

Comparing Marginal Structural Cox Proportional Hazards Models (MSCM) to Standard Methods for Estimating Causal Effects of ART on the Survival of HIV-Infected Patients in a Regional Referral Hospital in Western Kenya, 2011-2014

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Abstract- Estimating causal inferences in observational studies with time varying covariates require methods that can address complexities such as non-random allocation of patients' to treatment groups, possible censoring of, exposure variables e.g., time to antiretroviral therapy (ART) initiation, and outcome variables e.g., mortality. Marginal Structural Cox Proportional Hazard Model (MSCM) adopts inverse probability of treatment and censoring weights to correct for non-random allocation of treatment groups, patient attrition or administrative censoring and confounding. We set out to evaluate the causal effects of 'time to ART initiation' on the survival of human immunodeficiency (HIV) infected patients enrolled in Jaramogi Oginga Odinga Teaching and Referral Hospital (JOTRH), a high HIV-burden hospital in Western Kenya. A retrospective review of observational data was conducted at JOTRH for patients aged ≥ 15 years enrolled between May 2011 and December 2013. Patients were categorized as 'early initiators' if they were initiated on ART within 12 weeks of determination of ART eligibility and 'late initiators' if they were initiated on ART after. We compared the results from MSCM to those from unadjusted standard Cox Proportional Hazard (Cox-PH) model and adjusted standard Cox-PH model (adjusting for age, gender, CD4 category, WHO stage, education level, marital status, and weight) to assess the extent to which standard methods can bias estimates for causal effects. Of 786 patients enrolled; 606 (77%) were ART-eligible of whom 444 (73%) had documented dates of ART initiation. Among patients who were initiated on ART, 41 (9%) were late-initiators. There were 3 deaths and 9.2 person-years of follow-up and 31 deaths and 115.8 person-years of follow-up among 'late-initiators' and 'early-initiators' respectively. Compared to 'early-initiators', the hazard of dying among 'late-initiators' computed using unadjusted standard Cox-PH model, adjusted standard Cox-PH model and MSCM was 1.6 (95% CI 0.5-5.4) and 1.9 (95% CI 0.5-6.7) and 3.2 (95% CI 1.7-6.4) respectively. Delays in ART initiation was associated with an increased risk of mortality only after employing MSCM. When randomized trials are not feasible due to costs or ethical concerns, causal inference could still be deduced from longitudinal observational data by applying appropriate causal models.

Index Terms- Censoring, Hazard ratios, Inverse probability of treatment and censoring weights, Marginal structural Cox-PH models, Stabilized weights

I. INTRODUCTION

In 2014, sub-Saharan Africa bore over two-thirds of the global Human Immunodeficiency Virus (HIV) burden and 66% of HIV-related deaths[1]. Without antiretroviral therapy (ART), majority(80%) of HIV-infected persons will have CD4 depletion and high HIV viraemia in approximately 8 years and once the infection has progressed to HIV/AIDS, death will occur within 2 years[2]. Survival with HIV infection however, has increased over time with the increasing use of ART [3].

Randomized Clinical Trials (RCTs), are the benchmark for evaluating causal inferences due to, (i) their inherent characteristics of unbiased assignment of treatment categories and therefore balancing both known and unknown prognostic factors and, (ii) the guarantee accorded to the validity of statistical tests of significance for the tested hypotheses[4-7]. However, RCTs are not always feasible; they are further complicated by ethical concerns in treatment assignment especially where the beneficial effects of treatment have been established [8-10]. Therefore, the effect of ART on patient survival has routinely been deduced from observational data comparing the pre-ART era to the ART era[3].

On the other hand, there are intrinsic complexities associated with estimating the effect of ART on survival of HIV-infected patients from observational data, (i) the non-random allocation of patients into treatment groups, (ii) the possibility of censoring of exposure variables (e.g. time to ART initiation which also impacts on patients' survival) due to attrition, death or close of the dataset (administrative censoring), (iii) the possibility of censoring of outcome variables (e.g. mortality) either at the close of the dataset (administrative censoring), or due to patient attrition[11] and (iv) time-dependent confounders i.e., covariates which "...influence decisions whether and when to switch (read: initiate) therapy and also affect mortality; therefore adjustment for confounding by these variables is needed..." [12]. CD4 counts are considered time-dependent confounders. This is because ART is only initiated when CD4 counts have reduced to predefined cut offs (impact on treatment

initiation), and CD4 count increase (or lack of it thereof) affects the prognosis of the disease (impact on outcome) [13, 14].

The standard Cox Proportional Hazards (Cox-PH) model (crude or covariates-adjusted) can be utilized for time-to-event outcomes. However, Cox-PH model does not adjust for time-dependent confounders and may therefore yield biased results in assessing the causal effects of time to ART initiation on the mortality of HIV-infected patients [13]. Marginal Structural Cox-PH Model (MSCM) provide a natural extension to the standard Cox-PH model as it can be used to estimate the causal effect of time-dependent exposures (e.g. 'time to ART initiation' which varies between patients), in the presence of time-dependent confounders (e.g. CD4 counts), on time-dependent outcomes (e.g. patients survival; alive or dead). Additionally, in observational studies, MSCM adjusts for non-random allocation of patients into treatment groups [13-15]. Patient attrition, which is common in Africa, may lead to unrepresentativeness of the data and selection bias, a limitation that is counteracted by MSCM by adjusting for censoring due to attrition [11, 16]. With a dataset rich with information on confounders, MSCM makes robust inferences about time-dependent exposures [9].

B. Objective Statement

We set out to evaluate causal effects of 'time to ART initiation' on the survival of HIV-infected patients using MSCM adopting Inverse Probability of Treatment and Censoring Weights (IPTCW) to correct for non-random allocation of treatment groups, patient attrition or administrative censoring and confounding at a regional referral hospital in a high HIV-burden area in Western Kenya. We purposed to compare the results from MSCM to those from standard Cox-PH model in order to assess the extent to which standard methods can bias estimates for causal effects.

II. METHODS

A. Study design and setting

A retrospective review of routinely collected data (observational data) was conducted at the Jaramogi Oginga Odinga Teaching and Referral Hospital (JOOTRH) HIV clinic to describe the effect of a time-dependent exposure ('time to ART initiation') on patient survival while considering time-dependent confounders (CD4 count). JOOTRH, a regional referral public hospital, is located in Kisumu County, western Kenya. Kisumu County's HIV prevalence (18.7% against a national average of 5.6%) is ranked second in HIV prevalence among the 47 counties in Kenya [17]. JOOTRH HIV clinic, which was inceptioned in 2003, has a cumulative patient enrollment of approximately 23,000, and 6,000 patients currently enrolled in care (L. Nguti, personal communication, October 22, 2014). The clinic is supported by the research and public health collaboration between Kenya Medical Research Institute (KEMRI) and the US Centers for Disease Control and Prevention (CDC) through *President's Emergency Plan for AIDS Relief* (PEPFAR).

B. Study population

This included all ART-naïve HIV-infected male and non-pregnant female patients aged ≥ 15 years enrolled at the HIV clinic between May 2011 and December 2013.

C. Clinical care

At the JOOTRH HIV clinic, all patients are routinely initiated on Cotrimoxazole Preventative Therapy (CPT) at enrolment for prophylaxis against opportunistic infections. At initial and subsequent visits, all patients are reviewed to determine ART-eligibility, the presence of opportunistic infections, and other comorbidities. If deemed ART eligible using the WHO 2010 ART guidelines that were then in use, patients would be initiated on ART within 2 weeks of eligibility, or the earliest possible depending on their clinical and psychological preparedness [17-19]. After ART initiation, patients would be reviewed within 2 weeks to assess for the presence of adverse drug reactions. Patients would subsequently visit the clinic monthly for prescription refills, and quarterly for a clinical consultation to determine response to treatment, and to review progress of disease. Patients who are not ART-eligible at any visit would continue visiting the clinic monthly for CPT prescription refills, and would be assessed bi-annually to determine the most appropriate time for ART initiation. Details of clinic follow up visits have been described by Kimeu et al. [18].

D. Allocation to treatment groups (exposure)

All ART-eligible patients were either initiated on ART at enrolment or during the follow-up period, or not initiated on ART at enrolment or any point during the follow up period. Among patients initiated on ART, 'time to ART initiation' was defined as the time from the earliest determination of ART eligibility (by WHO stage of disease or CD4 counts or both) to date of ART initiation. Patients were categorized as early-initiators (ART initiated within 12 weeks of determination of ART-eligibility) or late-initiators (ART initiated ≥ 12 weeks after determination of ART-eligibility) [19]. This categorization was chosen empirically based on the period it takes for ART to achieve steady state [20]. 'Time to ART initiation' would be determined by the attending physician based on comorbid conditions that may have influenced the decision to initiate ART, or determined by the patient's psychological preparedness or other psychosocial factors [19]. Compared to RCTs where selection into treatment categories is by chance, treatment selection in these patients was non-random.

E. Patient follow-up

This analysis focused on patients who were ART-eligible between 1st May, 2011 and 31st December, 2013. ART-eligible patients were followed-up from the time of eligibility to 30th September, 2014 to ascertain exposure ('time to ART initiation') for a total duration of 0.17-3.75 years. After ART initiation, patients were then followed up to 31st March, 2015 to ascertain the outcome (death) for a total duration of 0.50-4.00 years.

At the end of the follow up period, patients were either, alive, or may have died, or left the facility (either they formally transferred to other HIV clinics or were lost to follow up, LTFU). This categorization was done based on the unavailability of

patient outcomes for both these groups of patients. Definition of patient status as ‘alive’, ‘dead’, ‘LTFU’, or ‘transferred out’ in this facility has been described by Kimeu et al. [18].

F. Outcome ascertainment and computation of ‘time to event’

The primary outcome of interest was occurrence of ‘all-cause mortality’ among the HIV-infected patients. Death ascertainment has been described elsewhere by Kimeu et al [18]. For this analysis the primary outcome of interest (death), a ‘time to event’ outcome, was computed as the time accrued from ART-initiation to, (i) death, (ii) leaving the facility or (iii) close of the dataset (administrative censoring on 31st March, 2015).

G. Patient categories based on ‘exposure’ (ART initiation) and ‘outcome’ (death)

The main exposure variable ‘time to ART initiation’ was administratively censored at 30th September, 2014 while the outcome (death) was administratively censored at 31st March, 2015. Due to censoring (by administrative closure, death, or leaving the facility), the following six exposure-outcome scenarios were possible (Figure 1) observed.

- a) Both exposure and outcome were observed before end of the follow up period
- b) Exposure was observed but outcome was **not** observed due to patient leaving the facility before end of the follow up period
- c) Exposure observed but outcome was **not** observed due to administrative censoring at the end of the follow up period
- d) Both exposure and outcome were **not** observed due to patient leaving the facility before the end of the follow up period
- e) Exposure was **not** observed due to death occurring before ART initiation
- f) Both exposure and outcome were **not** observed due to administrative censoring at the end of the follow up period

Patients groups d), e), and f) were further excluded from the analysis because the exposure (‘time to ART initiation’) was not

Figure 1: Patient categories in relation to the exposure (ART initiation) and Outcome (death)

Exposure (ART Initiation)	End of Study
Left facility (d)	Alive at end of study (f)
Died (e)	
Not started on ART	
Started on ART Died (a)	
Started on ART Left facility (b)	
Started on ART	
	Alive at end of study (c)

H. Data collection

We collected patients’ demographic data (e.g., age, gender, education level, marital status, referral source etc.), clinical characteristics (CD4 counts, WHO staging), prescriptions both at enrollment and follow-up visits and patient outcomes during and at the end of the follow-up period, from the electronic patient database. For this analysis, the baseline covariates included, age, gender, education level, marital status, weight, CD4 counts at enrolment, and WHO stage at enrollment. The time-varying covariates included the most recent CD4 counts and WHO stage.

I. Data analysis

Data analysis was done by fitting Cox-PH models to obtain Hazard ratios and Kaplan-Meier survival curves. Data analysis

was done using SAS version 9.3 [21] while graphs were created using R version 3.2.1. [22].

Computation of Hazards ratios using Cox-PH models

To compute causal effects of ‘time-to-ART initiation’ on survival of HIV-infected patients, threemodels were fitted:

1. The standardunadjusted Cox-PH model
2. The standardCox-PH model adjusted for baseline covariates
3. MSCM adjusting for censoring and bias due to nonrandom allocation of treatment groups

Standard Cox-PH models unadjusted and adjusted for baseline covariates (Model 1 and 2)

The proportionality assumption of the standard Cox-PH models (Model 1 and 2) was assessed using two methods: i) graphical plot of 'log-negative-log' of the Kaplan-Meier estimator of survival function and, ii) graphical plot of Schoenfeld residuals. Survival curves for the Kaplan-Meier estimator were presented for each covariate for which assumptions were being verified, and the distance between the survival curves for early and late initiators was not expected to change over time for the proportionality assumption to hold. The plot of 'log-negative-log' of the Kaplan-Meier estimator of survival function revealed that distance between curves of the exposure variable ('early-initiators' vs. 'late-initiators') was not constant for all values of time. The plot of the Schoenfeld residuals, which were expected to have a mean of zero and not to show a trend over time, also suggested non-proportional hazards in the exposure variable (plots not shown). The proportionality assumption was therefore violated in both Models 1 and 2.

To mitigate on violations of proportionality of the Cox-PH model, we included the following in the model; i) for covariates which the proportionality assumption was violated, their interactions with time-to-death to create an interaction model, and ii) a stratification variable (that was not the primary exposure i.e. 'time to ART initiation') that would violate the proportionality assumption to create a stratification model. We selected the CD4 category as our stratification variable [23]. We compared the interaction model to the stratification model using the information criteria values (-2LogLikelihood) and partial likelihood function values (Akaike Information criterion [AIC], Schwarz's Bayesian criterion [SBC]). We chose the model with the minimum values for information criteria and partial likelihood function in both the unadjusted and adjusted Cox-PH model [24].

Cox proportional hazards were used to compare the risks of death between 'early'- and 'late' initiators, with and without adjusting for baseline covariates. Hazard ratios (HR) with corresponding 95% confidence intervals were reported. Robust sandwich estimator was used to provide conservative 95% confidence intervals to account for uncertainty in estimation of both the model and weights. This is because confidence intervals are function of the standard error which is derived from the variance [14, 25, 26]. Statistical significance was considered at α -level of 5% [27].

Marginal Structural Cox Proportional Hazards Model (MSCM) (Model 3)

The complexities associated with assessing causal inference of time-to-ART initiation on mortality among HIV-infected patients were addressed by computing Inverse Probability of Treatment Censoring Weights (IPTCW) as follows:

- a. To control for non-random allocation of time-to-ART initiation, Inverse Probability of Treatment Weights (IPTW) were used
- b. To control for censoring of outcome (death) due to dropout and leaving the facility, Inverse Probability of Censoring Weights (IPCW) were used

The Inverse Probability of Treatment and Censoring Weights (IPTCW), for each patient, is the product of IPTW and IPCW assuming no unmeasured confounders for treatment and censoring.

We will illustrate how these were used to address the complexities listed in patient groups a), b) and c) above.

Computing the Inverse Probability of Treatment Weights (IPTW)
A logistic regression model was used; the binary response variable was 'time to ART initiation' (early/late ART initiation) with baseline characteristics; age, gender, education level, marital status, weight, CD4 counts, and WHO stage as covariates. Each patient was assigned a weight based on his/her probability of commencing ART at a time interval in which they actually commenced treatment (p^i); the IPTW was computed as an inverse of the probability ($1/p^i$). The probability of treatment assignment for each patient tends to vary greatly and may be affected by probable extreme propensity scores; this may result in large weights that can bias the treatment effects [15]. To stabilize each patient's weight, their weights were multiplied by a proportion of the sample size for each of the treatment groups [28].

The stabilized weights for IPTW ranged from 0.63 to 6.85 (interquartile range [IQR] 1.19-1.38).

Computing the Inverse Probability of Censoring Weights (IPCW)

Two logistic regression models were fitted; each model resulted in weights that were used to compute the IPCW. The binary response variable in both models was censoring (patient was censored if s/he either left the facility or was alive at time of close out of the dataset).

The first model, computed the numerator for the weights; it modelled the probability of remaining uncensored given the baseline covariates i.e., patient's age, gender, education level, marital status, weight, CD4 counts, and WHO stage at enrollment.

The second model, computed the denominator for the weights; it modelled the probability of remaining uncensored given the baseline covariates (as above) and the time-varying covariates (i.e., CD4 counts and WHO stage at last follow-up visit or data close out).

The IPCW for each patient was defined as a ratio of the numerator to the denominator above [29, 30].

The stabilized weights for IPCW ranged from 0.03-9.39 (IQR 0.83-1.92).

Computing the Inverse Probability of Treatment and Censoring Weights (IPTCW)

Assuming no unmeasured confounders for treatment and censoring, the overall weight for each patient, IPTCW, was the product of IPTW and IPCW.

The stabilized weights for IPTCW ranged from 0.04-28.52 (IQR 1.09-3.22).

Using IPTCW to address complexities associated with assessing causal inference of time-to-ART initiation on mortality among HIV-infected patients

The stabilized IPTCW weights for each patient were used in the weighted MSCM to adjust for censoring, time dependent confounders, and bias due to nonrandom allocation of treatment. The MSCM stabilized weights for each subject are construed as the number of copies that each subject contributes to the pseudo population in which censoring does not exist and time-dependent covariate(s) do not predict initiation of ART [15]. It has been argued that, compared to unstabilized weights, stabilized weights produce narrower confidence intervals with actual coverage rates [15, 31].

Plotting of Kaplan Meier Survival curves

We plotted, ordinary Kaplan Meier Curves, ordinary Kaplan Meier Curves adjusted for baseline covariates and MSCM adjusted (weighted) Kaplan Meier curves. Unadjusted Kaplan-Meier survival curves may be misleading due to confounding [25]; therefore, we plotted MSCM using IPTCW to create adjusted survival curves as proposed by Cole and Hernan [25, 29].

J. Ethical considerations

Approval to conduct this study was granted by the Kenya Medical Research Institute Ethics Review Committee (SSC. 1525)

III. RESULTS

A. Participant characteristics

A total of 786 HIV-infected patients were enrolled at the HIV clinic during the study period, of whom 606 (77%) were

ART-eligible between 1st May, 2011 and 31st December, 2013 (Figure 2).

Of the ART-eligible patients, the median age at enrolment was 32 years (IQR 27-39 years). Among all ART-eligible patients, 50% were female, either currently or previously married (78%) and had attained primary or lower level of education (54%). Majority had CD4 count ≤ 350 cells/mm³ (76%) and 51% presented with WHO clinical stage I & II of disease at enrollment (Table 1).

Figure 2: Patient selection and outcomes for HIV infected patients enrolled at the JOOTRH between May 2011 and December 2013 as at March 31st 2015

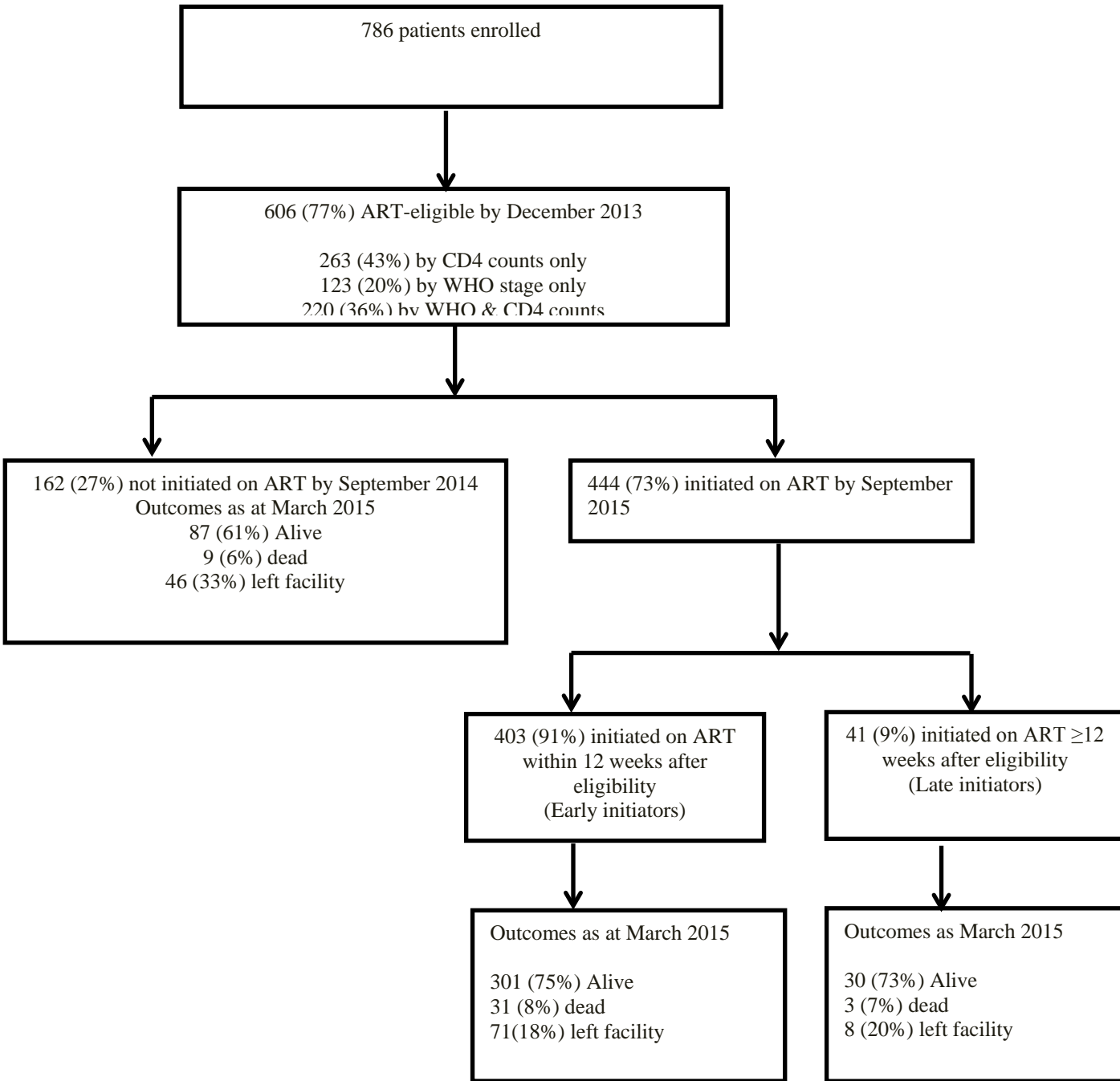


Table 1: Baseline socio-demographic and clinical characteristics among ART-eligible HIV-infected adults in JOOTRH, 2011-2013

Characteristics	All initiated N=444 n (%)	Initiating ART ≤12 weeks (early-initiators) N=403 n (%)	Initiating ART ≤12 weeks (late-initiators) N=41 n (%)	P-values
Gender				
Female	218 (49)	194 (48)	24 (59)	0.205
Male	226 (51)	209 (52)	17 (41)	
Age, median (IQR), years	34 (28-40)	34 (28-40)	32 (28-38)	0.369
Marital status				
Single	88 (20)	81 (20)	7 (17)	0.898
Ever married [†]	335 (75)	303 (75)	32 (78)	
Missing	21 (5)	19 (5)	2 (5)	
Education level				
Primary or less	230 (52)	205 (52)	25 (61)	0.465
Post primary	202 (46)	187 (46)	15 (37)	
Missing	12 (3)	11 (3)	1 (2)	
WHO stage				
Stage I & II	233 (52)	206 (51)	27 (66)	0.190
Stage III & IV	206 (46)	192 (48)	14 (34)	
Missing	5 (1)	5 (1)	0 (0)	
CD4 count, cell/mm ³				
≤ 350	356 (80)	340 (84)	16 (39)	<0.001*
> 350	88 (20)	63 (16)	25 (61)	

Abbreviations: IQR, Interquartile range.

[†]Ever married include those currently married and those previously married

*Statistically significant (at α=0.05) difference in proportions between ‘early-initiators’ and ‘late-initiators’

B. ART eligibility and ART initiation

Majority (n=606; 77%) of the patients were ART-eligible for ART initiation either at enrolment (n=303), or averagely within 3 months of enrolment (n=303). ART-eligibility was determined by CD4 count (43%), WHO stage (20%), or both CD4 count and WHO stage (36%). Among the ART-eligible patients, 444 (73%) had documented dates of ART initiation whereas 162 (27%) patients had not been initiated on ART by the end of the follow-up period. Among patients who were initiated on ART during the follow-up period 403 (91%) were early-ART-initiators, and 41(9%) were late initiators (Figure 2).

Early-ART-initiators were more likely to have had a CD4 count ≤350 cells per ml compared to late initiators (80% vs.39%, p<0.001). ART-eligible patients that were initiated on ART did not differ from ART-eligible patients that were not initiated on ART by other baseline socio-demographic and clinical characteristics (Table 1).

C. Patient outcomes at the end of follow up

Among the 444 patients who were initiated on ART, 34 died (a), 79 left the facility before the end of follow up (b) and 331 were alive (c) at the end of follow up(Figure 2).

D. Illustrating the causal effect of time to ART initiation on patient survival using Hazard ratios

The casual estimates for the effect of late-ART-initiation compared to early-ART-initiation on patient survival computed using MSCM and standard Cox-PH models are shown in Table 2. The standard models revealed no statistically significant difference in the risk of dying between late-initiators and early-initiators. The risk of death among late-initiators compared to early-initiators, computed using **unadjusted** standard Cox PH model (Model 1) was 1.6 (conservative 95% CI 0.5-5.4), and using **adjusted** standard Cox PH model (adjusted for baseline covariates) (Model 2) was 1.9 (conservative 95% CI 0.5-6.7). On the contrary, the MSCM, with an IPTCW weighted estimate, showed a statistically significant higher risk of death among late-initiators compared to early-initiators (HR 3.2, conservative 95% CI 1.7-6.4).

Table 2: Hazard ratios for the effect of ART initiation time on mortality rate[‡]

ART initiation time	Standard Cox-PH models		Marginal Structural Cox-PH model (MSM) (Model 3) HR (95% CI)
	Unadjusted Cox-PH (Model 1) HR (95% CI)	Adjusted Cox-PH [§] (Model 2) HR (95% CI)	
≤12 weeks	ref	ref	ref
>12 weeks	1.6 (0.5-5.4)	1.9 (0.5-6.7)	3.2 (1.7-6.4)*

List of abbreviations: HR, Hazard ratio; CI, Confidence interval

[‡]Conservative 95% confidence intervals computed from robust sandwich estimates

[§]Adjusted for baseline characteristics; age, gender, CD4 category, WHO stage, education level, marital status, and weight (Adjustments for age, and WHO stage were significant to the Cox proportional hazard model)

*Significant at $\alpha=0.05$

E. Graphical illustration of the causal effect of time to ART initiation on patient survival

The unadjusted survival curves from unadjusted Cox-PH model (Model 1) revealed that survival probabilities were lower for early-initiators compared to late-initiators up to approximately 52 weeks after ART-initiation beyond which the survival probabilities become lower for late-initiators (top panel). The adjusted (adjusted for baseline covariates only) Cox-PH model (Model 2) illustrated similar survival probabilities for early- and late-initiators up to 20 weeks after ART-initiation

beyond which survival probabilities of earlier initiators were higher than that of late initiators (middle panel). The weighted survival curves (to include baseline and time-varying covariates) from the MSM (Model 3), illustrated higher survival probabilities among early-initiators compared to late-initiators from the time of ART-initiation to end of follow-up; with survival probabilities of earlier initiators increasing from 16 weeks after ART-initiation to the end of follow up (bottom panel) (Figure 3).

Figure 3 Title: Estimated survival curves stratified by time to ART initiation

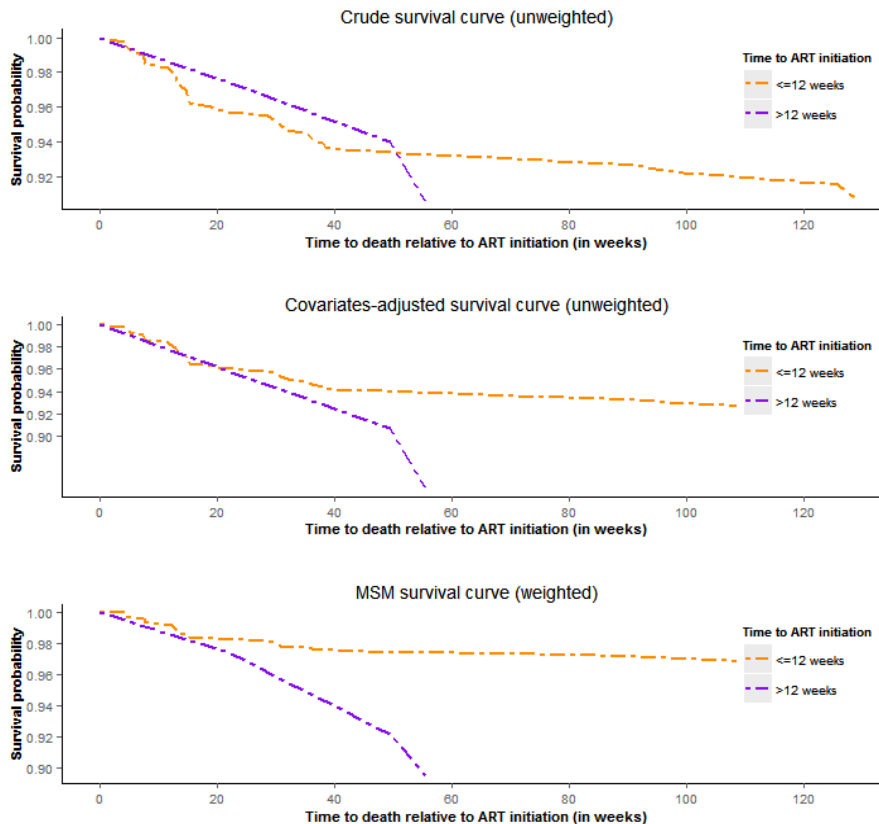


Figure 3 Legend: Top panel is survival curve derived from *unadjusted* Cox-PH model (Model 1), middle panel is survival curve derived from *adjusted* Cox-PH model (Model 2) and bottom panel is survival curve derived from MSCM (Model 3)

IV. DISCUSSION

A. Discussion of Study results

We set out to determine the causal effects of ‘time to ART initiation’ on the survival of HIV-infected patients using MSCM while comparing it to the standard Cox-PH Models at a regional referral hospital in a high HIV-burden area in Western Kenya. Our findings revealed that, delays in ART initiation among ART-eligible patients was associated with a higher risk of death compared to timely ART initiation. This causal effect was only realized by using MSCM. MSCM adequately accounted for censoring for patients who left the facility (LTFU and transfers) via IPCW whereas standard Cox-PH model assumed random censoring. These findings suggest that non-random allocation of treatment, time-dependent confounding and censoring potentially bias the true causal effects of ‘time to ART initiation’ on the survival of HIV-infected patients. This would therefore underestimate the benefits of early ART initiation[32].

The Cox-PH model assumes that the effect of time to ART initiation on the risk of the death among HIV-infected patients on ART is constant at all times[33]. Whenever the proportionality assumption is violated, the Cox-PH models extended for non-proportional hazards should be adopted [23]. While early mortality (before 4 months of ART) has been associated with patient characteristics at baseline, mortality beyond this time-point has been associated with poor response to ART (i.e., follow up CD4 cell counts and viral loads)[34].

Our hazard ratios estimates and graphical illustration revealed changes in survival probabilities over time between early and late initiators after adjusting for confounding and patient attrition illustrating the impact of time-dependent confounders on causal estimates [29]. The observed differences could also be explained by the fact that estimates from MSCM are marginal estimates of the counterfactual variables which estimate the difference between initiating all patients on ART early versus delaying no one. Conversely, standard estimates are conditional estimates that estimate the effect of early versus late initiation while holding all the other variables constant[14, 15, 35].

Similar to patients in the US, patients with more advanced HIV disease (lower CD4 counts) were more likely to be started on ART earlier. This may have been due to better adherence to clinical visits [36] as was also observed in a separate analysis at the JOOTRH HIV clinic [18]. A comparable risk of death between early and late initiators during the first weeks of ART treatment prior to achieving steady state, could be attributed to more advanced disease among early initiators [20].

B. Assumptions

In causal inference models, the validity of the results is often pegged on some assumptions. Our analysis assumed that the dates documented within our patients’ dataset were accurate; the measured covariates were also adequate to adjust for both confounding and selection bias due to patient’s attrition.

However, we could not account for all possible unmeasured confounders e.g., adherence which was not well documented in our data[37]. Furthermore, we did not conduct a sensitivity analyses to determine whether results were sensitive to the assumptions that there were no unmeasured confounders[38]. We also relied on the assumptions that the Logistic models for computing IPTW and IPCW were correctly specified and that our MSCM model was correctly specified[29].

C. Strengths

Given a correctly specified model and no violations of the essential model assumptions, our causal estimates from the MSCM could be said to be interpretable as that which would have been observed in an RCT [35]. Additionally, our results from clinic-data, are more representative of the “real-world” than data from “interval” cohorts assembled for research or clinical trials which have numerous exclusion criteria and occur in controlled environments[39, 40]. Although the rationale of MSCM may be interrogated as we move towards HIV ‘test and treat’ approaches, there may still be variations in time to ART initiation due to patient and health system factors[41].

D. Limitations

Our study had some limitations. We employed a proxy date for date of ART initiation as the 15th of each month for all patients initiated on ART. This was based on the data collection tool that only recorded ‘month’ and not ‘actual dates’ of ART initiation. Although this may have affected patient categorization into treatment groups, it was unlikely to affect the precision of our causal estimates as both ‘early’ and ‘late’ initiators were equally likely to be misclassified. We were unable to include data on Tuberculosis co-infection due to missing data and viral load measurements which were only done for selected patients during the study period. Additionally, MSCM cannot be used to test the null hypothesis of no treatment; for this reason we excluded all ART-ineligible patients. MSCM also assumes that the treatment regimen is fixed over time; however, ART treatment is sometimes dynamic as it may be affected by treatment interruptions, adherence and HIV resistance[29, 37]. History-adjusted models (generalized marginal structural models) can be employed to accommodate the dynamic nature of long-term ART[9, 37].

E. Conclusion

When randomized trials are not feasible due to costs or ethical concerns, causal inference could still be deduced from longitudinal observational data by applying appropriate causal models e.g., MSCM [13-15]. To ensure accurate parameter estimates, all model assumptions should be assessed; to ensure conservative confidence intervals, robust variance estimators should be adopted; and to ensure the true causal effects are obtained, methods such as inverse probability weights should be employed. Furthermore, the weights should be stabilized to reflect sample sizes of different treatments groups. Given a longitudinal observational data with adequate information on, confounders for exposure and censoring, and ignorable missing data, MSCMs are suitable models for causal inference [9].

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Competing interests: The authors declare that they have no competing interests.

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