoding of the information in $L_{p+j}(t)$ leads to the following factorization

$$Q_{L_{p+j}(t)} = \prod_{m=1}^{n(t,p+j)-1} Q_{L_{p+j,m}(t)}, \tag{5}$$

where $Q_{L_{p+j,m}(t)}$ represents the conditional probability of $L_{p+j,m}(t)$ given $Pa(L_{p+j}(t))$ and $L_{p+j,l}(t)$ for $l = 1, \ldots, m-1$:

$$Q_{L_{p+j,m}(t)} \equiv P(L_{p+j,m}(t) \mid Pa(L_{p+j,m}(t))) \text{ with } Pa(L_{p+j,m}(t)) \equiv (Pa(L_{p+j}(t)), L_{p+j,1}(t), \ldots, L_{p+j,m-1}(t)).$$

Note that this conditional probability is degenerate, i.e. equal to 1 at $L_{p+j,m}(t) = 0$, if one of the indicators $L_{p+j,l}(t)$ in $Pa(L_{p+j,m}(t))$ is 1. Note also that if $L_{p+j}(t)$ is binary ($n(t, p+j) = 2$), then $L_{p+j,1}(t) = L_{p+j}(t)$ and $Q_{L_{p+j,1}(t)} = Q_{L_{p+j}(t)}$. Based on equation (5), the likelihood (4) can be further factorized as

$$P = Q_{L(0)} \prod_{t=1}^{\tilde{T}+\Delta} \prod_{j=1}^{n_{\tilde{T}}(t)} \prod_{m=1}^{n(t,p+j)-1} Q_{L_{p+j,m}(t)} \prod_{t=0}^{\tilde{T}} g_{A_1(t)} g_{A_2(t)}. \tag{6}$$

4 Target parameter as mapping from the distribution of the data

In this section, the causal effect of interest in this analysis is introduced as the effect on a cumulative risk of cancer onset of so called dynamic interventions on ART. Under an identifiability assumption, it is expressed as a function of the likelihood of the observed data. This latter estimand is referred to as the target parameter. First, however, the definition of effects of treatment interventions on a survival outcome is formalized with the counterfactual statistical framework (Neyman (1990); Robins (1986, 1987)) based on static treatment interventions to introduce the concepts and notation on which the more complex definition of effects of dynamic treatment interventions is based.

4.1 Effect definition based on static interventions

A natural approach for defining causal effects relies on a priori specification of interventions on one treatment or a sequence of treatments over time. Such treatment interventions are referred to as static interventions since they may not be modified based on the patients baseline condition nor in response to the patient's changing condition over time (that may have resulted from the earlier sequence of treatment interventions), i.e. the sequence of treatments to be experienced by a patient according to any of these interventions is statically determined by a treatment decision made at baseline only and independent of the patient's baseline condition. Although often implicit, the effects of these treatment interventions on an outcome are formally defined as contrasts between the distributions of potential outcomes (a.k.a. counterfactual outcomes). A potential outcome refers to the outcome following a particular treatment intervention. These effect definitions based on static treatment interventions are illustrated below based on fictitious "ideal experiments" to investigate the effects on cancer onset of static interventions on ART use over one or more time intervals.

The following two-step experiment is conceptualized for each patient in the cohort to investigate the effect of ART use during time interval $t = 0$ on the risk of cancer onset before time interval $t = 1$:

- Implement the following ART intervention denoted by $a_1(0) = 0$: Treatment with ART is withheld from the patient during time interval $t = 0$. The patient's indicator of failure (i.e. cancer onset) before time interval $t = 1$, denoted by $I(T \leq 0)$, is recorded. This potential outcome is denoted by $Y_{a_1(0)=0}(1)$ where the subscript represents the intervention that led to this outcome.

- Next, go back in time to $t = 0$ (so that the experimental conditions at baseline are identical) and proceed with the following ART intervention denoted by $a_1(0) = 1$: Treatment with ART is imposed on the patient. The patient's indicator of failure at time interval $t = 1$, denoted by $I(T \leq 0)$, is recorded. This new potential outcome is now denoted by $Y_{a_1(0)=1}(1)$.

This conceptual experiment is ideal in the sense that it permits the direct estimation of the following contrast between the distributions of the two intervention-specific outcomes described above:

$$P(Y_{a_1(0)=1}(1) = 1) - P(Y_{a_1(0)=0}(1) = 1).$$

By definition of the potential outcomes, this contrast is interpretable causally as representing the average effect of ART use during time interval $t = 0$ on the risk of failure before time interval $t = 1$.

This experiment can be extended to investigate the average effects of ART use during two time intervals $t = 0$ and $t = 1$ on the cumulative risks of failure before both time intervals $t = 1$ and $t = 2$:

- Implement the following ART intervention denoted by $(a_1(0), a_1(1)) = (0, 0)$: Treatment with ART is withheld from the patient during time intervals $t = 0$ and $t = 1$ and the resulting indicators of failure before time intervals $t = 1$ and $t = 2$ are recorded and denoted by $Y_{a_1(0)=0}(1)$ and $Y_{(a_1(0),a_1(1))=(0,0)}(2)$.

- Go back in time to $t = 0$ and proceed with the following ART intervention denoted by $(a_1(0), a_1(1)) = (0, 1)$: Treatment with ART is withheld from the patient during time interval $t = 0$ and then imposed during time interval $t = 1$. The outcome at time interval $t = 1$ corresponds with the outcome $Y_{a_1(0)=0}(1)$ previously recorded. The outcome at time interval $t = 2$, denoted by $Y_{(a_1(0),a_1(1))=(0,1)}(2)$, is recorded.

- Go back in time to $t = 0$ and proceed with the following ART intervention denoted by $(a_1(0), a_1(1)) = (1, 0)$: Treatment with ART is imposed on the patient during time interval $t = 0$ and then withheld during time interval $t = 1$. The outcomes at time intervals $t = 1$ and $t = 2$ are recorded and denoted by $Y_{a_1(0)=1}(1)$ and $Y_{(a_1(0),a_1(1))=(1,0)}(2)$.

- Go back in time to $t = 0$ and proceed with the following ART intervention denoted by $(a_1(0), a_1(1)) = (1, 1)$: Treatment with ART is imposed on the patient during both time intervals $t = 0$ and $t = 1$. The outcome at time interval $t = 1$ corresponds with the outcome $Y_{a_1(0)=1}(1)$ previously recorded. The outcome at time interval $t = 2$, denoted by $Y_{(a_1(0),a_1(1))=(1,1)}(2)$, is recorded.

With the data from the experiment above, the following causal parameters can be directly estimated and represent the average effects of ART use during two time intervals on the cumulative risks of failure before time intervals $t = 1$ and $t = 2$:

$$P(Y_{a_1(0)=1}(1) = 1) - P(Y_{a_1(0)=0}(1) = 1) \tag{7}$$

$$P(Y_{(a_1(0),a_1(1))=(1,1)}(2) = 1) - P(Y_{(a_1(0),a_1(1))=(0,0)}(2) = 1) \tag{8}$$

$$P(Y_{(a_1(0),a_1(1))=(1,1)}(2) = 1) - P(Y_{(a_1(0),a_1(1))=(0,1)}(2) = 1) \tag{9}$$

$$P(Y_{(a_1(0),a_1(1))=(1,1)}(2) = 1) - P(Y_{(a_1(0),a_1(1))=(1,0)}(2) = 1) \tag{10}$$

$$P(Y_{(a_1(0),a_1(1))=(0,0)}(2) = 1) - P(Y_{(a_1(0),a_1(1))=(0,1)}(2) = 1) \tag{11}$$

$$P(Y_{(a_1(0),a_1(1))=(0,0)}(2) = 1) - P(Y_{(a_1(0),a_1(1))=(1,0)}(2) = 1) \tag{12}$$

$$P(Y_{(a_1(0),a_1(1))=(0,1)}(2) = 1) - P(Y_{(a_1(0),a_1(1))=(1,0)}(2) = 1) \tag{13}$$

Note that all such contrasts are functions of the probabilities $P(Y_{\bar{a}_1(t)}(t+1))$ for $t = 0$ and $t = 1$. In the description above, the indicators of failure are assumed to always be observed at any time of the experiment, i.e. right-censoring is always prevented. This is conceptualized by an intervention on the right-censoring process, $\bar{a}_2(t)$, along with the interventions on ART use, $\bar{a}_1(t)$, for $t = 0$ and $t = 1$. The effects of ART use on the cumulative risks of failure over time is thus formally defined by contrasts between the probabilities $P(Y_{\bar{a}(t)}(t+1))$ for different joint interventions on both use of ART and occurrence of a right-censoring event denoted by $\bar{a}(t) = (\bar{a}_1(t), \bar{a}_2(t))$ such that $\bar{a}_2(t) = 0$ for $t = 0$ and $t = 1$.

Further extension over time of the conceptual experiment above permits the definition of the effects of interventions on ART use during more than two time intervals on the cumulative risks of failure over time denoted by $P(Y_{\bar{a}_1(t)}(t+1))$ for $t = 0, \ldots, K$ where K denotes a fixed, arbitrary follow-up time. To further extend this experiment, data on all other attributes represented by the covariates $L(t)$ in the real life experiment (see Table 1) can be collected through time K, in addition to the outcome attribute (indicator of failure). Similar to the outcome attribute, these attributes are represented by a multi-dimensional *potential* covariate at each time interval $t \leq K$ denoted by $L_{\bar{a}(K)}(t)$. Time ordering of action and covariate measurements in the ideal experiment implies the equality $L_{\bar{a}(K)}(t) = L_{\bar{a}(t-1)}(t)$. Note that the potential covariate at any time interval t, $L_{\bar{a}(t-1)}(t)$, includes the potential outcome $Y_{\bar{a}(t-1)}(t)$: $Y_{\bar{a}(t-1)}(t) \in L_{\bar{a}(t-1)}(t)$. Under any action interventions $\bar{a}(K)$ in this conceptual experiment, failure may occur during follow-up. Such *potential* failure times are denoted by $T_{\bar{a}_1(K)} \leq K$ and defined by $(\bar{Y}_{\bar{a}(K)}(T_{\bar{a}_1(K)}) = 0, Y_{\bar{a}(K)}(T_{\bar{a}_1(K)}+1) = 1, \ldots, Y_{\bar{a}(K)}(K+1) = 1)$. By convention, if failure does not occur during follow-up under action intervention $\bar{a}(K)$, i.e. $\bar{Y}_{\bar{a}(K)}(K+1) = 0$, the potential failure time $T_{\bar{a}_1(K)}$ is defined as ∞ and, otherwise, the remainder of the potential covariate process after failure time $T_{\bar{a}_1(K)}$ occurs is defined by the degenerate variables:

$$L_{\bar{a}(t-1)}(t) = Y_{\bar{a}(K)}(T_{\bar{a}_1(K)} + 1), \text{ where } P(L_{\bar{a}(t-1)}(t) = 1) = 1 \text{ for } t = T_{\bar{a}_1(K)} + 2, \ldots, K + 1.$$

The collection of all potential covariates collected over time during this extended ideal experiment are referred to as the full data and denoted by X:

$$X \equiv (\bar{L}_{\bar{a}(K)}(K+1))_{\bar{a}(K)\in\mathcal{A}(K)} \sim F_X,$$

where $\mathcal{A}(K)$ represents the collection of ART and right-censoring interventions of interest: $\mathcal{A}(K) \equiv \{\bar{a}(K) = (\bar{a}_1(K), \bar{a}_2(K)) : \bar{a}_2(K) = 0\}$, and F_X represents the distribution of the full data process X.

As illustrated above with the causal contrasts (7) through (13), causal effects of interventions on ART use through time K on time to cancer onset are formally defined as a function of the distribution of these full data. In particular, they can be defined by the collection of contrasts between cumulative risks of failure

$$P(Y_{\bar{a}(t)}(t+1) = 1) - P(Y_{\bar{a}'(t)}(t+1) = 1) = P(T_{\bar{a}_1(t)} \leq t) - P(T_{\bar{a}'_1(t)} \leq t) \tag{14}$$

for $t = 0, \ldots, K$ and any two different action interventions $\bar{a}(K) \in \mathcal{A}(K)$ and $\bar{a}'(K) \in \mathcal{A}(K)$. Thus, causal parameters can be denoted by $\Psi(F_X)$ and in particular the causal parameter in this analysis defined in the next subsections. Unlike the causal contrasts (14) which are defined based on so-called *static* interventions on the action process, the causal parameter of interest in this analysis is defined based on *dynamic* interventions on the action process as described below.

4.2 Effect definition based on dynamic interventions

In the previous subsection, causal effects were defined by contrasting the distribution of potential outcomes following treatment interventions a priori specified (i.e. independently of the patient's condition). Clinical practice, however, involves treatment decisions which are continuously adjusted to the patient's evolving medical history (e.g. response to previously experienced treatments) and are not set a priori at baseline. Thus, it may often be less clinically relevant to compare the health effect of static treatment interventions than to compare the effectiveness of competing medical guidelines, i.e. adaptive treatment strategies which map the patient's unfolding medical history to subsequent treatment decisions. Following such treatment strategies leads to treatment interventions over time which are referred to as dynamic interventions since the treatment experienced by each patient at any point in time is not set a priori at baseline but is rather adjusted based on the patient's current circumstances.

The effect of interest in this study (see section 1) is an example of a causal effect defined by dynamic treatment interventions. Specifically, our aim is to evaluate the comparative effectiveness between two ART initiation strategies guided by the patient's evolving CD4 count. These adaptive treatment strategies are referred to as individualized action rules. The individualized action rules of interest are each indexed by a CD4 count threshold, denoted by $\theta \in \Theta$ where $\Theta = \{200, 350\}$, and are each defined as a vector function $d_\theta = (d_\theta(0), \ldots, d_\theta(K))$ where each function, $d_\theta(t)$ for $t = 0, \ldots, K$, is a decision rule for determining the action (treatment and right-censoring) to be experienced by a patient during time interval t. A decision rule $d_\theta(t)$ maps the action and covariate history measured up to a given time interval t to an action regimen (i.e. an intervention) during time interval t: $d_\theta(t) : (\bar{L}(t), \bar{A}(t-1)) \mapsto (a_1(t), a_2(t))$. In this analysis, the decision rules of interest are defined such that $d_\theta(t)((\bar{L}(t), \bar{A}(t-1))$ is:

- $(a_1(t), a_2(t)) = (0, 0)$ (i.e. no ART use and no right-censoring) if and only if the patient was not previously treated with ART (i.e. $\bar{A}(t-1) = 0$) and the previous CD4 count measurement was greater than or equal to the threshold θ (i.e. $L_{p+1}(t) \geq \theta$).
- $(a_1(t), a_2(t)) = (1, 0)$ (i.e. ART use and no right-censoring) otherwise.

The individualized action rules, d_θ for $\theta \in \Theta$, implied by the time-specific decision rules above, $d_\theta(t)$ for $t = 0, \ldots, K$, are monotone in the sense that if a patient follows one of these rules, d_θ, then s/he is not treated with ART until his/her CD4 count falls below the threshold θ for the first time and from then on the patient remains treated with ART.

The potential covariate process that could be observed on a patient in an ideal experiment where interventions on the action process according to a decision rule d_θ are carried out through time K is denoted by $\bar{L}_{d_\theta}(K+1)$ respectively. This process corresponds with one of the potential covariate processes in the full data: $\bar{L}_{d_\theta}(K+1) = \bar{L}_{\bar{a}(K)}(K+1)$ such that the action regimen $\bar{a}(K) = (\bar{a}_1(K), \bar{a}_2(K))$ corresponds to interventions according to the individualized action rule d_θ, i.e. $a(0) = d_\theta(0)(L(0))$, $a(1) = d_\theta(1)(\bar{L}(1), a(0))$, ..., $a(K) = d_\theta(K)(\bar{L}(K), \bar{a}(K-1))$ (in particular: $a_2(t) = 0$ for all $t = 0, \ldots, K$). Note that such dynamic treatment interventions through time K according to the adaptive treatment strategy d_θ, i.e. $\bar{a}(K)$ above, are only functions of the observed covariate process $\bar{L}(K)$ and are thus denoted by $d_\theta(\bar{L}(K))$. Similar to the case of static interventions, failure may occur during follow-up under any such dynamic treatment intervention, $d_\theta(\bar{L}(K))$. Such *potential* failure times are denoted by $T_{d_\theta} \leq K$ and defined by $(\bar{Y}_{d_\theta}(T_{d_\theta}) = 0, Y_{d_\theta}(T_{d_\theta}+1) = 1, \ldots, Y_{d_\theta}(K+1) = 1)$.

As with static ART interventions, causal effects of adaptive ART strategies on time to cancer onset are formally defined as a function of the distribution of the full data process X. In particular, they can be defined by the collection of contrasts between cumulative risks of failure

$$P(Y_{d_\theta}(t+1) = 1) - P(Y_{d_{\theta'}}(t+1) = 1) = P(T_{d_\theta} \leq t) - P(T_{d_{\theta'}} \leq t)$$

for $t = 0, \ldots, K$ and any two different individualized action rules d_θ with $\theta \in \Theta$ and $d_{\theta'}$ with $\theta' \in \Theta$.

4.3 Target parameter

For our research question, the comparative effectiveness between the two adaptive ART strategies indexed by the CD4 thresholds 200 and 350 is of interest. Fig. 3 represents the percentages of patients following the

corresponding two individualized action rules over time denoted by d_{200} and d_{350}.

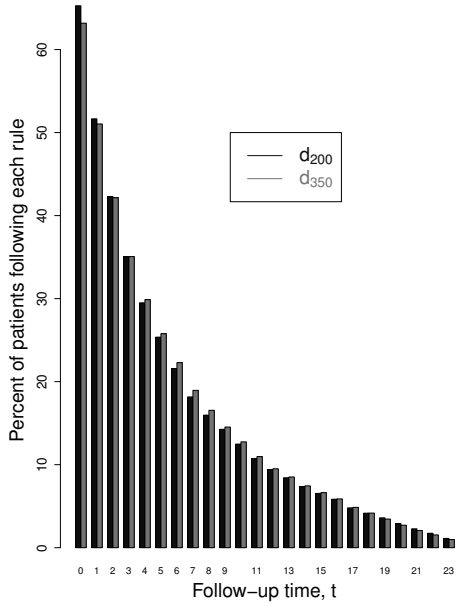

Figure 3: Percentages of patients following each of the two individualized action rules of interest indexed by a CD4 count threshold of 200 and 350 cells per μl (reminder: $t = 0$ represents the first 180 days of follow-up).

The empirical distribution of observed events described in Table 9 indicates that two thirds of the observed cancer onsets occurred in the first four time points of follow-up. Thus, to ease the computing time required for implementation of the targeted maximum likelihood estimation procedure while illustrating the computing steps involved without loss of generality, we restrict the focus of this analysis to the evaluation of a single causal contrast between the cumulative risks of failure within two years from study entry under the individualized action rules d_{350} and d_{200}:

$$\begin{aligned} \psi &= P(T_{d_{350}} \leq 3) - P(T_{d_{200}} \leq 3) \\ &= P(Y_{d_{350}}(K+1) = 1) - P(Y_{d_{200}}(K+1) = 1), \end{aligned} \tag{15}$$

where $K = 3$. Note that this parameter is a function of the full data distribution as is made explicit with the notation $\psi = \Psi(F_X)$.

Under the sequential randomization assumption (SRA) (Robins (1986))

$$Y_{\bar{a}(K)}(K+1) \perp A(t) \mid \bar{L}(t), \bar{A}(t-1) \text{ for all } \bar{a}(K) \in \mathcal{A}(K) \text{ and } t = 0, \ldots, K, \tag{16}$$

the marginal distribution of the counterfactual process $(T_{d_\theta} = t, \bar{L}_{d_\theta}(t+1))$ with $t \leq K$ from the full data is equal to the Q part of the observed data likelihood (6) where 1) T_{d_θ} plays the role of the follow-up time $\tilde{T}$, 2) Δ is set to 1, and 3) the action values are set according to the decision rule d_θ in any of the conditioning events, i.e.

$$P(T_{d_\theta} = t, \bar{L}_{d_\theta}(t+1)) = Q_{L(0)} \prod_{t'=1}^{t+1} \prod_{j=1}^{n_t(t')} \prod_{m=1}^{n(t',p+j)-1} Q_{L_{p+j,m}(t')|Pa_{d_\theta}(L_{p+j,m}(t'))}, \tag{17}$$

where the conditional probabilities $Q_{L_{p+j,m}(t')|Pa_{d_\theta}(L_{p+j,m}(t'))}$ are the conditional probabilities $Q_{L_{p+j,m}(t')}$ defined in section 3 where the action values are set according to the decision rule d_θ in the conditioning events and where the outcome values are set to $l_{p+1}(t') = 0$ for $t' = 1, \ldots, t$ and $l_{p+1}(t') = 1$ for $t' = t+1$. Equality (17) is referred to as the G-computation formula (Murphy et al. (2001); Robins (1986)). Recall that the covariate $L_{p+1,d_\theta}(t)$ of $L_{d_\theta}(t)$ corresponds with the outcome variable also denoted by $Y_{d_\theta}(t)$ and that

$P(T_{d_\theta} = t) = P(\bar{Y}_{d_\theta}(t) = 0, Y_{d_\theta}(t+1) = 1)$. By integrating out covariates from the right-hand side of the G-computation formula (17), the distribution of the counterfactual failure times, $P(T_{d_\theta} = t)$, can be derived as a function of the Q part of the observed data likelihood:

$$P(\bar{Y}_{d_\theta}(t) = 0, Y_{d_\theta}(t+1) = 1) = \sum_{l(0),\, l_{p+j,m}(t'), j\neq 1, t'\neq t+1} Q_{l(0)} \prod_{t'=1}^{t+1} \prod_{j=1}^{n_t(t')} \prod_{m=1}^{n(t',p+j)-1} Q_{l_{p+j,m}(t')|Pa_{d_\theta}(l_{p+j,m}(t'))}, \tag{18}$$

where $Q_{l(0)}$ is the probability $Q_{L(0)}$ at $L(0) = l(0)$ for a given value $l(0)$ and $Q_{l_{p+j,m}(t')|Pa_{d_\theta}(l_{p+j,m}(t'))}$ are the conditional probabilities $Q_{L_{p+j,m}(t')|Pa_{d_\theta}(L_{p+j,m}(t'))}$ at 1) $L_{p+j,m}(t') = l_{p+j,m}(t')$ for $t' \neq t+1$ and $j \neq 1$ for given values $l_{p+j,m}(t')$, and at 2) $L(0) = l(0)$. We denote the right-hand side of equality (18) with $\Phi(Q, t, \theta)$. Using that $P(Y_{d_\theta}(t+1) = 1) = \sum_{t'=0}^{t} P(\bar{Y}_{d_\theta}(t') = 0, Y_{d_\theta}(t'+1) = 1)$ and equality (18), the causal estimand ψ defined by (15) can be expressed as a function of the Q part of the observed data likelihood under the SRA:

$$\psi = \sum_{t=0}^{K} \Phi(Q, t, 350) - \sum_{t=0}^{K} \Phi(Q, t, 200) \tag{19}$$

The parameter ψ as defined by equality (19) is the target parameter in this analysis: It is a mapping from the Q part of the likelihood of the observed data into a one-dimensional euclidean parameter as made explicit by the notation $\psi = \Psi(Q)$. We denote its true value with $\psi_0 = \Psi(Q_0)$ where Q_0 denotes the Q part of the true likelihood of the observed data denoted by P_0. Note that under the SRA, the target parameter can be interpreted causally since it then corresponds to the causal parameter $\psi = \Psi(F_X)$ from equality (15). The validity of the SRA in this analysis is discussed in section 5.4.

5 Targeted maximum likelihood estimation procedure

In this section, we develop an "inverse probability of action weighted-reduced data-targeted minimum loss-based estimator" (IPAW-R-TMLE) for estimation of the previously defined target parameter ψ (van der Laan (2008)). Implementation of this IPAW-R-TMLE is illustrated with data from the KPNC electronic medical record. Section 5.1 provides a formal presentation of the IPAW-R-TMLE. Section 5.2 describes the R-TMLE which provides the basis for implementation of the IPAW-R-TMLE in this analysis. Finally, section 5.3 describes the implementation of the IPAW-R-TMLE and the corresponding results for the estimation of the target parameter ψ.

5.1 Definition and property of the IPAW-R-TMLE

A targeted minimum loss-based estimator (TMLE) of a target parameter $\psi_0 = \Psi(Q_0)$ is characterized by two ingredients: a choice of loss function for Q_0, and a parametric fluctuation working model to fluctuate Q. These two choices combined determine the estimating function $D(Q, \eta) \equiv \frac{d}{d\epsilon} L(Q_\eta(\epsilon))\big|_{\epsilon=0}$ whose estimating equation $P_n D(Q_n^*, \eta_n) = 0$ will be solved by the resulting (iterative) TMLE Q_n^*. If D is the efficient influence curve, then this TMLE is an efficient TMLE. The efficient TMLE, based on (e.g.) the log-likelihood loss function $L(Q)$ and efficient influence curve estimating function $D^*()$, can be quite involved for complex longitudinal data structures with time-dependent covariates, since Q_0 may be a very high-dimensional function. Therefore, it is of interest to also provide TMLE for which Q_0 is chosen to be of lower dimension, at cost of having to work with a loss function $L_{\eta_0}(Q)$ that is indexed by an unknown nuisance parameter, and fluctuation model that generates an inefficient estimating function $D()$. For that purpose van der Laan (2008) proposed a general class of so called inverse probability of censoring weighted-reduced data-TMLE (IPCW-R-TMLE), which only requires computation of the efficient TMLE for a user supplied reduced (simplified) data structure, but weights the loss function in this procedure with inverse probability of censoring weights.

Let $O = (L(0), A(0), \ldots, L(K), A(K), L(K+1)) \sim P_0$. Assume a non-parametric structural equation model (NPSEM): $A(t) = f_{A(t)}(Pa(A(t)), U_{A(t)})$, $t = 1, \ldots, K$, $L(t) = f_{L(t)}(Pa(L(t)), U_{L(t)})$, $t = 1 \ldots, K+1$, where

$Pa(A(t)) = (\bar{A}(t-1), \bar{L}(t))$, and $Pa(L(t)) = (\bar{A}(t-1), \bar{L}(t-1))$. Here $A(t)$ denote the intervention nodes which can include both treatment and censoring actions and we may then refer to the IPCW-R-TMLE by IPAW-R-TMLE as is done in this article to make the dual nature of the intervention nodes explicit. This NPSEM allows us to define counterfactuals L_a or L_d indexed by static interventions a or dynamic treatments d, respectively. We assume the sequential randomization assumption on the error nodes U in the NPSEM, so that the G-computation formula provides us with the identifiability of any parameter of the distribution of a counterfactual L_d for a given rule d, possibly a static rule.

Specifically, under this SRA, the probability distribution of the observed data random variable $O = (A, L = L_A)$ factorizes into a factor Q_0 implied by the full data distribution of the counterfactuals $X = (L_a : a)$ and a factor $g_0(\cdot \mid X) = \prod_{t=0}^{K} g_{0A(t)}(A(t) \mid Pa(A(t)))$ that corresponds with the conditional distribution of A, given X:

$$P_{Q_0,g_0}(O) \quad = \quad \prod_{t=0}^{K+1} Q_{0L(0)}(L(t) \mid Pa(L(t)) \prod_{t=0}^{K} g_{0A(t)}(A(t) \mid Pa(A(t)))$$

Note that for clarity, we used the notation A for $\bar{A}(K)$ and a for $\bar{a}(K)$ above. By the SRA which implies coarsening at random (see section 1.2.3 of van der Laan and Robins (2003)), we have $Q_{0L(t)}(l(t) \mid \bar{l}(t-1), \bar{a}(t-1)) = P(L_a(t) = l(t) \mid \bar{L}_a(t-1) = \bar{l}(t-1))$ so that indeed Q_0 represents the identifiable part of the full data distribution of the counterfactuals X.

A statistical model $\mathcal{M}$ for P_0 can be represented as all probability distributions $P_{Q,g}$ with $Q \in \mathcal{Q}$ and $g \in \mathcal{G}$ for some specified models $\mathcal{Q}$ and SRA-model $\mathcal{G}$ for Q_0 and g_0, respectively. Given a parameter $\Psi : \mathcal{Q} \to \mathbb{R}^d$, our goal is to estimate $\Psi(Q_0)$.

The basic idea of IPCW-R-TMLE is now the following. Our target parameter can also be written as a function of the distribution of a reduction L_a^r of the counterfactual L_a, obtained by removing a number of the time-dependent components of $L_a(t)$. Thus, we can write our parameter as $\Psi(Q_0) = \Psi^r(Q_0^r)$, where $Q_0^r(a, l^r)$ represents the distribution of L_a^r: $Q^r_{0L^r(t)}(l^r(t) \mid \bar{l}^r(t-1), \bar{a}(t-1)) = P(L_a^r(t) = l^r(t) \mid \bar{L}_a^r(t-1) = \bar{l}(t-1))$. Now, we note that the inverse-weighted log-likelihood loss function, for any marginal probability distribution g^r of A, $L_{g_0}(Q^r) \equiv -g^r/g_0 \log Q^r$, is a valid loss function for Q_0^r, since

$$Q^r \to P_0 \log Q^r g^r/g_0 = P_{Q_0,g^r} \log Q^r = P_{Q_0^r,g^r} \log Q^r,$$

is maximized at Q_0^r. To see this, we use the representation $O = (A, L_A)$ and that $Q_0(a, l) = P_0(L_a = l)$ so that:

$$E_{Q_0,g^r} \log Q^r(A, L_A^r) = E_{Q_0^r} \sum_a \log Q^r(a, L_a^r) g^r(a),$$

which is indeed maximized at Q_0^r. In addition, the inverse probability weighted reduced data efficient influence curve, $D(Q^r, g^r, g_0) \equiv D^{*r}(Q^r, g^r) g^r/g_0$, is a targeted estimating function for the target parameter $\Psi^r(Q_0^r)$, which has good robustness properties. We can now apply this TMLE as described in the next subsections with this inverse weighted log likelihood loss function, a fluctuation working model $\{Q_{g^r}^r(\epsilon) : \epsilon\}$ with score at $\epsilon = 0$ equal to the reduced data efficient influence curve $D^{r*}(Q^r, g^r)$.

We go beyond this choice of IPCW-log-likelihood loss function since it is more efficient to inverse weight the factors $Q_{0L^r(t)}$ of Q_0^r separately with more stable weights $g^r(\bar{A}(t-1) \mid X^r)/g_0(\bar{A}(t-1) \mid X)$. This results in the IPCW-log-likelihood loss function

$$L_{g^r,g_0}(Q^r) \equiv \sum_t - \log Q^r_{L^r(t)} \frac{g^r(\bar{A}(t-1) \mid X^r)}{g_0(\bar{A}(t-1) \mid X)},$$

which defines the IPAW-R-TMLE we implemented in this article.

From a practical implementation point of view, this just means that we apply the TMLE (referred to as R-TMLE) for the reduced data structure presented in the next subsection, but assign weights to observations and time-points at each step of the estimation procedure as described in subsection 5.3: Thus, the initial estimator, and the fitting of ϵ involve now weighted regressions.

5.2 R-TMLE implementation and results

In this analysis, the R-TMLE is implemented for the data structure described in section 2 where all measurements of the time-dependent covariates corresponding to viral load ('VL') and past clinical AIDS-defining events ('clinicalAIDS') are ignored after baseline, i.e. where the covariates $L_{p+j}(t)$ for $j = 3, \ldots, q+q^{'}$ and $t > 0$ in the observed data O are treated as nil (see Table 2). In other words, the R-TMLE described below corresponds with the TMLE applied to the simplified data where the only time-dependent covariates considered after baseline represent outcome and CD4 count measurements. Below, we describe the steps involved in the implementation of this R-TMLE starting with the presentation of the IPAW estimating function which provides the basis for the derivation of the efficient influence curve and the clever covariates associated with this R-TMLE. In an abuse of notation, the R-TMLE implementation is described using the same notation for the reduced data as the one previously adopted to represent the original data. Thus, all references to the covariates $L_{p+j}(t)$ for $j = 3, \ldots, q+q^{'}$ and $t > 0$ in the notation below should be ignored (i.e. these variables are considered nil in this subsection) since they are not part of the reduced data.

5.2.1 IPAW estimating function

An inverse probability of action weighted (IPAW) estimating function (van der Laan and Robins (2003); Tsiatis (2006)) for the target parameter ψ is defined as

$$D_{\text{IPAW}}(g,\psi) \equiv \frac{I\big(\bar{A}(\check{T}) = d_{350}(\bar{L}(\check{T}))\big)}{\prod_{t=0}^{\check{T}} g_{A_1(t)} g_{A_2(t)}} Y(\check{T}+1) - \frac{I\big(\bar{A}(\check{T}) = d_{200}(\bar{L}(\check{T}))\big)}{\prod_{t=0}^{\check{T}} g_{A_1(t)} g_{A_2(t)}} Y(\check{T}+1) - \psi \tag{20}$$

where $\check{T}$ is defined as the minimum between the follow-up time, $\tilde{T}$, and $K = 3$, i.e. $\check{T} = \min(K, \tilde{T})$. Recall that the outcome variable $Y(t+1)$ is also denoted by $L_{p+1}(t+1)$ and $L_{p+1,1}(t+1)$ (see section 3). We use these three representations for the same variable interchangeably in the next subsections.

5.2.2 Efficient influence curve and clever covariate

As described in section 3.2 of van der Laan (2010), the IPAW estimating function can be mapped into the efficient[1] influence curve for ψ, denoted by $D^*(Q,g,\psi)$, by projecting it onto the tangent space of Q:

$$D^*(Q,g,\psi) = \Pi\big(D_{\text{IPAW}} \mid T_Q\big),$$

where D_{IPAW} is short-hand notation for $D_{\text{IPAW}}(g,\psi)$ (see definition (20)). Theorem 2 in van der Laan (2010) applied to the factorization (6) of the likelihood of the reduced, observed data leads to the following result:

$$\Pi\big(D_{\text{IPAW}} \mid T_Q\big) = \Pi\big(D_{\text{IPAW}} \mid T_{L(0)}\big) + \sum_{t=1}^{\tilde{T}} \sum_{j=1}^{2} \sum_{m=1}^{n(t,p+j)-1} \Pi\big(D_{\text{IPAW}} \mid T_{L_{p+j,m}(t)}\big) + \Delta\Pi\big(D_{\text{IPAW}} \mid T_{L_{p+1,1}(\tilde{T}+1)}\big),$$

where $\Pi\big(D_{\text{IPAW}} \mid T_{L(0)}\big) = E(D_{\text{IPAW}} \mid L(0))$ and $\Pi\big(D_{\text{IPAW}} \mid T_{L_{p+j,m}(t)}\big) = H^*_{L_{p+j,m}(t)}\big(L_{p+j,m}(t) - Q_{L_{p+j,m}(t)}(1)\big)$ for $t = 1, \ldots, \tilde{T}$, $j = 1, 2$ and $m = 1, \ldots, n(t,p+j)-1$ or $(t,j,m) = (\tilde{T}+1, 1, 1)$, with $Q_{L_{p+j,m}(t)}(1)$ representing the conditional probability of $L_{p+j,m}(t)$ defined in section 3 and evaluated at $L_{p+j,m}(t) = 1$, and

$$H^*_{L_{p+j,m}(t)} = E\big(D_{\text{IPAW}} \mid L_{p+j,m}(t) = 1, Pa(L_{p+j,m}(t))\big) - E\big(D_{\text{IPAW}} \mid L_{p+j,m}(t) = 0, Pa(L_{p+j,m}(t))\big). \tag{21}$$

Note that the ψ component of D_{IPAW} is a constant that appears in both expectations defining $H^*_{L_{p+j,m}(t)}$. Equality (21) thus reduces to

$$H^*_{L_{p+j,m}(t)} = E\big(D^{'}_{\text{IPAW}} \mid L_{p+j,m}(t) = 1, Pa(L_{p+j,m}(t))\big) - E\big(D^{'}_{\text{IPAW}} \mid L_{p+j,m}(t) = 0, Pa(L_{p+j,m}(t))\big) \tag{22}$$

[1] relative to the reduced data

with

$$D^{'}_{\text{IPAW}}(g) = \frac{I\big(\bar{A}(\check{T}) = d_{350}(\bar{L}(\check{T}))\big)}{\prod_{t=0}^{\check{T}} g_{A_1(t)} g_{A_2(t)}} Y(\check{T}+1) - \frac{I\big(\bar{A}(\check{T}) = d_{200}(\bar{L}(\check{T}))\big)}{\prod_{t=0}^{\check{T}} g_{A_1(t)} g_{A_2(t)}} Y(\check{T}+1).$$

Note that $D^{'}_{\text{IPAW}}(g)$ is only a function of the observed data collected up to $\check{T}+1$ which excludes $L_{p+j,m}(t)$ for $t > \check{T}+1$. As a result, the equality (22) for $t > \check{T}+1$ reduces to $H^{*}_{L_{p+j,m}(t)} = 0$. Note also that $D^{'}_{\text{IPAW}}(g)$ can be represented as $D^{'}_{\text{IPAW}}(O \mid g) = \frac{D_1(\bar{A}(\check{T}),\bar{L}(\check{T}+1))}{\prod_{t=0}^{\check{T}} g_{A_1(t)} g_{A_2(t)}}$ with $D_1(\bar{A}(\check{T}), \bar{L}(\check{T}+1))$ defined as

$$\Big(I\big(\bar{A}(\check{T}) = d_{350}(\bar{L}(\check{T}))\big) - I\big(\bar{A}(\check{T}) = d_{200}(\bar{L}(\check{T}))\big)\Big) Y(\check{T}+1).$$

From theorem 2 in van der Laan (2010), equality (22) can thus be rewritten as

$$H^{*}_{L_{p+j,m}(t)} = \frac{1}{\prod_{t'=0}^{t-1} g_{A_1(t')} g_{A_2(t')}} \times \Big(E_Q\big(\sum_{\bar{a}(t,K)} D_1 \mid L_{p+j,m}(t) = 1, Pa(L_{p+j,m}(t))\big) - E_Q\big(\sum_{\bar{a}(t,K)} D_1 \mid L_{p+j,m}(t) = 0, Pa(L_{p+j,m}(t))\big)\Big), \quad (23)$$

where 1) D_1 is short-hand notation for $D_1(\bar{A}(t-1), \bar{a}(t,\check{T}), \bar{L}(\check{T}+1))$ and 2) $\bar{a}(t,t^{'}) = (a(t),\ldots,a(t^{'}))$ for $t^{'} \geq t$ and nil otherwise. In addition, note that the second expectation in (23) is 0 when $j = 1$ and $t = K+1$. We thus have

$$H^{*}_{L_{p+1,1}(K+1)} = \frac{I\big(\bar{A}(\check{T}) = d_{350}(\bar{L}(\check{T}))\big) - I\big(\bar{A}(\check{T}) = d_{200}(\bar{L}(\check{T}))\big)}{\prod_{t'=0}^{K} g_{A_1(t')} g_{A_2(t')}}.$$

Finally, note that both expectations in (23) are equal when $j = 2$ and $t = K+1$. We thus have: $H^{*}_{L_{p+2,m}(K+1)} = 0$.

From all the results above, the efficient[2] influence curve for ψ, $D^{*}(Q,g,\psi)$ is defined as

$$\Pi\big(D_{\text{IPAW}} \mid T_{L(0)}\big) + \sum_{t=1}^{\check{T}} \sum_{j=1}^{2} \sum_{m=1}^{n(t,p+j)-1} \Pi\big(D_{\text{IPAW}} \mid T_{L_{p+j,m}(t)}\big) + \Delta^{I(\tilde{T}\leq K)} \Pi\big(D_{\text{IPAW}} \mid T_{L_{p+1,1}(\check{T}+1)}\big), \quad (24)$$

with $I(\tilde{T} \leq K)$ representing the indicator that the follow-up time $\tilde{T}$ is lower than or equal to K,

$$\Pi\big(D_{\text{IPAW}} \mid T_{L(0)}\big) = E(D_{\text{IPAW}} \mid L(0)),$$

$$\Pi\big(D_{\text{IPAW}} \mid T_{L_{p+j,m}(t)}\big) = H^{*}_{L_{p+j,m}(t)}\big(L_{p+j,m}(t) - Q_{L_{p+j,m}(t)}(1)\big), \text{ where}$$

for $t = 1,2,3$

$$H^{*}_{L_{p+j,m}(t)} = \frac{1}{\prod_{t'=0}^{t-1} g_{A_1(t')} g_{A_2(t')}} \times \Big(E_Q\big(\sum_{\bar{a}(t,K)} D_1 \mid L_{p+j,m}(t) = 1, Pa(L_{p+j,m}(t))\big) - E_Q\big(\sum_{\bar{a}(t,K)} D_1 \mid L_{p+j,m}(t) = 0, Pa(L_{p+j,m}(t))\big)\Big), \quad (25)$$

and

$$H^{*}_{L_{p+1,1}(K+1)} = \frac{I\big(\bar{A}(K) = d_{350}(\bar{L}(K))\big) - I\big(\bar{A}(K) = d_{200}(\bar{L}(K))\big)}{\prod_{t'=0}^{K} g_{A_1(t')} g_{A_2(t')}}. \quad (26)$$

The variables $H^{*}_{L_{p+1,1}(t)}$ and $H^{*}_{L_{p+2,m}(t)}$ are the clever covariates that are used for updating the initial estimators of $Q_{L_{p+1,1}(t)}$ and $Q_{L_{p+2,m}(t)}$, respectively, during the implementation of the R-TMLE of the target parameter ψ.

[2]relative to the reduced data

5.2.3 Obtain Q_n^0, an initial estimate of Q_0

The efficient influence curve defined by equality (24) is a function of only a subset of the Q components of the reduced, observed data likelihood[3]. Specifically, the following 14 components of Q are relevant for implementation of the R-TMLE of the target parameter ψ and thus needed to be estimated:

- $Q_{L(0)} \equiv P(L(0))$.
- $Q_{L_{p+1,1}(t)} \equiv P(Y(t) \mid \bar{L}(t-1), \bar{A}(t-1))$ for $t = 1, 2, 3, 4$ (only relevant at $\bar{Y}(t-1) = 0$, $\bar{A}_2(t-1) = 0$ and non-missing[4] $\bar{A}_1(t-1)$).
- $Q_{L_{p+2,m}(t)} \equiv P(I(L_{p+2}(t) = m) \mid \bar{L}(t-1), Y(t), \bar{A}(t-1), I(L_{p+2}(t) = 1), \ldots, I(L_{p+2}(t) = m-1))$ for $t = 1, 2, 3$ and $m = 1, 2, 3$ (only relevant at $\bar{Y}(t) = 0$, $\bar{A}_2(t-1) = 0$ and non-missing $\bar{A}_1(t-1)$ and only unknown at $I(L_{p+2}(t) = 1) = 0, \ldots, I(L_{p+2}(t) = m-1) = 0$).

Thus, estimation of the target parameter $\psi_0 = \Psi(Q_0)$ with the R-TMLE relies on initial estimation of the corresponding 14 Q_0 components of the true reduced data generating distribution, P_0. The initial estimate of $Q_{0,L(0)}$ is denoted by $Q^0_{0,L(0),n}$. It was defined based on non-parametric estimation of $Q_{0,L(0)}$ with the empirical distribution of $L(0)$. The initial estimates of $Q_{0,L_{p+1,1}(t)}$ and $Q_{0,L_{p+2,m}(t)}$ are denoted by $Q^0_{0,L_{p+1,1}(t),n}$ and $Q^0_{0,L_{p+2,m}(t),n}$ respectively. They were defined based on sieve estimation of $Q_{0,L_{p+1,1}(t)}$ and $Q_{0,L_{p+2,m}(t)}$ with the DSA algorithm from Sinisi and van der Laan (2004) as described below.

The initial estimate of $Q_{0,L_{p+1,1}(1)}$ (at $A_2(0) = 0$ and non-missing $A_1(0)$) was obtained separately. Ten classes of candidate estimators were considered and indexed by the size of working models ranging from 1 to 10. Candidate estimators in the class indexed by a model size s were defined by main-term, working, logistic models composed of s terms each. Table 14 lists the variables that were considered as potential main terms in these working models. Both deletion and substitution moves were enabled as part of the DSA algorithm (Neugebauer and Bullard (2010)). Estimator selection was based on cross-validation with Z random 5-fold splits of the learning set. It was repeated 10 times with $Z = 10$. If the same estimator was selected at least 8 times, then it was considered the initial estimator of $Q_{0,L_{p+1,1}(1)}$. Otherwise, the procedure was repeated with a larger value for $Z \leq 30$ until the initial estimator was defined. If the initial estimator remained undefined according to the rule above at $Z = 30$, the estimator selected with the highest frequency was then considered the initial estimator.

The DSA approach described above was implemented to obtain the remaining 12 estimates based on the following three data pooling schemes:

- The initial estimates of $Q_{0,L_{p+1,1}(t)}$ for $t = 2, 3, 4$ (at $\bar{Y}(t-1) = 0$, $\bar{A}_2(t-1) = 0$ and non-missing $\bar{A}_1(t-1)$) were obtained simultaneously through a unique, DSA-selected, pooled estimator over the three time intervals, t.
- The initial estimates of $Q_{0,L_{p+2,m}(1)}$ for $m = 1, 2, 3$ (at $Y(1) = 0$, $A_2(0) = 0$, non-missing $A_1(0)$, and $I(L_{p+2}(t) = 1) = 0, \ldots, I(L_{p+2}(t) = m-1) = 0$) were obtained simultaneously through a unique, DSA-selected, pooled estimator over the three CD4 count levels, m.
- The initial estimates of $Q_{0,L_{p+2,m}(t)}$ for $t = 2, 3$ and $m = 1, 2, 3$ (at $\bar{Y}(t) = 0$, $\bar{A}_2(t-1) = 0$, non-missing $\bar{A}_1(t-1)$, and $I(L_{p+2}(t) = 1) = 0, \ldots, I(L_{p+2}(t) = m-1) = 0$) were obtained simultaneously through a unique, DSA-selected, pooled estimator over the two time intervals, t, and the three CD4 count levels, m.

Table 14 lists the variables of the reduced data that were considered as potential main terms in the working, logistic models involved in each of the four estimator selection procedures described above. With the exception of the variables 'enrollyear' and 'm', each categorical variable X in Table 14 with $l > 2$ levels was not directly considered as a potential main term. Instead, l binary variables that each represents the indicator that X is equal to m (denoted by $I(X = m)$) for $m = 1, \ldots, l$ were considered as potential main terms. The variable 't' was not only treated as a categorical variable but was also considered directly as a potential main term.

[3] See equality (6) tailored to the reduced data structure.

[4] Recall that treatment is coded as missing after first ART discontinuation (see section 2).

The initial estimates resulting from the application of the four estimator selection procedures described above are summarized in Tables 15 through 18.

Table 14: Variables considered as potential main terms in the working, logistic models involved in the estimator selection for $Q_{0,L_{p+1,1}(1)}$, $Q_{0,L_{p+1,1}(t)}$ for $t = 2, 3, 4$, $Q_{0,L_{p+2,m}(1)}$ for $m = 1, 2, 3$, and $Q_{0,L_{p+2,m}(t)}$ for $t = 2, 3$ and $m = 1, 2, 3$. The notation $I(\cdot)$ denotes the indicator that statement $\cdot$ is true.

Variable	Shorthand	$Q_{0,L_{p+1,1}(1)}$	$Q_{0,L_{p+1,1}(t)}$	$Q_{0,L_{p+2,m}(1)}$	$Q_{0,L_{p+2,m}(t)}$
t	t		✓		✓
m	m			✓	✓
$L_1(0)$ to $L_{15}(0)$	see Table 2	✓	✓	✓	✓
$L_{22}(0)$ to $L_{26}(0)$	see Table 2	✓	✓	✓	✓
$I(L_{11}(0) = 1$ or $L_{12}(0) = 1)$	everAlcoholDrug	✓	✓	✓	✓
$I(L_{13}(0) = 1$ or $L_{14}(0) = 1)$	everHepatitisBorC	✓	✓	✓	✓
$L_{17}(0)$	CD4.0	✓	✓	✓	✓
$L_{18}(0)$	VL.0	✓	✓	✓	✓
$L_{19}(0)$	clinicalAIDS.0	✓	✓	✓	✓
$L_{17}(t-1)$	CD4		✓		✓
$L_{17}(t-1) - L_{17}(t-2)$	lastCD4change		✓		✓
$\sum_{l=0}^{t-1} L_{17}(l)$	sumPastCD4		✓		✓
$A_1(t-1)$	ART	✓with $t = 1$	✓	✓with $t = 1$	✓
$\sum_{l=0}^{t-1} A_1(l)$	sumPastART		✓		✓

5.2.4 Calculate the optimal fluctuation

Estimation of the target parameter $\psi_0 = \Psi(Q_0)$ with the R-TMLE involves the fluctuation of the initial estimators of $Q_{0,L_{p+1,1}(t)}$ and $Q_{0,L_{p+2,m}(t)}$ obtained previously. The optimal fluctuation of each of these initial estimators are based on the clever covariates, H^*, defined by equalities (25) and (26). R-TMLE implementation thus requires calculation of these clever covariates. They are functions of $Q_{0,L_{p+1,1}(t)}$ for $t = 1, 2, 3, 4$ and $Q_{0,L_{p+2,m}(t)}$ for $t = 1, 2, 3$ and $m = 1, 2, 3$ but also the following components of the action mechanism defined in section 3: $g_{0,A_1(t)}$ and $g_{0,A_2(t)}$ for $t = 0, 1, 2, 3$. Therefore, the derivation of estimates of $g_{0,A_1(t)}$ and $g_{0,A_2(t)}$ is first needed prior to computing the clever covariates. These estimates, combined with the initial estimates of $Q_{0,L_{p+1,1}(t)}$ and $Q_{0,L_{p+2,m}(t)}$ can then be mapped into an estimate of the clever covariates using Monte Carlo simulations.

Obtain g_n, an estimate of g_0. The following 8 components of the action mechanism, i.e. the g part of the reduced, observed data likelihood[5], are relevant for implementation of the R-TMLE of the target parameter ψ and thus needed to be estimated:

- $g_{A_1(t)} \equiv P(A_1(t) \mid \bar{A}(t-1), \bar{L}(t), A_2(t))$ for $t = 0, 1, 2, 3$ (only relevant at $\bar{Y}(t) = 0$, $\bar{A}_2(t) = 0$, and non-missing[6] $\bar{A}_1(t)$).
- $g_{A_2(t)} \equiv P(A_2(t) \mid \bar{A}(t-1), \bar{L}(t))$ for $t = 0, 1, 2, 3$ (only relevant at $\bar{Y}(t) = 0$, $\bar{A}_2(t-1) = 0$, and non-missing $\bar{A}_1(t-1)$).

Thus, estimation of the target parameter $\psi_0 = \Psi(Q_0)$ with the R-TMLE relies on estimation of the corresponding 8 g_0 components of the true reduced data generating distribution, P_0. The 8 estimates of $g_{0,A_1(t)}$ and $g_{0,A_2(t)}$ are denoted by $g_{0,A_1(t),n}$ and $g_{0,A_2(t),n}$ respectively. They were obtained based on sieve estimation with the same estimator selection procedure adopted for initial estimation of the 14 Q_0 components described in the previous section. The following four data stratification/pooling schemes were applied to derive each of the 8 estimates:

[5] See equality (6) tailored to the reduced data structure.
[6] Recall that treatment is coded as missing after first ART discontinuation (see section 2).

Table 15: DSA-selected estimate of $Q_{0,L_{p+1,1}(1)}$ (reminder: $L_{p+1,1}(1)$ is the outcome at time 1). Only the linear part of the working, logistic model that defines the estimate is presented. See Tables 2 and 14 for interpretation of each term.

Intercept	clinicalAIDS.0
−4.865	2.14

Table 16: DSA-selected estimates of $Q_{0,L_{p+1,1}(t)}$ for $t = 2, 3, 4$ (reminder: $L_{p+1,1}(t)$ is the outcome at time t). Only the linear part of the pooled, working, logistic model that defines the estimates is presented. See Tables 2 and 14 for interpretation of each term.

Intercept	I(ageAtEntry=1)	everDrug	ART	I(CD4=1)	sumPastART
−5.835	−1.137	0.521	2.137	1.3	−0.873

Table 17: DSA-selected estimates of $Q_{0,L_{p+2,m}(1)}$ for $m = 1, 2, 3$ (reminder: $L_{p+2,m}(1)$ is the indicator that the CD4 level at time 1 is equal to m). Only the linear part of the pooled, working, logistic model that defines the estimates is presented. See Tables 2 and 14 for interpretation of each term.

Intercept	m	I(race=White)	I(yearsHIV=1)	I(yearsHIV=2)	I(CD4.0=1)	I(CD4.0=2)	I(CD4.0=4)	I(VL.0=4)	clinicalAIDS.0	ART
−4.887	1.94	−0.188	−0.444	−0.323	4.228	1.709	−2.371	−0.391	0.311	−0.497

Table 18: DSA-selected estimates of $Q_{0,L_{p+2,m}(t)}$ for $t = 2, 3$ and $m = 1, 2, 3$ (reminder: $L_{p+2,m}(t)$ is the indicator that the CD4 level at time t is equal to m). Only the linear part of the pooled, working, logistic model that defines the estimates is presented. See Tables 2 and 14 for interpretation of each term.

Intercept	m	sex	I(yearsHIV=1)	I(VL.0=2)	I(CD4.0=4)	lastCD4change	I(CD4=1)	I(CD4=2)	I(CD4=4)	ART
−6.095	2.381	−0.34	−0.16	0.254	−0.428	0.553	5.129	2.109	−2.419	−0.671

- The estimate of $g_{0,A_1(0)}$ (at $A_2(0) = 0$, and non-missing $A_1(0)$) was obtained separately.
- The estimates of $g_{0,A_1(t)}$ for $t = 1, 2, 3$ (at $\bar{Y}(t) = 0$, $\bar{A}_2(t) = 0$, and non-missing $\bar{A}_1(t)$) were obtained simultaneously through a unique, DSA-selected, pooled estimator over the three time intervals, t.
- The estimate of $g_{0,A_2(0)}$ was obtained separately.
- The estimates of $g_{0,A_2(t)}$ for $t = 1, 2, 3$ (at $\bar{Y}(t) = 0$, $\bar{A}_2(t-1) = 0$, and non-missing $\bar{A}_1(t-1)$) were obtained simultaneously through a unique, DSA-selected, pooled estimator over the three time intervals, t.

Table 19 lists the variables of the reduced data considered as potential main terms in the working, logistic models involved in each of the four estimator selection procedures described above. With the exception of the variables 'enrollyear' and 'm', each categorical variable X in Table 19 with $l > 2$ levels was not directly considered as a potential main term. Instead, l binary variables that each represents the indicator that X is equal to m (denoted by $I(X = m)$) for $m = 1, \ldots, l$ were considered as potential main terms. The variable 't' was not only treated as a categorical variable but was also considered directly as a potential main term.

The estimates resulting from the application of the four estimator selection procedures described above are summarized in Tables 20 through 23.

Monte Carlo simulation based on g_n^0 and Q_n^0. The 13 clever covariates that need to be computed are defined by equalities (25) and (26): $H^*_{L_{p+1,1}(t)}$ for $t = 1, 2, 3, 4$ and $H^*_{L_{p+2,m}(t)}$ for $t = 1, 2, 3$ and $m = 1, 2, 3$. Each of these clever covariates are used to fluctuate the initial estimators of $Q_{0,L_{p+1,1}(t)}$ for $t = 1, 2, 3, 4$ and $Q_{0,L_{p+2,m}(t)}$ for $t = 1, 2, 3$ and $m = 1, 2, 3$ respectively.

By extending the definition of the observed outcome, $Y(t) \equiv I(T \leq t-1)$, to time points t beyond the time of an event when it is observed, i.e. for $t > T$ when $\tilde{T} = T$, the clever covariate for updating the initial estimator of $Q_{0,L_{p+1,1}(t)}$ at $\bar{Y}(t-1) = 0$, $\bar{A}_2(t-1) = 0$, and non-missing $\bar{A}_1(t-1)$ for $t = 1, 2, 3, 4$ can be rewritten as:

$$H^*_{L_{p+1,1}(t)} = \frac{1}{\prod_{t'=0}^{t-1} g_{A_1(t')} g_{A_2(t')}} \times \left[I\big(\bar{A}(t-1) = d_{350}(\bar{L}(t-1))\big) \Big(1 - E_Q\big(Y_{d_{350}}(4) \mid \bar{L}(t-1), \bar{A}(t-1), Y(t) = 0\big)\Big) - I\big(\bar{A}(t-1) = d_{200}(\bar{L}(t-1))\big) \Big(1 - E_Q\big(Y_{d_{200}}(4) \mid \bar{L}(t-1), \bar{A}(t-1), Y(t) = 0\big)\Big)\right]. \quad (27)$$

Note that at $t = 4$, equality (27) does indeed simplify to equality (26). Similarly, the clever covariate for updating the initial estimator of $Q_{0,L_{p+2,m}(t)}$ at $\bar{Y}(t) = 0$, $\bar{A}_2(t-1) = 0$, non-missing $\bar{A}_1(t-1)$, and $L_{p+2,1}(t) = 0, \ldots, L_{p+2,m-1}(t) = 0$ for $t = 1, 2, 3$ and $m = 1, 2, 3$ can be rewritten as:

$$H^*_{L_{p+2,m}(t)} = \frac{1}{\prod_{t'=0}^{t-1} g_{A_1(t')} g_{A_2(t')}} \Big[I\big(\bar{A}(t-1) = d_{350}(\bar{L}(t-1))\big) \times \Big(E_Q\big(Y_{d_{350}}(4) \mid Pa(L_{p+2,m}(t)), L_{p+2,m}(t) = 1\big) - E_Q\big(Y_{d_{350}}(4) \mid Pa(L_{p+2,m}(t)), L_{p+2,m}(t) = 0\big)\Big) - I\big(\bar{A}(t-1) = d_{200}(\bar{L}(t-1))\big) \Big(E_Q\big(Y_{d_{200}}(4) \mid Pa(L_{p+2,m}(t)), L_{p+2,m}(t) = 1\big) - E_Q\big(Y_{d_{200}}(4) \mid Pa(L_{p+2,m}(t)), L_{p+2,m}(t) = 0\big)\Big)\Big]. \quad (28)$$

where $Pa(L_{p+2,m}(t)) \equiv \big(\bar{L}(t-1), \bar{A}(t-1), Y(t), L_{p+2,1}(t), \ldots, L_{p+2,m-1}(t)\big)$.

The above formulation of the clever covariates makes explicit how they can be computed by first approximating each expectation in equalities (27) and (28) by Monte Carlo simulations: Following the factorization of the reduced, observed data likelihood[7] according to the time-ordering of actions and covariates, many[8] observations

[7] See equality (6) tailored to the reduced data structure.

[8] For this analysis, 10,000 observations of each potential outcome are simulated.

of the potential outcomes $Y_{d_\theta}(4)$ (for $\theta = 200, 350$) are simulated by sequentially generating future covariates starting at the fixed covariate and action history specified by the conditional event in each expectation and by setting future actions to the interventions implied by the individualized action rule d_θ. This simulation process ends when the outcome at time point 4 is simulated or earlier if the simulated event occurs before time point 4. The averages of these simulated potential outcomes approximate the expectations in equalities (27) and (28).

Table 19: Variables considered as potential main terms in the working, logistic models involved in the estimator selection for $g_{0,A_1(0)}$, $g_{0,A_1(t)}$ for $t = 1, 2, 3$, $g_{0,A_2(0)}$, and $g_{0,A_2(t)}$ for $t = 1, 2, 3$. The notation $I(\cdot)$ denotes the indicator that statement $\cdot$ is true.

Variable	Shorthand	$g_{0,A_1(0)}$	$g_{0,A_1(t)}$	$g_{0,A_2(0)}$	$g_{0,A_2(t)}$
t	t		✓		✓
$L_1(0)$ to $L_{15}(0)$	see Table 2	✓	✓	✓	✓
$L_{22}(0)$ to $L_{26}(0)$	see Table 2	✓	✓	✓	✓
$I(L_{11}(0) = 1$ or $L_{12}(0) = 1)$	everAlcoholDrug	✓	✓	✓	✓
$I(L_{13}(0) = 1$ or $L_{14}(0) = 1)$	everHepatitisBorC	✓	✓	✓	✓
$L_{17}(0)$ to $L_{19}(0)$	see Table 2	✓		✓	
$L_{17}(t)$	CD4		✓		✓
$L_{17}(t) - L_{17}(t-1)$	lastCD4change		✓		✓
$A_1(t-1)$	ART		✓		✓
$\sum_{l=0}^{t-1} A_1(l)$	sumPastART		✓		✓

5.2.5 Obtain Q^*, a targeted estimate of Q

The optimal fluctuations of the initial estimators of $Q_{0,L_{p+1,1}(t)}$ and $Q_{0,L_{p+2,m}(t)}$ based on the clever covariates computed previously, $H^*_{L_{p+1,1}(t)}$ and $H^*_{L_{p+2,m}(t)}$, result in the definition of updated, one-step estimates of $Q_{0,L_{p+1,1}(t)}$ and $Q_{0,L_{p+2,m}(t)}$ denoted by $Q^1_{0,L_{p+1,1}(t),n}$ and $Q^1_{0,L_{p+2,m}(t),n}$ respectively.

Specifically in this analysis, each updated estimate $Q^1_{0,L_{p+1,1}(t),n}$ for $t = 1, 2, 3, 4$ is defined by a separate, t-specific maximum likelihood regression of the outcome at time t, $L_{p+1,1}(t)$, on the clever covariate $H^*_{L_{p+1,1}(t)}$ based on a logistic model with offset equal to the logit transformation of the initial estimate $Q^0_{0,L_{p+1,1}(t),n}$ and based on the same observations at time t that contributed to the initial estimate of $Q_{0,L_{p+1,1}(t)}$, i.e. the updated estimate is defined by

$$Q^1_{0,L_{p+1,1}(t),n} = \frac{1}{1 + exp\big(- (logit(Q^0_{0,L_{p+1,1}(t),n}) + \epsilon_n H^*_{L_{p+1,1}(t)})\big)},$$

where ϵ_n is a maximum likelihood estimate.

Similarly, each updated estimate $Q^1_{0,L_{p+2,m}(t),n}$ for $t = 1, 2, 3$ and $m = 1, 2, 3$ is defined by a separate, (t, m)-specific maximum likelihood regression of the indicator of CD4 count at time t equal to level m, $L_{p+2,m}(t)$, on the clever covariate $H^*_{L_{p+2,m}(t)}$ based on a logistic model with offset equal to the logit transformation of the initial estimate $Q^0_{0,L_{p+2,m}(t),n}$ and based on the same observations at time t that contributed to the initial estimate of $Q_{0,L_{p+2,m}(t)}$. The value of the coefficient in front of the clever covariate in each of the the logistic models defining the one-step estimates above is given in Table 24.

Implementation of the R-TMLE relies on iteration of the updating process described above until a convergence criterion is met: First, starting with $k = 1$, the clever covariates are first re-calculated by Monte Carlo simulations based on the latest updated estimates $Q^k_{0,L_{p+1,1}(t),n}$ and $Q^k_{0,L_{p+2,m}(t),n}$. Second, these latest updated estimates are fluctuated with the newly computed clever covariates to define newly updated estimates $Q^{k+1}_{0,L_{p+1,1}(t),n}$ and $Q^{k+1}_{0,L_{p+2,m}(t),n}$ using the updating process above where the initial estimates $Q^0_{0,L_{p+1,1}(t),n}$ and $Q^0_{0,L_{p+2,m}(t),n}$ are replaced with the latest updated estimates $Q^k_{0,L_{p+1,1}(t),n}$ and $Q^k_{0,L_{p+2,m}(t),n}$. Third, k is incremented by 1. The three-step process just described is repeated until a convergence criterion is met. Once con-

Table 20: DSA-selected estimate of $g_{0,A_1(0)}$ (reminder: $A_1(0)$ represents ART use at time 0). Only the linear part of the working, logistic model that defines the estimate is presented. See Tables 2 and 19 for interpretation of each term.

Intercept	enrollYear	I(yearsHIV=2)	I(yearsHIV=3)	I.race	I(CD4=1)	I(CD4=2)	I(CD4=3)	I(VL=2)	I(VL=3)	clinicalAIDS
−1.089	0.064	−0.363	−0.697	−0.62	2.807	1.972	0.806	−1.257	−1.513	0.712

Table 21: DSA-selected estimates of $g_{0,A_1(t)}$ for $t = 1, 2, 3$ (reminder: $A_1(t)$ represents ART use at time t). Only the linear part of the pooled, working, logistic model that defines the estimates is presented. See Tables 2 and 19 for interpretation of each term.

Intercept	I(riskHIV=MSM)	I(CD4=1)	I(CD4=3)	I(CD4=4)	lastCD4change	ART	sumPastART
−1.619	0.171	0.187	−0.67	−1.277	−0.067	3.877	0.561

Table 22: DSA-selected estimate of $g_{0,A_2(0)}$ (reminder: $A_2(0)$ is the indicator of right-censoring at time 0). Only the linear part of the working, logistic model that defines the estimate is presented. See Tables 2 and 19 for interpretation of each term.

Intercept	I(riskHIV=IDU)	I(censusEdu=4)	I(yearsHIV=2)	everDrug	everSmoke	everObese	enrollYear	I.race	I.riskHIV	clinicalAIDS
−2.505	0.582	0.28	0.258	−0.428	−0.547	−1.771	0.16	0.88	0.637	0.631

Table 23: DSA-selected estimates of $g_{0,A_2(t)}$ for $t = 1, 2, 3$ (reminder: $A_2(t)$ is the indicator of right-censoring at time t). Only the linear part of the pooled, working, logistic model that defines the estimates is presented. See Tables 2 and 19 for interpretation of each term.

Intercept	I(riskHIV=IDU)	everObese	everSmoke	I(ageAtEntry=1)	I(censusInc=1)	enrollYear	I.race	ART	sumPastART
−2.954	0.581	−1.422	−0.584	0.391	0.199	0.25	0.827	−0.619	0.174

Table 24: Estimates ϵ_n of the coefficients in front of the clever covariates in the logistic models defining the one-step, updated estimates of $Q_{0,L_{p+1,1}(t)}$ for $t = 1, 2, 3, 4$ and $Q_{0,L_{p+2,m}(t)}$ for $t = 1, 2, 3$ and $m = 1, 2, 3$.

t	$L_{p+1,1}(t)$	$L_{p+2,1}(t)$	$L_{p+2,2}(t)$	$L_{p+2,3}(t)$
1	0.114	7.544	−24.694	34.977
2	−0.005	5.061	−20.949	29.879
3	0.031	1.886	−2.207	−1.892
4	0.013			

verged, the last updated estimates are referred to as the targeted estimates. A brief description of a convergence criterion is provided below along with the procedure for drawing inference with the R-TMLE based on its influence curve. In this analysis, the updating process for estimation of Q was halted after one iteration, i.e. the estimates $Q^1_{0,L_{p+1,1}(t),n}$ and $Q^1_{0,L_{p+2,m}(t),n}$ were deemed the targeted estimates of $Q_{0,L_{p+1,1}(t)}$ and $Q_{0,L_{p+2,m}(t)}$ denoted by $Q^*_{0,L_{p+1,1}(t),n}$ and $Q^*_{0,L_{p+2,m}(t),n}$ respectively.

5.2.6 A substitution estimator of the parameter of interest

The R-TMLE estimate of the target parameter $\psi_0 = \Psi(Q_0)$ defined by equality (19) is derived by substitution of the relevant distributions Q_0 in the right hand-side of equality (19), i.e. $Q_{0,L(0)}$, $Q_{0,L_{p+1,1}(t)}$ for $t = 1, 2, 3, 4$, and $Q_{0,L_{p+2,m}(t)}$ for $t = 1, 2, 3$ and $m = 1, 2, 3$, with the estimates of the empirical distribution of $Q_{0,L(0)}$ denoted by $Q_{0,L(0),n}$ and the targeted estimates $Q^*_{0,L_{p+1,1}(t),n}$ and $Q^*_{0,L_{p+2,m}(t),n}$ respectively.

Concretely, this substitution estimate can be calculated using the following two-step procedure: First, the conditional expectations $E(Y_{d_\theta}(4) \mid L(0))$ (for $\theta = 200, 350$ and each unique observation of $L(0)$) are approximated by Monte Carlo simulation based on the targeted estimates $Q^*_{0,L_{p+1,1}(t),n}$ and $Q^*_{0,L_{p+2,m}(t),n}$ using the general simulation protocol described previously for the computation of the clever covariates. The resulting estimates of $E(Y_{d_\theta}(4) \mid L(0))$ are denoted by $E_{Q^*_{0,n}}(Y_{d_\theta}(4) \mid L(0))$. Second, these estimates are mapped into the R-TMLE estimate of ψ denoted by $\Psi(Q^*_{0,n})$ using the formula:

$$\Psi(Q^*_{0,n}) = \frac{1}{n}\sum_{i=1}^{n} E_{Q^*_{0,n}}(Y_{d_{350}}(4) \mid L(0) = l_i(0)) - \frac{1}{n}\sum_{i=1}^{n} E_{Q^*_{0,n}}(Y_{d_{200}}(4) \mid L(0) = l_i(0)).$$

Application of this two-step procedure in this analysis lead to the following R-TMLE point estimate of the target parameter ψ_0: 1.98e-03.

5.2.7 Influence curve based inference

Under regularity conditions, the R-TMLE estimator is asymptotically linear with influence curve (Tsiatis (2006); van der Laan (2010)) denoted by $D^*(O \mid Q_0, g_0, \psi_0)$ and given by formula (24) evaluated at Q_0, g_0 and ψ_0, i.e.:

$$\Psi(Q^*_{0,n}) - \psi_0 = \frac{1}{n}\sum_{i=1}^{n} D^*(o_i \mid Q_0, g_0, \psi_0) + o(\frac{1}{\sqrt{n}}) \tag{29}$$

A first order approximation of the variance of the R-TMLE can thus be derived as follows:

$$Var_n(\Psi(Q^*_{0,n})) = \frac{1}{n^2}\sum_{i=1}^{n} D^*(o_i \mid Q_{0,n}, g_{0,n}, \psi_{0,n})^2, \tag{30}$$

where $Q_{0,n}$, $g_{0,n}$ and $\psi_{0,n}$ are consistent estimates of Q, g and ψ respectively. The R-TMLE point estimate was used as the estimate $\psi_{0,n}$ for the computation of the influence curve evaluated at each observation i, i.e. $D^*(o_i \mid Q_{0,n}, g_{0,n}, \psi_{0,n})$, along with the estimates $g_{0,A_1(t),n}$ and $g_{0,A_2(t),n}$. To simplify computation in this

analysis, the influence curve evaluated at each observation i was approximated based on the initial estimate $Q^0_{0,L_{p+1,1}(t),n}$ and $Q^0_{0,L_{p+2,m}(t),n}$ to derive the estimates of all components of $D^*(O \mid Q_{0,n}, g_{0,n}, \psi_{0,n})$ except for the projection $\Pi(D_{IPAW} \mid L(0))$ which was instead approximated using the targeted estimates $Q^*_{0,L_{p+1,1}(t),n}$ and $Q^*_{0,L_{p+2,m}(t),n}$. This simplification permits straightforward calculation of the influence curve evaluated at each observation i, $D^*(o_i \mid Q_{0,n}, g_{0,n}, \psi_{0,n})$, using the intermediate results from the previous computing steps, i.e. the clever covariate calculations based on the initial estimate of Q and the Monte Carlo simulations based on the targeted estimate of Q to derive the substitution estimator, without the need for additional computation. Based on this approach, the estimate of the standard error associated with the R-TMLE is $\sigma_{0,n}$=2.71e-03 resulting in the following 95%-confidence interval for ψ_0: [-3.32e-03;7.28e-03].

The influence curve associated with the R-TMLE can also be used as a convergence criterion to determine whether the updating process leading to the targeted estimate of Q should be halted. Indeed, convergence of the updating process is reached when the estimating equation associated with the efficient influence curve given by formula (24) is solved, i.e. when $\frac{1}{n}\sum_{i=1}^{n} D^*(o_i \mid Q_{0,n}, g_{0,n}, \psi_{0,n}) = 0$. The empirical mean of the influence curve can thus serve as a stopping criterion during the updating process: an empirical mean close to 0 indicates that a solution of the estimating equations is found. The empirical mean of the influence curve approximated with the simplified approach described above is 3.93e-03. For simplicity and because most of the bias reduction in the R-TMLE algorithm typically occurs during the first update of the initial estimate of Q, the updating process for estimation of Q was iterated once only for this analysis leading to the so-called one-step R-TMLE.

5.2.8 Diagnose sparse data bias

Examination of the distribution of the inverse probability of action (IPA) weights, $\left(\prod_{t=0}^{\check{T}} g_{A_1(t)} g_{A_2(t)}\right)^{-1}$, associated with all observations of cancer onset, $Y(\check{T}+1) = 1$, from patients who followed at least one of the two individualized action rules of interest (d_{350} or d_{200}) up to time point $\check{T}$ provides evidence of practical violation of the experimental treatment assignment assumption. As discussed in section 5.4, reliable inference with the R-TMLE is based on the validity of this assumption. Table 25 summarizes the distribution of the IPA weights and indicates that the weights associated with a few observations are relatively large which suggests that dynamic treatment with ART according to at least one of the two rules of interest is almost deterministic based on the levels of covariates that may also be confounders of the effect of ART on the risk of cancer onset.

Table 25: Distribution of the inverse probability of action (IPA) weights.

IPA weights	Frequency	%	Cumulative Frequency	Cumulative %
<10	2523	95.03	2523	95.03
[10, 20[	105	3.95	2628	98.98
[20, 30[	8	0.30	2636	99.28
[30, 40[	5	0.19	2641	99.47
[40, 50[	2	0.08	2643	99.55
[50, 100[	10	0.38	2653	99.92
≥ 100	2	0.08	2655	100.00

To mitigate the higher variability of the R-TMLE resulting from practical violation of the ETA assumption, truncation of the IPA weights can be used as part of the R-TMLE implementation to improve the mean squared error associated with R-TMLE estimation of the target parameter. Based on the distributions of the IPA weights in this analysis, we used a truncation level of 20 for the implementation of the R-TMLE, i.e. the clever covariates on which implementation of the R-TMLE is based were computed based on IPA weights which were set to 20 if their values implied by the estimates $g_{0,A_1(t)}$ and $g_{0,A_2(t)}$ were greater than 20. The point estimate and estimate of the standard error associated with the R-TMLE based on truncated IPA weights is $\Psi(Q^*_{0,n})$=1.44e-03 and $\sigma_{0,n}$=2.68e-03 respectively which results in the following 95%-confidence interval for ψ_0: [-3.81e-03;6.69e-03].

5.3 IPAW-R-TMLE implementation and results

To account for potential time-dependent confounding that was ignored by the R-TMLE as a consequence of the data reduction step, the IPAW-R-TMLE relies on an estimate of the true action mechanism, i.e. the components of the action mechanism defined by equality (3) and denoted by $g_{A_1(t)}$ and $g_{A_2(t)}$. These conditional distributions should not be confused with the components of the reduced data action mechanism that were estimated in the previous section (see Tables 20 through 23) as part of the R-TMLE implementation and that we now denote with $g^r_{A_1(t)}$ and $g^r_{A_2(t)}$. Estimates of $g_{A_1(t)}$ and $g_{A_2(t)}$ for $t = 0, 1, 2, 3$ were obtained based on sieve estimation with the same estimator selection procedures implemented previously to obtain estimates of $g^r_{A_1(t)}$ and $g^r_{A_2(t)}$ for $t = 0, 1, 2, 3$ with the difference that the potential main terms in the working, logistic models involved in each of the four estimator selection procedures for estimation of $g_{A_1(t)}$ and $g_{A_2(t)}$ for $t = 1, 2, 3$ consist of not only the variables in Table 19 but also the following time-dependent variables: $L_{18}(t)$ ('VL'), $L_{19}(t)$ ('clinicalAIDS'), $L_{20}(t)$ ('I.CD4'), $L_{21}(t)$ ('I.VL') and $L_{20}(t) - L_{20}(t-1)$ ('I.lastCD4change'). The estimates resulting from the application of the four estimator selection procedures to estimate $g_{A_1(t)}$ and $g_{A_2(t)}$ for $t = 0, 1, 2, 3$ are presented in Tables 20, 28, 22 and 29. Note that the estimates for $g_{A_1(0)}$ and $g_{A_2(0)}$ are identical to the estimates for $g^r_{A_1(0)}$ and $g^r_{A_2(0)}$ since $g_{A_1(0)} = g^r_{A_1(0)}$ and $g_{A_2(0)} = g^r_{A_1(0)}$. The initial estimates of $Q_{0,L_{p+1,1}(t)}$ and $Q_{0,L_{p+2,m}(t)}$ were derived by refitting the logistic models of Tables 15 through 18 with weights equal to $w(t) \equiv \frac{\prod_{j=0}^{t-1} g^r_{A_1(t)} g^r_{A_2(t)}}{\prod_{j=0}^{t-1} g_{A_1(t)} g_{A_2(t)}}$. Note that $w(1) = 1$ and thus the initial estimates of $Q_{0,L_{p+1,1}(1)}$ and $Q_{0,L_{p+2,m}(1)}$ for implementation of the IPAW-R-TMLE are the same as the initial estimates of $Q_{0,L_{p+1,1}(1)}$ and $Q_{0,L_{p+2,m}(1)}$ for implementation of the R-TMLE (see Tables 15 and 17). For $t > 0$, the initial estimates of $Q_{0,L_{p+1,1}(t)}$ and $Q_{0,L_{p+2,m}(t)}$ for implementation of the IPAW-R-TMLE are presented in Tables 30 and 31. The clever covariates for fluctuation of the initial estimates of $Q_{0,L_{p+1,1}(t)}$ and $Q_{0,L_{p+2,m}(t)}$ were computed with Monte Carlo simulations as described for the R-TMLE with the only difference that these Monte Carlo simulations were based on the estimates of $Q_{0,L_{p+1,1}(t)}$ and $Q_{0,L_{p+2,m}(t)}$ from Tables 15, 30, 17, and 31 instead of the estimates from Tables 15 through 18. The updated, one-step estimates of $Q_{0,L_{p+1,1}(t)}$ and $Q_{0,L_{p+2,m}(t)}$ were derived based on the updating procedure used for implementation of the R-TMLE with the difference that the logistic models were fitted with the weights $w(t)$ defined above. The value in front of the clever covariate in each of the logistic models defining the one-step estimates of $Q_{0,L_{p+1,1}(t)}$ and $Q_{0,L_{p+2,m}(t)}$ is presented in Table 26. These one-step estimates were deemed the targeted estimates of $Q_{0,L_{p+1,1}(t)}$ and $Q_{0,L_{p+2,m}(t)}$.

Table 26: Estimates ϵ_n of the coefficients in front of the clever covariates in the logistic models defining the one-step, updated estimates of $Q_{0,L_{p+1,1}(t)}$ for $t = 1, 2, 3, 4$ and $Q_{0,L_{p+2,m}(t)}$ for $t = 1, 2, 3$ and $m = 1, 2, 3$ for the implementation of the IPAW-R-TMLE.

t	$L_{p+1,1}(t)$	$L_{p+2,1}(t)$	$L_{p+2,2}(t)$	$L_{p+2,3}(t)$
1	0.114	7.980	−19.327	33.373
2	−0.050	5.385	−21.797	−2.666
3	0.043	1.791	−11.161	27.413
4	0.013			

The resulting substitution estimate of the target parameter ψ_0 is equal to 1.41e-03 and corresponds to the one-step IPAW-R-TMLE point estimate. Note that the only difference in implementation of the R-TMLE point estimate versus that of the IPAW-R-TMLE point estimate is in the use of the weights $w(t)$ to obtain the initial and updated estimates of $Q_{0,L_{p+1,1}(t)}$ and $Q_{0,L_{p+2,m}(t)}$. Inference with the IPAW-R-TMLE can be derived based on its influence curve (24) evaluated at the estimator of the action mechanism g and the targeted estimator of Q defined by the procedure above. Note that evaluation of formula (24) to derive inference with the IPAW-R-TMLE involves the estimates of $g_{A_1(t)}$ and $g_{A_2(t)}$ instead of the estimates of $g^r_{A_1(t)}$ and $g^r_{A_2(t)}$, i.e. the clever covariates used for fluctuation of the initial estimators of Q in the implementation of the IPAW-R-TMLE should be multiplied by $w(t)$ to derive the clever covariates that appear in formula (24). Based on this approach and the same implementation shorcut employed earlier to simplify calculation of the R-TMLE influence curve evaluated

at each observation i, the estimate of the standard error associated with the IPAW-R-TMLE is $\sigma_{0,n}$=2.48e-03 resulting in the following 95%-confidence interval for ψ_0: [-3.45e-03;6.27e-03].

Table 27 summarizes the distribution of the estimated IPA weights, $\left(\prod_{t=0}^{\check{T}} g_{A_1(t)}g_{A_2(t)}\right)^{-1}$, associated with all observations of cancer onset, $Y(\check{T}+1)=1$, from patients who followed at least one of the two individualized action rules of interest (d_{350} or d_{200}) up to time point $\check{T}$. A few observations are characterized by relatively large IPA weights (>20) which suggests some practical violation of the ETA assumption discussed in section 5.4. The ratios $w(t)$ of the IPA weights, $\left(\prod_{t=0}^{\check{T}} g_{A_1(t)}g_{A_2(t)}\right)^{-1}$, summarized in Table 27 to the IPAW weights, $\left(\prod_{t=0}^{\check{T}} g^r_{A_1(t)}g^r_{A_2(t)}\right)^{-1}$, summarized in Table 25 ranges from 0.35 to 2.01. Thus, to mitigate the higher variability of the IPAW-R-TMLE resulting from practical violation of the ETA assumption, the IPAW-R-TMLE was implemented as described above with the difference that the clever covariates were computed based on reduced data IPA weights, $\left(\prod_{t=0}^{\check{T}} g^r_{A_1(t)}g^r_{A_2(t)}\right)^{-1}$, that were truncated at 20. The point estimate and estimate of the standard error associated with this truncated IPAW-R-TMLE is $\Psi(Q^*_{0,n})$=7.6e-04 and $\sigma_{0,n}$=2.46e-03 respectively which results in the following 95%-confidence interval for ψ_0: [-4.07e-03;5.59e-03].

Table 27: Distribution of the inverse probability of action (IPA) weights.

IPA weights	Frequency	%	Cumulative Frequency	Cumulative %
<10	2544	95.82	2544	95.82
[10, 20[	80	3.01	2624	98.83
[20, 30[	15	0.56	2639	99.40
[30, 40[	3	0.11	2642	99.51
[40, 50[	2	0.08	2644	99.59
[50, 100[	9	0.34	2653	99.92
$\geq$ 100	2	0.08	2655	100.00

Table 28: DSA-selected estimates of $g_{0,A_1(t)}$ for $t = 1, 2, 3$ (reminder: $A_1(t)$ represents ART use at time t) for implementation of the IPAW-R-TMLE. Only the linear part of the pooled, working, logistic model that defines the estimates is presented. See Tables 2 and 19 for interpretation of each term.

Intercept	clinicalAIDS	I.CD4	I(CD4=4)	I(CD4=3)	lastCD4change	I(VL=4)	lastART	sumPastART
−1.429	0.362	−1.607	−1.205	−0.651	−0.084	1.213	4.164	0.457

Table 29: DSA-selected estimates of $g_{0,A_2(t)}$ for $t = 1, 2, 3$ (reminder: $A_2(t)$ is the indicator of right-censoring at time t) for implementation of the IPAW-R-TMLE. Only the linear part of the pooled, working, logistic model that defines the estimates is presented. See Tables 2 and 19 for interpretation of each term.

Intercept	I(riskHIV=IDU)	everObese	everSmoke	I(ageAtEntry=1)	enrollYear	I.race	I.lastCD4change
−3.144	0.613	−1.41	−0.586	0.407	0.25	0.801	0.408

Table 30: Initial estimates of $Q_{0,L_{p+1,1}(t)}$ for $t = 2, 3, 4$ (reminder: $L_{p+1,1}(t)$ is the outcome at time t) for implementation of the IPAW-R-TMLE. Only the linear part of the pooled, working, logistic model that defines the estimates is presented. See Tables 2 and 14 for interpretation of each term.

Intercept	I(ageAtEntry=1)	everDrug	ART	I(CD4=1)	sumPastART
−5.846	−1.084	0.557	1.8	1.381	−0.767

Table 31: Initial estimates of $Q_{0,L_{p+2,m}(t)}$ for $t = 2, 3$ and $m = 1, 2, 3$ (reminder: $L_{p+2,m}(t)$ is the indicator that the CD4 level at time t is equal to m) for implementation of the IPAW-R-TMLE. Only the linear part of the pooled, working, logistic model that defines the estimates is presented. See Tables 2 and 14 for interpretation of each term.

Intercept	m	sex	I(yearsHIV=1)	I(VL.0=2)	I(CD4.0=4)	lastCD4change	I(CD4=1)	I(CD4=2)	I(CD4=4)	ART
−6.061	2.367	−0.328	−0.191	0.245	−0.404	0.543	5.105	2.098	−2.39	−0.642

5.4 Assumptions

Valid causal inference based on the IPAW-R-TMLE of the target parameter ψ_0 relies on the following assumptions:

- **The sequential randomization assumption (SRA) or sequential deconfounding (SD).** The validity of any of these two assumptions insures that sufficient information is collected to possibly identify the effect of interest with the observed data based on the G-computation formula (17). Both the SRA and SD are not testable with the data alone but may be motivated based on a graphical model that encodes subject-matter assumptions about the causal links between the variables involved in the problem, i.e. a causal directed acyclic graph (DAG) as the one implied by Figure 2. Based on such a DAG, satisfaction of independencies that involve counterfactual variables like the SRA expressed by formula (16) may be evaluated with the twin network method described in section 7.1.4 of Pearl (2009). Alternatively, SD may be evaluated with the DAG based on the simpler sequential back-door criterion described in sections 4.4.3 and 11.3.7 of Pearl (2009): In the DAG implied by Figure 2, the sequential back-door criterion is met since every action-avoiding back-door path from $A(t)$ to $Y(K+1)$ is blocked by $\bar{L}(t)$ and $\bar{A}(t-1)$ for $t = 0, \ldots, K$.

- **The experimental treatment assignment (ETA) assumption (a.k.a. positivity assumption).** It insures that the conditional distributions of the observed data in the G-computation formula (17) are well-defined and thus insures the non-parametric identifiability of the target parameter ψ_0. In other words, satisfaction of the ETA assumption permits reliable estimation of the target parameter based on true information in the data instead of extrapolation from limited information based on parametric modeling assumptions (see section 10.1 of Gelman and Hill (2007)). Formally (van der Laan (2006); Orellana et al. (2006)), this assumption insures that any patient may follow any of the two individualized treatment rules of interest at any point in time:

$$g_0(A(t) = d_\theta(\bar{L}(t)) \mid \bar{L}(t), \bar{A}(t-1) = d_\theta(\bar{L}(t-1))) > 0 \quad F_X \text{ a.e. for } t = 0, \ldots, K.$$

  Practical violation of this assumption may be tested with the data by exploring the distribution of the inverse probability of action weights as implemented in this analysis. Minor practical violation of the ETA assumption may be handled by weight truncation (Cole and Hernan (2008); Bembom and van der Laan (2008)) as described earlier to potentially improve the mean squared error associated with estimation of the target parameter. Major violations of this assumption indicate however that reliable inference is not possible with the available data and motivate the alteration of the goal of the analysis through the definition of a 'less ambitious' target parameter (Moore et al. (2009); Petersen et al. (2010)).

- **Consistent estimation of the treatment mechanism.** This assumption motives the application of a data-adaptive estimation procedure as the one implemented in this analysis based on the DSA algorithm to estimate g defined by formula (3) as an alternative to the more common reliance on a priori specification of parametric models which often do not reflect true subject-matter knowledge and may thus lead to incorrect inference for the target parameter ψ_0.

6 Discussion

Table 32 summarizes the results from the application of each estimator of the target parameter ψ_0 implemented in this analysis. Note that all inferences are consistent: The null hypothesis of a null effect ψ_0 may not be rejected based on the data from the KPNC electronic medical record and the three assumptions described above.

If the three assumptions on which these estimators rely for drawing valid causal inference indeed hold, the null result may reflect a truly null effect, bias due to the erroneous inclusion of patients with a prevalent AIDS-defining cancer at study entry, and/or a lack of power to detect a relatively small[9] causal risk difference

[9]The 95% confidence intervals suggest that the absolute value of the true causal risk difference is less than 1%.

Table 32: Comparison of the results from the application of each estimator of the target parameter ψ_0. The estimate of the standard error of the IPAW estimators are based on 1,000 bootstrap samples. The estimator selection procedures were not repeated for each bootstrap sample to estimate the action mechanism. Instead, the estimators selected on the original sample were applied to each bootstrap sample resulting in new estimates for the action mechanism. The truncated IPAW estimators based on the truncation level of 20 resulted in the same output (i.e. the IPA weights - based on either g or g^r - associated with all events occurring under one of the two rules of interest were lower than 20).

Estimator	Point estimate	Standard error	95% confidence interval	p-value
R-IPAW (based on g^r)	1.42e-03	2.69e-03	[-3.86e-03 ; 6.69e-03]	0.6
R-TMLE	1.98e-03	2.71e-03	[-3.32e-03 ; 7.28e-03]	0.46
truncated R-TMLE	1.44e-03	2.68e-03	[-3.81e-03 ; 6.69e-03]	0.59
IPAW (based on g)	6.9e-04	2.48e-03	[-4.16e-03 ; 5.54e-03]	0.78
IPAW-R-TMLE	1.41e-03	2.48e-03	[-3.45e-03 ; 6.27e-03]	0.57
truncated IPAW-R-TMLE	7.6e-04	2.46e-03	[-4.07e-03 ; 5.59e-03]	0.76

between the two adaptive treatment strategies of interest in this analysis. Below, we comment on three possible explanations before discussing possible reasons for potential estimation bias due to violation of one or more of the three identifiability assumptions.

Prior research evaluating appropriate treatment rules for initiation of ART have not evaluated cancers specifically. Instead, studies have focused on more common outcomes, including all AIDS-defining events, which includes these cancers, or all-cause mortality. Recent studies for these events have indicated that initiation of ART at higher CD4 thresholds may reduce the risk of AIDS and death (Hernan et al. (2006); Kitahata et al. (2009); Sterne et al. (2009)).

This analysis was restricted to the first two years of follow-up during which two thirds of all observed onsets of AIDS-defining cancers occurred: Out of the corresponding 118 events, 13 occurred to patients who only followed rule d_{200} at the time of the event, 12 occurred to patients who only followed rule d_{350} at the time of the event, 51 occurred to patients who followed both rules at the time of the event, and 42 occurred to patients who followed none of these two rules at the time of the event. The extension of this analysis to follow-up data past two years after study entry (i.e. $K > 3$) may provide additional power to detect a larger, delayed differential cumulative risk of cancer onset between the two adaptive treatment strategies of interest. In addition, an analysis to study the effects of 1) adaptive treatment strategies that allow for a grace period between the time a CD4 threshold is reached and the time ART is initiated (Cain et al. (2010)), and/or 2) adaptive treatment strategies that are indexed by CD4 thresholds that are not restricted to two levels only but that would instead include many levels θ (e.g. CD4 levels from 200 to 500 by increments of 50 cells/μl) may permit the inclusion of observations that are currently excluded from the analysis as they do not concord with the two rules d_{200} and d_{350}. These observations may permit the relatively precise estimation of causal estimands defined by a parametric, working, Cox dynamic marginal structural model from which the causal contrast ψ_0 can be derived and possibly more precisely estimated under the smoothing assumptions encoded in such a model, e.g. the working model $\lambda_{T_{d_{200}}(t)} \exp(\beta(\theta - 200))$ for $\lambda_{T_{d_\theta}}(t)$ where $\lambda_{T_{d_\theta}}(t)$ represents the instantaneous hazard of cancer at time t if the target population were to follow rule d_θ. The computing and programming difficulties involved in the estimation of such a causal estimand β with the TMLE are currently deterrents[10] to the application of the TMLE in such modeling approaches and are topics for potential future development of the application of targeted maximum likelihood learning.

An alternative explanation for the null finding is the incorrect inclusion of prevalent cancers in the analysis. About 30% and 20% of patients in the cohort had a CD4 count at study entry below 200 cells/μl and between 200 and 350 cells/μl respectively. It is possible that many of these HIV patients had existing, but undiagnosed

[10]These difficulties are compounded by the decision to discretize the time line in finer intervals (e.g. $\tau = 30$).

cancers at study entry when they also initiated ART. If these patients remained treated with ART through out follow-up, the data from such patients with a CD4 count at study entry below 200 cells/μl were then deemed consistent with following both rules d_{200} and d_{350} up to cancer diagnosis while data from such patients with a CD4 count at study entry between 200 and 350 cells/μl were then deemed consistent with following only rule d_{350}. The inclusion of patients with undiagnosed ADC at study entry could thus have resulted in over estimation of the risk of cancer onset under both rules, with the over estimation of the risk under rule d_{350} being possibly of a larger magnitude.

The SRA/SB assumptions may be violated in this analysis due to measurement error for some of the baseline covariates (overweight or obese status, smoking, alcohol and drug use) which were not captured by the KPNC electronic medical record for research purposes, but rather for clinical use. These variables, however, are not expected to have a strong effect on ART prescription decisions, thus mitigating the concern of bias due to mis-classification of these attributes. Practical violation of the ETA assumption is not a primary concern in this analysis since only about 1% of the observations that contributed to the estimate suffered from large IPA weight with even fewer weights deemed 'extreme'. This analysis was not concerned with theoretical violation of the ETA assumption. ART initiation is essentially based on CD4 counts and symptomatic AIDS in clinical practice. Concern that 'clinicalAIDS' may deterministically determine which adaptive treatment strategies may be followed by a patient may be handled by modifying the individualized rules such that ART initiation is not only based on a CD4 count threshold but also AIDS status. Theoretical violation of the ETA assumption due to non-compliance with ART once treatment is initiated and due to right-censoring caused by death may be handled by the consideration of intention-to-treat individualized treatment rules (Cain et al. (2010)) and by including death as an end point in an analysis with a combined outcome definition. Only classes of models with no more than 10 terms and with no interaction terms were considered as part of the data-adaptive estimation approach for g implemented in this analysis. Such decisions may be too restrictive and may have led to biased estimation of the treatment mechanism. More aggressive data-adaptive procedures (van der Laan et al. (2007)) may be considered to alleviate this concern.

Finally, note that the inference from the IPAW and TMLE estimators in this analysis do not significantly differ. In general, inference with the IPAW-R-TMLE may provide additional robustness compared to the IPAW estimator if no time-dependent covariates other than the one retained in the reduced data structure confound the effect of interest since the IPAW-R-TMLE estimator is then doubly robust (van der Laan (2008)). In most real life applications however, several time-dependent covariates confound the effect of interest and while both the IPAW (based on g) and IPAW-R-TMLE estimators may estimate the effect of interest consistently based on the same three assumptions described above, the IPAW-R-TMLE estimator may provide a more precise effect estimate when the time-dependent covariate retained in the reduced data structure has a relatively strong effect on the outcome of interest (van der Laan (2008)). In this analysis, there was no clear gain in estimation precision achieved by the IPAW-R-TMLE over the IPAW estimator which may be explained by a relatively weak effect of CD4 count on the onset of AIDS-defining cancer or by a suboptimal data-adaptive estimation procedure for modeling the relevant Q part of the reduced data likelihood. A more aggressive data-adaptive procedures (van der Laan et al. (2007)) that includes weighting by the IPA weights based on g may be considered to alleviate this concern.

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