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Characterization of the Association of Time to ART Initiation from HIV Diagnosis and Survival to Fatal and Non-Fatal Severe Events: An Analysis of the HIV Atlanta Veterans Affairs Cohort Study

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Abstract

Characterization of the Association of Time to ART Initiation from HIV Diagnosis and Survival to Fatal and Non-Fatal Severe Events: An Analysis of the HIV Atlanta Veterans Affairs Cohort Study

By Elizabeth Rabold

Studies in low-resource settings have shown benefits in viral load suppression and clinical outcomes in people living with HIV who initiate antiretroviral treatment (ART) immediately after diagnosis, but few studies report on early treatment initiation in high-resource settings. This analysis aimed to compare time to death and other severe non-fatal events between veterans who initiated ART within 60 days of HIV diagnosis (early) and intermediate (61-365 days) or late (>365 days) initiation. Using data from the HIV Atlanta Veterans Affairs Cohort Study (HAVACS) and Clinical Case Registry, we identified all treatment-naive veterans who initiated ART at the Atlanta Veterans Affairs Medical Center between January 2005 and May 2018; veterans missing key dates such as HIV diagnosis or ART initiation date were excluded from the analysis. Using Cox proportional hazards models, we calculated the unadjusted and Veterans Aging Cohort Study (VACS) index-adjusted hazard ratios (HR) for the primary composite outcome (death, AIDS-defining diagnosis, malignancy, severe renal or liver disease, atherosclerotic cardiovascular disease, or invasive infection) and all-cause mortality. In total, 520 veterans (2991.8 person-years) were included in this analysis with 159 total events and 65 deaths. Unadjusted models for the composite outcome and all-cause mortality were not statistically significant. Compared to veterans with early initiation, only late initiation was associated with an increased adjusted hazard of the composite outcome (adjusted HR 1.27; 95% confidence interval [CI], 0.76-2.12 and 1.81; 95% CI, 1.15-2.87 for intermediate and late initiation, respectively). Both intermediate and late initiation increased the adjusted hazards of all-cause mortality (adjusted HR 2.49; 95% CI, 1.05-5.94 and 2.81; 95% CI, 1.24-6.33, respectively). Shorter delay in ART initiation is associated with improved event-free survival, independent of baseline characteristics such as CD4 count, viral load, age, renal function, liver function, anemia, and hepatitis C status. These findings highlight the importance of rapid diagnosis and linkage to care, with a 2-month delay in treatment initiation associated with an increased hazard of death. Adopting strategies to streamline treatment initiation soon after diagnosis may lead to improved morbidity and mortality, potentially serving to close the gap in survival in people with and without HIV.

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BACKGROUND

Overview

In the 38 years since HIV was first described in a cohort of men in Los Angeles, our understanding and treatment of the disease have changed drastically. Once considered a terminal condition, it is now being managed as a chronic disease [1]. Advancements in antiretroviral therapy (ART), earlier access to treatment, and recognition and treatment of opportunistic infections has reduced the short-term mortality of HIV infection. Though overall life expectancy has improved, an 8-year gap relative to HIV-uninfected individuals still persists, even when starting therapy before overt immunosuppression with CD4 count ≥500 cells/mm^3[2]. With opportunistic infections contributing less to overall morbidity and mortality in PLHIV, most deaths are now attributable to other conditions, such as cardiovascular disease, non-AIDS defining cancers, and other non-communicable causes [3]. PLHIV may be at higher risk than the general population for these conditions, which may partially mitigate the reduction in mortality seen from improved HIV care and treatment. While many studies have evaluated survival after ART initiation by CD4 count at baseline, fewer have reviewed how overall duration of disease impacts survival and non-fatal events, such as atherosclerotic cardiovascular disease and malignancy, adjusting for CD4 count and other baseline characteristics. This analysis will examine the trend in the development of severe conditions and all-cause mortality in PLHIV based on time to initiation of ART for veterans receiving healthcare at the Atlanta Veterans Affairs Medical Center (AVAMC) in the HIV Atlanta VA Cohort Study (HAVACS).

HIV Epidemiology

Nearly 40,000 Americans received a new diagnosis of HIV in 2017, and approximately 1.1 million Americans were living with HIV in 2018 [4, 5]. The disease disproportionately affects

minorities; despite African Americans making up only 13% of the population, they make up 44% of new cases of HIV [6]. African American gay and bisexual men are the most severely affected. Not only is the burden of disease higher in these populations, they also present with later stage disease and have worse outcomes [7, 8]. A review of data from black men who have sex with men enrolled in HPTN 061 showed that 39% of participants presented with a CD4 count below 350 cells/mm^3, of which 20% presented with a CD4 count below 200 cells/mm^3 [9]. In 2012, the rate of death per 1,000 PLHIV among African Americans was 21.9, as compared to Whites (18.1) or Hispanic/Latinos (13.9) [10]. Though the U.S. is on track to achieve the UNAIDS 90-90-90 targets (90% of people with HIV aware of their status, 90% of those individuals on treatment, and 90% of those individuals virally suppressed) by 2020 [11], African Americans tend to fall behind Whites and Hispanics/Latinos. For every 100 African Americans living with HIV, only 47 were retained in care and 48 achieved viral load suppression, as compared to 53 and 60 among Whites and 58 and 60 among Hispanics/Latinos, respectively [12]. Stigma, poverty, access to services, treatment of sexually transmitted infections, and other factors contribute to these populations seeking care later and having worse outcomes [13].
By region, the South has the largest number of PLHIV [14]. In 2017, Georgia had the highest rate of new cases among all 50 states at 24.9 per 100,000 people, with the region around Atlanta particularly affected [14].

Approach to HIV Treatment

For the first several years after AIDS was described in the U.S., there was no treatment available [15]. The first effective medication, zidovudine, was FDA-approved in 1987, and the first three-drug combination therapy was introduced in 1996 [16]. This combination therapy resulted in the first decline in HIV-related deaths in the U.S. since 1987, the first year mortality data was

available [17, 18]. Unfortunately, these first regimens required frequent dosing, had many drug-drug interactions, and had significant side effects. In 2006, the FDA approved a once daily pill comprised of three active medications, which marked a notable period in HIV treatment [16]. Since then, advancements in drug therapy have further simplified regimens, reduced side effects, and increased potency. Currently, many patients can control the infection with one pill daily, with minimal side effects.

As medications have improved, there has been a shift in when an individual should begin therapy. A treat-all approach was first adopted during the era of triple therapy, but intolerable side effects shifted the approach to only treating those with a threshold CD4+ T cell count of 200 cc/mm^3 or when an individual had AIDS-defining symptoms. Multicenter trials subsequently showed a mortality benefit in starting therapy at earlier points in the disease process, and guidelines changed to initiating therapy with a CD4 count threshold of 350 cc/mm^3 [19-21]. The START and TEMPRANO studies, both published in 2015, rapidly changed the approach to treatment [22, 23]. The START trial, a multi-center, multi-country randomized control trial, compared immediate initiation of ART to a threshold CD4 count of 350 cells/mm^3 or other indication for initiating therapy; the immediate initiation group had a hazard ratio for the composite primary endpoint of death from any cause, any serious AIDS-related event, and serious non-AIDS-related events of 0.43; 95% CI, 0.38-0.97 [22]. Most primary endpoints occurred in individuals with CD4 counts >500 cells/mm^3. The TEMPRANO study, a multi-center study across several African countries, showed a dramatic reduction in the hazard ratio for the composite outcome of death, AIDS (defined by illness or CD4 count), cancer, or invasive bacterial disease, with adjusted hazard ratio 0.56; 95% CI, 0.41-0.76 [23]. Additional studies showed the benefits of treatment as prevention, with the serodiscordant study, HPTN 052

demonstrating a 93% reduction in the transmission to HIV-negative partners when treatment is initiated early (350-550 cells/mm^3) as opposed to delayed initiation [24], and PopART (HPTN 071) showed that an HIV prevention strategy that included HIV testing for all with referral and treatment for all found positive could substantially reduce new infections by 30% [25]. Findings from these studies among others resulted in recommendations by the Department of Health and Human Services and WHO to initiate therapy as soon as is appropriate after diagnosis [26]. Subsequent studies have continued to show the benefit of multi-modal, treat-all approaches in terms of improved outcomes (viral load suppression, mortality), reduced transmission, and progress towards surpassing the 90-90-90 targets [27, 28].

Rapid Start

With recommendations to begin therapy as soon as possible, several healthcare centers in low- and middle-income countries developed service delivery models that emphasized starting individuals on treatment immediately, within 14 days of diagnosis. Ford, *et al* analyzed the first studies published in this field, including 11 observational studies and 4 RCTs [29]. Same day and rapid initiation of care, compared to standard of care, resulted in increased initiation of ART at 90 days (RR 1.35; 95% CI, 1.13–1.62), increased viral suppression at 12 months (RR 1.17; 95% CI, 1.07-1.27). Loss to follow up and mortality at 12 months, though not statistically significant, were clinically relevant (RR 0.66; 95% CI, 0.42-1.04 and RR 0.53; 95% CI, 0.24-1.08, respectively). A recent Cochrane review described the results of 7 randomized controlled trials that compared rapid ART initiation (within 7 or 14 days) to standard of care. The meta-analysis showed an equivocal stance on mortality at 12 months (RR 0.72; 95% CI, 0.51, 1.01) but a probable increased likelihood of viral suppression at 12 months (RR 1.18; 95% CI, 1.10-1.27), retention in care at 12 months (RR 1.22; 95% CI, 1.11-1.35), ART uptake at 90 days (RR

1.31; 95% CI, 1.18-1.45) and 12 months (RR 1.09; 95% CI, 1.06-1.12) [30]. See Appendix A for full details. This review only included low- and middle-income countries, as the approach is not fully integrated into all health care systems in the United States due to the intensive resources and multiple-disciplinary setting required. Other places around the country, including New York City and San Francisco, have developed intensive, comprehensive programs to support rapid initiation of ART. In a San Francisco cohort of 225 patients with multiple psychosocial issues, viral load suppression was achieved in >90% of participants at a median of 1.09 years [31]. AVAMC was an early adopter of the rapid start approach, making it their standard of care in December 2016.

HIV Pathogenesis and Relationship to Other Conditions

Because HIV weakens the immune system by infecting and depleting CD4 cells, PLHIV are susceptible to opportunistic infections that may not be harmful to others without the infection (e.g. *Pneumocystis jirovecii* pneumonia, toxoplasmosis, and cryptococcal meningitis), or they may have a more severe response to common diseases, such as to viruses that cause the common cold. Individuals with CD4 counts below 200 cells/mm^3 or diagnosed with conditions only seen in severely immunocompromised states are classified as having AIDS [32].

Fortunately, as treatment has improved for PLHIV, fewer individuals with HIV progress to AIDS, particularly if treatment is begun at higher CD4 counts. Trickey, *et al* showed an overall improvement in all-cause mortality in PLHIV who began ART in 2008-2010 as compared to those who began ART in 2000-2003, when adjusted for CD4 count and other baseline factors [33]. However, individuals with HIV are often at above average risk for non-infectious diseases such as cardiovascular disease, cancer (particularly lymphoma), diabetes, interstitial lung disease, and neurodegenerative diseases [1]. Though PLHIV may be more likely to have

traditional risk factors for conditions such as cardiovascular disease (e.g. tobacco use), other factors, such as chronic immune activation from immune dysregulation, may also play a role in their elevated risk [34, 35]. Side effects of ART medications, including metabolic abnormalities such as dyslipidemia and diabetes, may also contribute to adverse cardiovascular outcomes [36]. In a meta-analysis, Dorjee, *et al* reported that abacavir, a medication in a commonly used combination therapy, is associated with a summary relative risk of cardiovascular disease of 1.61 (95% CI, 1.48-1.75) even when adjusting for other traditional risk factors [37]. Moreover, Freiburg, *et al* showed that even beyond traditional risk factors, HIV is associated with a 50% increased risk of acute myocardial infarction [38]. These factors combined may contribute to cardiovascular disease now being among the top causes of death among PLHIV on ART [39, 40]. With increased life expectancy, the impact of non-communicable diseases becomes more prominent, prompting the need for understanding how HIV- and non-HIV related risk factors impact chronic disease development.

Atlanta Veterans Affairs Medical Center

The Atlanta VAMC serves the largest HIV-positive veteran population in the country. In 1982, the HIV Atlanta VA Cohort Study (HAVACS) began, with all veterans who received care at AVAMC since that time enrolled in the cohort, with information used for direct patient care, surveillance, and research purposes. The AVAMC ID Clinic currently provides outpatient continuity of care for approximately 2000 PLHIV. Veterans typically are referred to the clinic from within the VA system. All veterans in the region are eligible to receive care at this multi-disciplinary clinic, where they have access to infectious disease physicians, nurses, social workers, pharmacists, mental health specialists, and home medication delivery services.

In 2016, Guest, *et al* published summary information of the 4,334 veterans enrolled in the database since data collection began in 1982 [41]. Overall, the patient population is largely reflective of the AVAMC population, with 97% male, 72% African American, 26% Caucasian, and 2% Hispanic. Primary risk factors included men who have sex with men (MSM, 53%), injection drug use (IDU, 16%), and high-risk heterosexual contact (5%). As of 2014, 60% of veterans had suppressed viral loads and CD4 levels above 500 cells/mm^3. The study follows patients closely and monitors transitions to other providers, with only 3% lost to follow up since 1982. As described above, the clinic adopted a rapid start approach in December 2016, aiming to have the first clinic visit within 3 days of diagnosis and initiation of ART on the first clinic day. By reducing time and eliminating barriers to initiating therapy, the overall expectations are to increase viral load suppression, increase retention, decrease long-term morbidity and mortality, and decrease transmission to HIV negative individuals. Preliminary data shows that the protocol was effective at decreasing time to first clinic visit and same-day initiation of ART, but long-term outcome data are not yet available [42]. Now that the rapid start approach has been in place for more than 2 years, we may begin to review impacts on severe events, mortality, and other outcomes.

Research question

In this veteran population, is there an association between time from HIV diagnosis to ART initiation and time to death or severe non-fatal events?

METHODS

Study Design and Setting

This retrospective study is a secondary analysis of cohort data and was designed to examine mortality and significant health events among veterans newly initiating ART at AVAMC between January 1, 2005 and May 31, 2018.

Primary and secondary analyses

For the primary analysis, participants were followed until the first of the following events: a severe non-fatal condition (defined below), death, transfer of care, loss to follow up, or censoring on May 31, 2019. As a secondary outcome, participants were followed until death for any reason, transfer of care, loss to follow up, or censoring on May 31, 2019.

Data Source

HAVACS was used as the primary data source. HAVACS has been described in detail elsewhere [41]. Further clinical data were gathered from Clinical Case Registries (CCR), a database that extracts data from the electronic medical record to provide population-based data on participants with specific infectious and chronic diseases [43]. CPRS, the electronic medical record system used by the VA, was reviewed as necessary to verify information. Some variables, such as laboratory variables, were extracted almost exclusively from CCR. Most other variables were available both in HAVACS and CCR; these variables were cross-matched to identify the most complete and accurate data.

Inclusion Criteria

All adult veterans aged 18 years and older who initiated ART at the AVAMC between January 1, 2005 and May 31, 2018 and were included in the HAVACS cohort were eligible for inclusion in this study.

Exclusion Criteria

Participants were excluded from this study if they had missing data from HAVACS, CCR, or CPRS for key variables (including laboratory-confirmed HIV diagnosis date, first infectious disease clinic (IDC) visit date, ART initiation date, initial ART regimen, and CD4 count either 90 days prior to or 14 days after initiating ART). Participants who received <3 medications for initial HIV-treatment regimen, any anti-retroviral therapy prior to 2005, or initial therapy from an outside clinic were excluded. First IDC visit was required within 30 days of initiation of ART to account for inpatient initiation of treatment. Elite controllers and long-term non-progressors as documented in HAVACS were excluded from the analysis.

Primary endpoint

The primary endpoint was a composite of all-cause mortality or other severe non-fatal clinical events, including AIDS-defining illness (as classified by WHO), atherosclerotic cardiovascular disease (ASCVD), end-stage liver disease, end-stage renal disease, invasive infection, or cancer (excluding non-melanoma skin cancers and AIDS-defining cancers). These competing conditions have been combined as a composite outcome in prior studies [22, 26]. Participants with a pre-existing severe non-fatal condition were excluded from developing that condition as a primary outcome; those that developed a different condition within the composite outcome were classified as having an event.

Secondary endpoint

The secondary endpoint was all-cause mortality.

Independent variable

The independent variable in this analysis was time from laboratory-confirmed HIV diagnosis to ART initiation per pharmacy-based records in CCR. A three-level categorical variable was created from this difference in time: ≤60 days, 61-365 days, and >365 days. These different time periods may be referred to as early initiators, intermediate initiators, and late initiators, respectively.

Demographic variables

Demographic variables at time of ART initiation were compared across the three groups, including age (<30, 30-39, 40-49, 50-59, ≥60 years), sex at birth, race (White, Black, Other/unknown), and ethnicity (Hispanic, non-Hispanic).

Diagnoses

International Classification of Diseases, Ninth Edition, Clinical Modification (ICD-9-CM) and International Classification of Diseases, Tenth Edition (ICD-10) from CCR were used to extract clinical diagnoses, including depression, diabetes, hepatitis C, hypertension, and the non-fatal primary outcomes including various AIDS-defining illnesses, non-AIDS defining cancer, atherosclerotic disease, severe infection, renal disease, or liver disease (see Appendix B for specific codes). Date of death was compared between CCR and HAVACS. Prevalent disease was defined as having at least one inpatient or outpatient diagnosis code prior to initiation of ART or up to 30 days after initiation. New events were defined as at least one inpatient or outpatient diagnosis code >30 days after initiation of ART, without having a prior diagnosis of that condition. AIDS at initiation was defined as either having an AIDS-defining illness or CD4 count <200 cells/mm^3.

Social/behavioral variables

Social and behavioral variables at time of ART initiation were compared across the three groups. Some variables were abstracted primarily from HAVACS (men who have sex with men (MSM)), some primarily from diagnostic codes (tobacco use, homelessness/financial instability), and others were abstracted from both (injection drug use).

Treatment variables

To account for differences in treatment strategy and approach, participants were divided into different treatment eras: 2005-2009 (simplified triple therapy regimens available), 2010-2014 (transition to treat all), 2015-2018 (test and treat and treatment as prevention). Participants were divided by type of therapy that they received as their initial regimen: integrase inhibitor-based (INSTI), non-nucleoside reverse transcriptase inhibitor-based (NNRTI), or protease-inhibitor-based (PI). Baseline values of CD4 count (<200, 200-349, 350-499, and ≥500 copies/mm^3), HIV-1 RNA (0-3.99, 4-4.99, and ≥5.00 log copies/mm^3), and VACS index (<20, 20-35, 36-50, >50) were included, as well as time to initiation of ART after diagnosis and time to initiation of ART after first IDC visit (≤60 days, 61-365 days, and >365 days). Median values of continuous variables were calculated with the 25^{th} and 75^{th} percentiles.

Loss to follow up, transfer out of care, and censoring

Participants were considered lost to follow up if the period between their last visit date and May 31, 2019 was more than 365 days; those participants were censored 180 days after the last visit date. Participants were censored on their last visit date if they were documented to have transferred care out of AVAMC. Participants still in care without any documented events were censored on the last day of the study period, May 31, 2019. Excluding those who had an event,

left care, or died within 1 year of ART initiation, all participants had a minimum of 1 year of follow up.

Statistical Analysis

Unadjusted hazard ratios for time to the composite outcome (AIDS-defining illness, non-AIDS defining malignancy, end-stage renal disease, end-stage liver disease, ASCVD, severe infection, and death) and time to all-cause mortality were estimated using Cox proportional hazard models, stratified by time from HIV diagnosis to ART initiation (≤60 days, 61-365 days, and >365 days). Individuals were considered to have an event within the composite model if they had an inpatient or outpatient ICD-9CM or ICD-10 code >30 days after ART initiation without ever previously having a diagnosis of that condition, meaning individuals with prevalent disease of one condition (*e.g.* AIDS-defining illness) were eligible to have an event of a different condition (*e.g.* ASCVD) but would not be eligible to develop an event from that same prevalent condition in the future (*e.g.* AIDS-defining illness). Only the first composite outcome was included per participant, and participants could no longer contribute person-years to the model after that first event. Within the all-cause mortality model, only time to death was assessed. The ≤60 days group (early initiators) was used as the referent group for all models. Participants who were lost to follow up or who transferred out were censored accordingly (as described above); remaining participants without an event as of May 31, 2019 were right-censored.

Adjusted hazard ratios for time to composite outcome and time to all-cause mortality were estimated by including the VACS index at time of ART initiation in the model. The VACS index includes age, CD4 count, HIV-1 RNA viral load, hepatitis C co-infection, estimated glomerular filtration rate (GFR) per the MDRD Equation, hemoglobin, and fibrosis-4 (FIB-4 index) for liver fibrosis (see Appendix C for parameters). The VACS index was calculated

manually using laboratory values from CCR and demographic values from both CCR and HAVACS.

The subdistribution model as described by Fine and Gray was used to examine the individual contributions of the seven competing risks within the composite model [44]. The adjusted model included the VACS index at ART initiation.

To account for higher mortality in the first year after ART initiation, additional adjusted composite and all-cause mortality models were created that included both VACS index at baseline and VACS index at 1 year, including only individuals still included in care without an event at 1 year.

The PH assumption was examined graphically by plotting the log (-log) survival estimates against time assessing for parallel curves and statistically using Schoenfeld residuals to assess the difference between observed and expected covariates.

Analyses were performed using SAS version 9.4 (Raleigh, NC), with the PHREG function used for hazards models. Significance was set at p=0.05, and 95% confidence intervals were included with all hazard ratios.

Ethical Considerations

The HAVACS cohort study is approved by the Emory Institutional Review Board; analyses in this paper fall under “The Continuum of HIV Care” protocol IRB00068877.

RESULTS

Descriptive data

Of 4,765 veterans included in the HAVACS cohort, 520 (10.9%) were eligible for analysis, with 3,391 (71.1%) excluded due to initiating ART prior to the January 1, 2005 (see Figure 1). The remaining 1,710 veterans were excluded for various reasons, including not initiating ART or initiating a regimen with <3 medications, a missing HIV diagnosis date, a missing baseline CD4 count, being an elite controller/long-term non-progressor, or initiating therapy after May 31, 2018. The participants included in the analysis contributed 2991.8 person-years (see Table 4).

The three different exposure groups had similar demographic characteristics. The median age was 45.9 (IQR 36.5-53.8) (see Table 1). The population was predominantly male (96.2%), with fewer females in the >365 days group (7, 2.7%) as compared to the ≤60 days group (6, 5.5%) and the 61-365 days group (7, 4.6%). Participants were mostly black (85.6%), and non-Hispanic (93.3%).

Half (260/520) of the participants were men who have sex with men (MSM). Injection drug use was reported by 42 (8.1%) of the participants, with the majority of those (36/42, 85.7%) in the late initiation group.

The prevalence of mental health disorders and other comorbid conditions was high. A prior or current history of homelessness was documented for 177 (34.0%) participants. Tobacco use (28.8%), depression (56.5%), and hypertension (40.0%) were also commonly reported. The prevalence of hepatitis C was 7.9%, with 78.0% (32/41) in the late initiation group. Participants also presented with conditions included in the primary outcome, with 8.8% having documented ASCVD, 11.3% with a non-AIDS defining malignancy, and 6.9% with invasive infection.

In general, participants were in an immunocompromised state when initiated on ART; 176 (33.8%) had AIDS at ART initiation, as determined by CD4 count <200 cells/mm^3 or an AIDS-defining illness; 287 (55.2%) had a CD4 count below 350 cells/mm^3. The median HIV-1 RNA was 4.7 log copies/ml (IQR 4.0-5.2). Integrase inhibitor-based regimens were more common in the early initiation group (37.6% compared to 16.7% in the late initiation group). Duration of time from IDC visit to initiation of ART was the least in the early initiation group (median 0 days) as compared to the intermediate initiation group (39 days) and the late initiation group (652 days).

During the study period, 69 (13.3%) participants transferred care and 81 (15.6%) participants were lost to follow-up (Table 3). Of the 520 enrolled, 498 (95%) were still in care at 1 year, with removal due to an event or death (2%), transfer (1%), and loss to follow up (2%).

Primary and secondary outcomes

Of the 520 participants, 159 (30.6%) had a primary composite outcome of death or a non-fatal severe event (see Table 2). The most common single composite outcome event was ASCVD in 38 (7.3%) participants, followed by death in 36 (6.9%) participants, invasive infection in 21 (40%), and malignancy in 20 (3.8%) (see Figure 2). Death as a composite outcome was least common among the ≤60 days group (3.7%) and most common among the >365 days group (6.3%). Events occurred in 22.0%, 17.8%, and 48.9% of participants respectively, across the 3 different groups (≤60 days, 61-365 days, and >365 days). The rate of the composite outcome decreased from the late initiation group (61.7 per 1000 person years) to 43.6 per 1000 person-years the medium initiation group and 45.4 per 1000 person-years in the early initiation group.

Of the 520 participants, 65 (12.5%) died during the study period (see Table 2), with 58.5% (38/65) of the deaths within the late initiation group. The rate of death decreased from 24.9 per

1000 person-years in the late initiation group to 21.3 in the intermediate initiation group to 13.2 in the early initiation group (see Table 4).

Survival analysis

The PH assumption was verified graphically for unadjusted composite and death models stratified by time to ART initiation by examination of the log (-log) estimated survival function and by calculation of the Schoenfeld residual statistics (see Figures 3, 4 and Table 5). Univariate analysis of VACS index at baseline and 1 year also met the PH assumption (Table 5).

Unadjusted hazards ratio for the composite outcome for the intermediate and late initiation groups was 0.97; 95% CI, 0.58-1.60 and 1.36; 95% CI, 0.87-2.14, respectively, using early initiation group as the reference group (see Table 6). Adjusted hazard ratio for the late initiation group showed an 81% increase in hazards of any event (95% CI, 1.15-2.87), but the intermediate group had a 95% CI that crossed 1 (aHR 1.27; 95% CI, 0.76-2.12). Notably the Wald Chi-square p-value was 0.02.

Unadjusted hazard ratio of all-cause mortality showed no difference in the hazard of an event for the intermediate and late initiation groups (HR 1.62; 95% CI, 0.68-3.84 and 1.80; 95% CI, 0.80-4.04, respectively; however, the adjusted model showed an 149% increase in hazards for the intermediate initiation group (95% CI, 1.05-5.94) and an 181% increase in hazards for the late initiation group (95% CI, 1.24-6.33). Figures 5 and 6 show the unadjusted survival curves for the composite outcome and all-cause mortality, respectively, with the decreased survival overall noted for the composite outcome.

To examine the subdistribution model, Figure 7 shows the cumulative incidence function of the competing risks within the composite outcome. Death and ASCVD have the highest cumulative incidence among the components of the composite outcome. Table 7 shows the unadjusted

subdistribution hazard models for the competing risks and the adjusted subdistribution hazard models, adjusted for VACS index at baseline. Direction of risk varied across competing risks. For individuals who survived >365 days, the addition of VACS index at 1 year did not greatly impact the models. The adjusted hazard ratios of any event at both time periods remain similar as the baseline model (aHR 1.3; 95% CI, 0.76-2.22 for the intermediate initiation group and aHR 1.67; 95% CI, 1.03-2.70 for the late initiation group). The adjusted HR for death at the intermediate initiation group increased to 2.80; 95% CI, 1.01-7.64 and 2.90; 95% CI, 1.12-752 for the late initiation group. Notably, the confidence interval increased in the all-cause mortality group.

Discussion

Event-free survival

Between 2005 and 2018, more than 500 veterans initiated HIV treatment at AVAMC. During that time period, strategies in timing of ART and type of therapy evolved, with the transition towards immediate treatment and the use of an integrase-based inhibitor, both of which have been shown to lead to improved life expectancy with fewer AIDS-related events [45, 46]. Descriptive review of the data showed an overall improvement in survival to any severe event when the time between diagnosis and ART initiation was reduced (22.0% for early initiators starting by 60 days as compared to 32.8% for those late initiators starting after 1 year). Considering the contribution of person-years, the rate of any event decreased for the early initiators compared to the late initiators (45.4 per 1000 person-years as compared to 61.7 per 1000 person-years). The unadjusted hazard ratios showed no difference in intermediate or late initiators as compared to the early initiators. Adjusted analysis using the VACS index showed an increase in the hazard for late initiators (aHR 1.81; 95% CI, 1.15-2.87). Though the hazard of a severe outcome for intermediate initiators appeared similar to early initiators, (aHR 1.27; 95% CI, 0.76-2.12), the Wald Chi-Square p-value=0.02 for the overall model. Overall, this suggests an improved event-free survival with shorter delay in initiating ART therapy, independent of baseline characteristics such as CD4 count, viral load, age, renal function, liver function, anemia, and hepatitis C status.

In comparison, the impact of delayed ART initiation was even more profound on all-cause mortality, with an inverse relationship in the rate of death as the delay increased (13.2, 21.3, and 24.9 per 1000 person-years for the early, intermediate, and late initiators, respectively). Intermediate and late initiation increased the hazards of death by 149% and 181%, respectively, when baseline features within the VACS index were included. These findings highlight the

importance of rapid diagnosis and linkage to care, with as little as a two-month delay in treatment initiation resulting in a 2.5-fold increased hazards of death.

The only covariate used in the adjusted hazards model was the VACS index, which has been shown to be an independent predictor of mortality at 1 year [47]. Because the index includes commonly used variables, such as age, renal and liver function, hepatitis C status, and baseline CD4 count and viral load, it would not be appropriate to additionally include those variables separately in the model. Notably, demographic variables not included in the index, such as sex and race, did not contribute meaningfully to the model, potentially due to the skewed sample population of primarily black men. Improvements in available medications and treatment strategies were assessed by including time period and initial ART regimen into a model. Notably, late initiators were preferentially in the 2005-2009 time period due to recommendations at the time to defer treatment in asymptomatic patients. None of these additional variables improved the fit of the model and thus were not included as covariates.

These analyses showed that independent of VACS index and the variables included within it, such as age, baseline disease status, and selected comorbid conditions, earlier initiation of ART lead to improved event-free and overall survival. This finding is notable because many prior studies have indicated that CD4 count or other markers of disease progression were the strongest predictors of survival. However, even when adjusting for CD4 count by using the VACS index, mortality and event-free survival were still impacted by time to treatment initiation. The Cochrane review described earlier and in Appendix A found positive trends primarily in intermediate outcomes (retention, viral load suppression, ART initiation) with rapid ART initiation but equivocal findings with 1-year mortality [30]. This work contributes to that meta-

analysis by looking at event-free survival, supporting the theory that earlier initiation of ART improves outcomes.

In the pediatric literature, earlier initiation of ART in newborns with vertical HIV transmission leads to a smaller HIV latent reservoir. Similarly, in adults, earlier initiation of ART may allow for a smaller reservoir of latent memory T-cells infected with HIV [48]. These cells may produce low-level viremia, even in patients appropriately managed with ART [49]. Thus, people living with HIV even with suppressed viral loads may still be at increased risk of inflammatory conditions due to some residual disease activity; reduction of the overall reservoir may reduce the chronic inflammatory impact of HIV on the development of chronic conditions [49, 50]. This theory may serve as a biological explanation for improved survival with earlier initiation of ART, even after adjusting for baseline CD4 count and viral load.

As expected, timing of ART initiation has a stronger effect on mortality than the development of serious clinical events; in middle-aged men, removing mortality from AIDS-related illnesses removes a previously leading cause of death. However, as noted by others, it allows for other illnesses to develop, at a higher rate than in the non-HIV population and a higher rate than the non-VA population [51, 52]. Having HIV for longer periods, both the disease itself and its treatment may contribute to diseases such as renal disease, liver disease, and atherosclerotic disease [53]. Additionally, traditional risk factors for malignancy, ASCVD, and renal disease are more common in the HIV population [54]. Even with appropriate medical treatment of comorbidities and ASCVD risk, behavioral and non-modifiable variables such as psychosocial stressors may impact the risk of developing disease [55]. The development of comorbid conditions may be due to the inherent increased risk for disease due to HIV infection itself or due to other contributors such as baseline risk factors, challenging medical management,

psychosocial situations. However, when added to the adjusted analysis, traditional risk factors or proxies for risk factors, such as tobacco use, depression, and homelessness, did not contribute to the model.

People living with HIV may not always receive optimal treatment to minimize risk factors, either due to drug-drug interactions or the mode of treatment that they receive. For example, certain statins may either be contraindicated with certain regimens or have reduced potency [56, 57]. Protease inhibitors contribute to higher triglyceride levels [58], and Maggi, *et al* describes the various impacts of various classes of medication on dyslipidemia in detail [59]. In a cohort of participants followed at Brigham and Women's Hospital and Massachusetts General Hospital, only 42.8% or 66.4% of those recommended to be on treatment by using either the ACC/ACA or ATPIII guidelines, respectively [60]. Though this may reflect a different patient population, the combination of potential under-prescription of statin therapy with suboptimal dosing due to drug interactions may lead to inadequate management of statin therapy in the general population of PLHIV. This may contribute to challenges in adequately controlling known risk factors for ASCVD. Another study in the same patient population of PLHIV showed that aspirin use for primary and secondary prevention of ASCVD was lower than in the general population (12.4% vs. 15.3%), which may also represent another risk factor with inadequate coverage [61]. These studies reflect the challenges in adequately assessing and medically managing risk factors in this population.

Some of the difficulties in providing primary care may arise from the healthcare delivery model. In a survey of Los Angeles PLHIV, 59% of patients use their HIV physician as their primary care physician (PCP), and 84% would prefer this model. This study emphases the strong relationship between HIV physicians and their patients. While this is the preferred approach by

many, it also requires infectious disease-focused (ID) clinics to have the resources of a primary care office, including nurse educators, social workers, pharmacists, and case managers. Whereas AVAMC has these resources available, it is worth noting that ID clinics without these resources may face disadvantages in managing chronic diseases that require routine follow-up such as diabetic and hypertension management [62]. To accommodate an aging HIV population, HIV clinics providing primary care must build on established resources in places to not only manage infectious complications but also chronic conditions and lifestyle risk factors.

Recognizing the many barriers to health and healthcare in this population may help to explain in part the larger and more consistent reduction in mortality seen with reduced time to ART initiation as compared to any composite event.

In addition to the primary and secondary analyses, the demographic data also sheds light on some notable characteristics of this veteran population. For example, a full 1/3 of participants had a history of homelessness, as compared to the rate of homelessness in the general Georgia population being 9 per 10,000 people. Among cis-gender veterans, the lifetime prevalence is estimated to be 6.7% [63]. The high prevalence in this population may mask other factors related to economic instability, poor access to services, and poor health literacy. Because homelessness is a challenging attribute to measure given the method of documentation (EMR diagnostic codes), the true lifetime prevalence may in actuality be higher than recorded.

Additionally, as described above, this predominantly black, male veteran population appears to be sicker than the general middle-aged male population, with higher prevalence of depression, hypertension, and diabetes [64-66]. Comorbidities were also more common in our cohort than the Veterans Aging Cohort Study (VACS) virtual cohort analyzed in 2007. As compared to that study, veterans in this cohort had a higher baseline prevalence of hypertension (20% compared to

40.0%) and diabetes (8% vs. 10.8%) but lower prevalence of liver disease (13% vs. 2.5%) and renal disease (3% vs. 0.8%) [67]. A caveat for liver and renal disease is that this study only included end-organ hepatic or renal disease, which may differ from the VACS study. Though this study only evaluated for depression, the prevalence was 56.5%, which is far higher than the more inclusive definition of psychiatric disorders identified in the VACS study (18%). Notably, adjusting for other comorbidities such as depression or diabetes did not contribute to either the composite outcome or all-cause mortality models, as well as period of ART initiation or class of medication used at ART initiation.

Limitations

This analysis is subject to some key limitations. First, the population is predominantly African American (86%), male (96%), and from an urban health center. Though this is reflective of the general Atlanta VA population, it is less reflective of the population in the United States, in which 42% are African American and 77% are male [14, 68]. This shift in demographics may limit the generalizability of these findings, though it is reflective of a high-risk, vulnerable population in the United States.

Second, the sample was not evenly distributed across the three initiation categories, with approximately half (1523.2/2991.8) of the person-years contributed by the late initiation group. This may limit the ability of the model to detecting true differences, given that the early initiation group was used as the referent group, which contributed only 17.7% (528.6/2991.8) of the person-year. As rapid start became standard practice in December 2016, individuals who fell within this group (i.e. the early initiators) only contributed 1-3 years of follow-up (until May 31, 2019), as compared to late initiators, who tended to have longer follow-up. This group has the additional challenge in that the first year of follow-up is associated with higher mortality, and a greater difference in events may not be seen until multiple years of follow up [14]. The unequal distribution, with relatively few events overall, may skew findings toward the null.

Third, the overall sample size was small. A prior study published by Trickey *et al* included more than 88,000 participants, contributing more than 153,000 person-years [33]. In comparison, our study comprised less than 1% of that sample size and approximately 1% of the person-years. Our sample is insufficiently powered to see small to medium reductions in the hazard ratio.

Fourth, another limitation in this study is the requirement to receive the entirety of HIV care at the VA prior to transfer out, loss to follow up, or death. Participants receiving medication at an

outside institution were excluded, as the absence of an event between ART initiation and transfer to the VA could not be verified. This resulted in the exclusion of a notable number of participants (See Figure 1) and a potential bias in the population that receives care exclusively at the VA. Participants who transferred to the VA after initiation of care transferred from other cities and regions as well as from different private and public clinics in Atlanta. Because of the benefits afforded veterans who receive services at the VA, many previously healthy men chose to switch the VA after receiving the HIV diagnosis after already initiating therapy. Participants already receiving care at the VA may represent a different population, including individuals with more comorbid conditions or potentially lower socioeconomic status. In general, the VA population represents a population with more comorbid conditions, worse outcomes, and lower socioeconomic status, which may also limit the generalizability of these results to the general population.

Fifth, some events may have occurred after the HIV diagnosis but before ART initiation. This may be more common in the group that had a longer delay in ART initiation. It may serve as a potential bias in two ways: first, there is a survivor bias, as we are missing individuals who died soon after diagnosis, and secondly, some non-fatal events, such as ASCVD, may have occurred after HIV diagnosis but before treatment initiation. These comorbidities are categorized as pre-existing conditions for the purpose of this study but may have been categorized as events if treatment had begun earlier. To mitigate this limitation, we could have included only individuals who received their initial HIV diagnosis and entirety of their care at AVAMC; however, that would have further reduced the sample size of this population. Both of these limitations may bias our findings toward the null.

Sixth, for simplicity, this analysis ignores treatment changes, interruptions in therapy, or degree of compliance, as these components are more challenging to abstract from the existing data sources. It also cannot comment on time from infection to diagnosis, which may vary based on access to health care, health literacy, and stigma. The duration of time from infection to diagnosis has decreased from 43 months in 2012 to 39 months in 2016 [69]. A delay of 2-3 months in initiating treatment as was studied in this analysis is small compared to an average 3-4 year delay in diagnosis. Thus, the delay in diagnosis may contribute an even greater amount to morbidity and mortality than what was observed in this study and argues for greater efforts associated with testing. Because a relatively small percentage of individuals are captured during acute infection, it would not be feasible to limit our study to only that population to limit this bias.

Finally, this data set represented notable challenges with data cleaning and data merging, with key variables often found exclusively within the manually-entered/string-text HAVACS database as opposed to the electronic medical record (CPRS). Information pertaining to prior regimens at times may only be found in HAVACS, so missing data may impact inclusion criteria, baseline information, and other key data elements. Typographic errors in HAVACS, particularly in patient identifying information, may result in incorrect merging of records, with the potential both for duplicate records or records being excluded in error. Data pulls from CCR were not always reflective of CPRS during chart review and required manual correction to reflect the record. Inconsistencies were reviewed manually when feasible.

Despite these limitations, these findings still support improved outcomes, both in severe events and all-cause mortality, with earlier initiation of ART.

Conclusions

This analysis demonstrated improved event-free and overall survival with early (<60 days) initiation of ART in a veteran population, independent of baseline characteristics such as age, CD4 count, viral load, renal function, hepatitis C status, and anemia. Notably, the improvement in all-cause mortality was more pronounced than severe events, suggesting the need for additional emphasis on primary care to manage chronic disease, behavioral factors, and psychosocial factors in people living with HIV. Even short (2-month) delays in ART initiation impacted survival, even when accounting for disease status. Adopting strategies to streamline treatment initiation soon after diagnosis may lead to improved morbidity and mortality, potentially serving to close the gap in survival in people with and without HIV.

Figures and Tables

Figure 1: Eligible veterans included in analysis

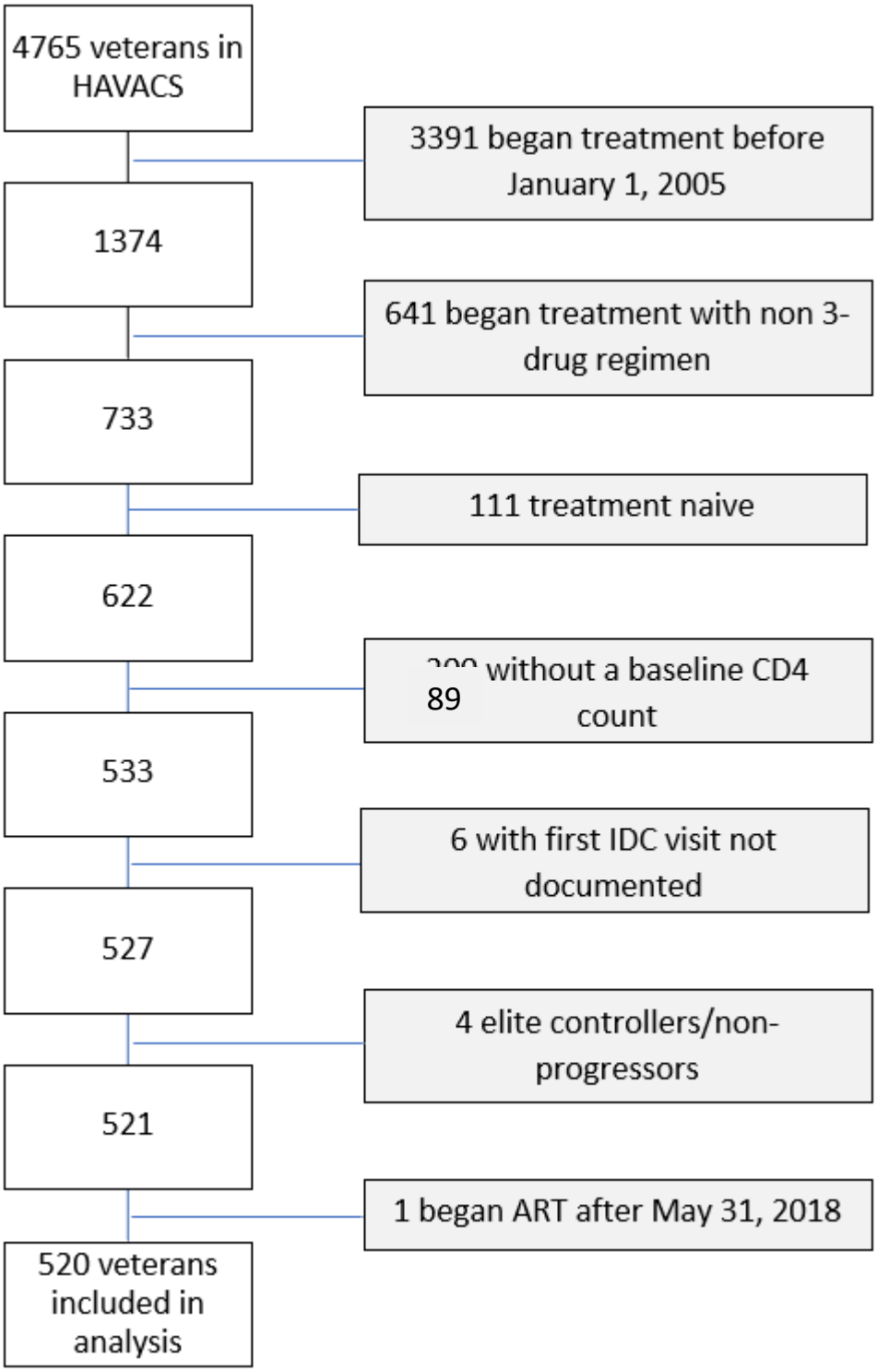

Table 1: Baseline characteristics of veterans at the time of initiating ART, by time since HIV diagnosis

	All		≤60 days		61-365 days		>365 days	
	n	%	n	%	n	%	n	%
	520	**100.0%**	**109**	**21.0%**	**153**	**29.4%**	**258**	**49.6%**
Age (years)								
Median (25%, 75%)	45.9 (36.5, 53.75)		45.4 (36.0, 53.76)		45.4 (36.1, 53.38)		46.0 (37.0, 54.2)	
<30	61	11.7%	13	11.9%	18	11.8%	30	11.6%
30-39	113	21.7%	24	22.0%	34	22.2%	55	21.3%
40-49	146	28.1%	27	24.8%	49	32.0%	70	27.1%
50-59	141	27.1%	31	28.4%	30	19.6%	80	31.0%
≥60	59	11.3%	14	12.8%	22	14.4%	23	8.9%
Sex								
Female	20	3.8%	6	5.5%	7	4.6%	7	2.7%
Male	500	96.2%	103	94.5%	146	95.4%	251	97.3%
Race								
White	66	12.7%	22	20.2%	19	12.4%	25	9.7%
Black	445	85.6%	86	78.9%	131	85.6%	228	88.4%
Other/unknown	7	1.3%	1	0.9%	2	1.3%	4	1.6%
Missing	2	0.4%	0	0.0%	1	0.7%	1	0.4%
Ethnicity								
Hispanic	6	1.2%	2	1.8%	3	2.0%	1	0.4%
Non-Hispanic	485	93.3%	100	91.7%	141	92.2%	244	94.6%
Unknown	29	5.6%	7	6.4%	9	5.9%	13	5.0%
Social/Behavioral factors								
Men who have sex with men	260	50.0%	50	45.9%	69	45.1%	141	54.7%
Injection drug use	42	8.1%	3	2.8%	3	2.0%	36	14.0%
Tobacco use (ever)	150	28.8%	24	22.0%	38	24.8%	88	34.1%
Homelessness (ever)	177	34.0%	33	30.3%	51	33.3%	93	36.0%

Comorbidities								
Depression	294	56.5%	59	54.1%	88	57.5%	147	57.0%
Diabetes	56	10.8%	13	11.9%	16	10.5%	27	10.5%
Hepatitis C	41	7.9%	3	2.8%	6	3.9%	32	12.4%
Hypertension	208	40.0%	40	36.7%	65	42.5%	103	39.9%
Pre-existing severe conditions								
AIDS at treatment initiation*	176	33.8%	48	44.0%	52	34.0%	76	29.5%
AIDS-defining illness**	59	11.3%	11	10.1%	15	9.8%	33	12.8%
ASCVD**	46	8.8%	7	6.4%	12	7.8%	27	10.5%
Invasive infection**	36	6.9%	8	7.3%	12	7.8%	16	6.2%
Malignancy**	41	7.9%	8	7.3%	7	4.6%	26	10.1%
Severe liver disease**	13	2.5%	3	2.8%	2	1.3%	8	3.1%
Severe renal disease**	4	0.8%	1	0.9%	1	0.7%	2	0.8%
Period of ART initiation								
2005-2009	200	38.5%	21	19.3%	59	38.6%	120	46.5%
2010-2015	254	48.8%	63	57.8%	76	49.7%	115	44.6%
2016-2018	66	12.7%	25	22.9%	18	11.8%	23	8.9%
CD4 count (copies/mm^3)								
Median (25%, 75%)	287 (161, 423)		251 (85, 426)		277 (144, 442)		291 (187, 412)	
<200	120	23.1%	46	42.2%	49	32.0%	70	27.1%
200-349	167	32.1%	21	19.3%	49	32.0%	97	37.6%
350-499	92	17.7%	20	18.3%	27	17.6%	45	17.4%
≥500	96	18.5%	22	20.2%	28	18.3%	46	17.8%
HIV-1 RNA (log copies/mm^3)								
Median (25%, 75%)	4.7 (4.0, 5.2)		4.9 (4.2, 5.4)		4.8 (4.2, 5.4)		4.6 (3.9, 5.1)	
0-3.99	121	23.3%	19	17.4%	30	19.6%	72	27.9%
4-4.99	200	38.5%	45	41.3%	65	42.5%	110	42.6%
≥5.00	179	34.4%	45	41.3%	58	37.9%	76	29.5%

VACS Index								
Median (25%, 75%)		31.5 (19, 50)		35 (19, 64)		30 (20, 46)		30 (19, 48)
<20	133	25.6%	31	28.4%	36	23.5%	66	25.6%
20-35	146	28.1%	19	17.4%	48	31.4%	79	30.6%
36-50	132	25.4%	26	23.9%	42	27.5%	64	24.8%
>50	109	21.0%	33	30.3%	27	17.6%	49	19.0%
Initial regimen								
Integrase inhibitor-based regimen	115	22.1%	41	37.6%	31	20.3%	43	16.7%
NNRTI-based regimen	301	57.9%	48	44.0%	88	57.5%	165	64.0%
Other regimen	104	20.0%	20	18.3%	34	22.2%	50	19.4%
Time to initiation of ART after diagnosis (days)								
Median (25%, 75%)		403 (74, 1782)		0 (0, 3)		39 (7, 100)		652 (50, 1747)
≤60	109	21.0%	109	100.0%	0	0.0%	0	0.0%
61-365	153	29.4%	0	0.0%	153	100.0%	0	0.0%
>365	258	49.6%	0	0.0%	0	0.0%	258	100.0%
Time to initiation of ART after first IDC visit (days)								
Median (25%, 75%)		50 (0, 722)		37 (22, 48)		121 (82, 209)		1781 (961, 2999)
≤60	270	51.9%	108	99.1%	96	62.7%	66	25.6%
61-180	50	9.6%	1	0.9%	37	24.2%	12	4.7%
181-365	32	6.2%	0	0.0%	19	12.4%	13	5.0%
>365	168	32.3%	0	0.0%	1	0.7%	167	64.7%

* AIDS as classified by an AIDS-defining illness or CD4 count <200 cells/mm^3

** Non-fatal components of composite outcome

Table 2: Primary outcomes by time from HIV diagnosis to ART initiation

	All		≤60 days		61-365 days		>365 days	
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**
	520	**100.0%**	**109**	**20.9%**	**153**	**29.3%**	**287**	**55.0%**
Any event (composite outcome)	159	30.6%	24	22.0%	41	26.8%	94	32.8%
AIDS-defining illness	20	3.8%	3	2.8%	6	3.9%	11	3.8%
ASCVD	38	7.3%	7	6.4%	12	7.8%	19	6.6%
Death*	36	6.9%	4	3.7%	12	7.8%	18	6.3%
Invasive infection	21	4.0%	2	1.8%	5	3.3%	16	5.6%
Malignancy	20	3.8%	0	0.0%	4	2.6%	16	5.6%
Severe liver disease	19	3.7%	6	5.5%	2	1.3%	11	3.8%
Severe renal disease	5	1.0%	2	1.8%	0	0.0%	3	1.0%
Total deaths	65	12.5%	7	6.4%	20	13.1%	38	13.2%

* When death is the first competing event to occur

Table 3: Transfer and loss to follow up by time from HIV diagnosis to ART initiation

	All		≤60 days		61-365 days		>365 days	
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**
	520	**100.0%**	**109**	**21.0%**	**153**	**29.4%**	**258**	**49.6%**
Transferred care	69	13.3%	11	10.1%	13	5%	45	17.4%
Lost to follow up	81	15.6%	14	12.8%	22	9%	45	17.4%

Figure 2: Composite outcomes, stratified by time from HIV diagnosis to ART initiation

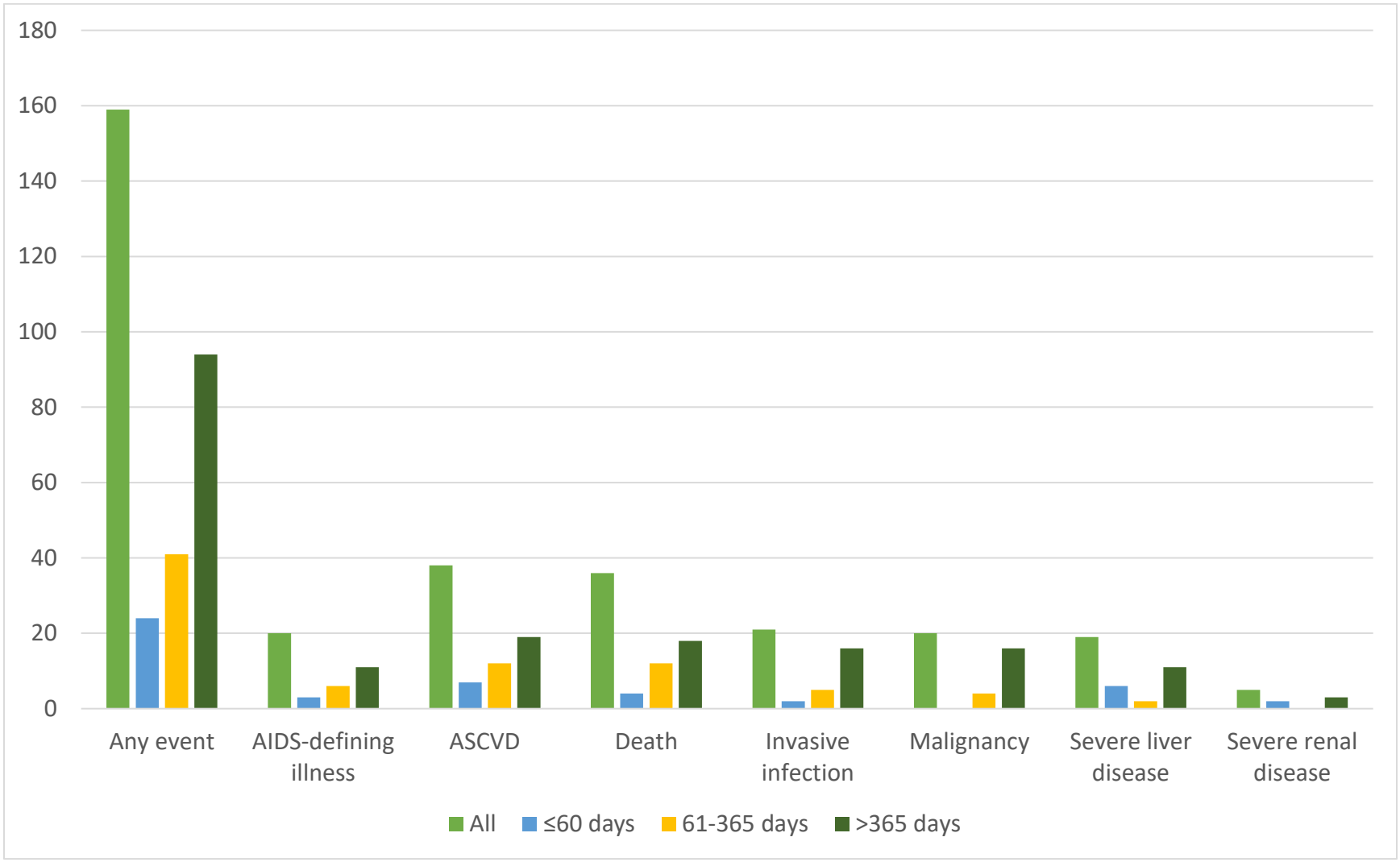

Table 4: Person-years contributed by group, stratified by time from HIV diagnosis to ART initiation

	Total	Median person-years	25th percentile	75th percentile	Rate of any events (per 1000 person-years)	Rate of death (per 1000 person-years)
All groups (person-years)	2991.8	5.5	2.8	8.6	53.1	21.7
≤60 days	528.6	4.8	1.9	7.3	45.4	13.2
61-365 days	940.0	6.0	3.2	8.6	43.6	21.3
>365 days	1523.2	5.7	2.7	8.9	61.7	24.9

Figure 3: Log(-Log) of Estimate Survivor Function for Composite Outcome

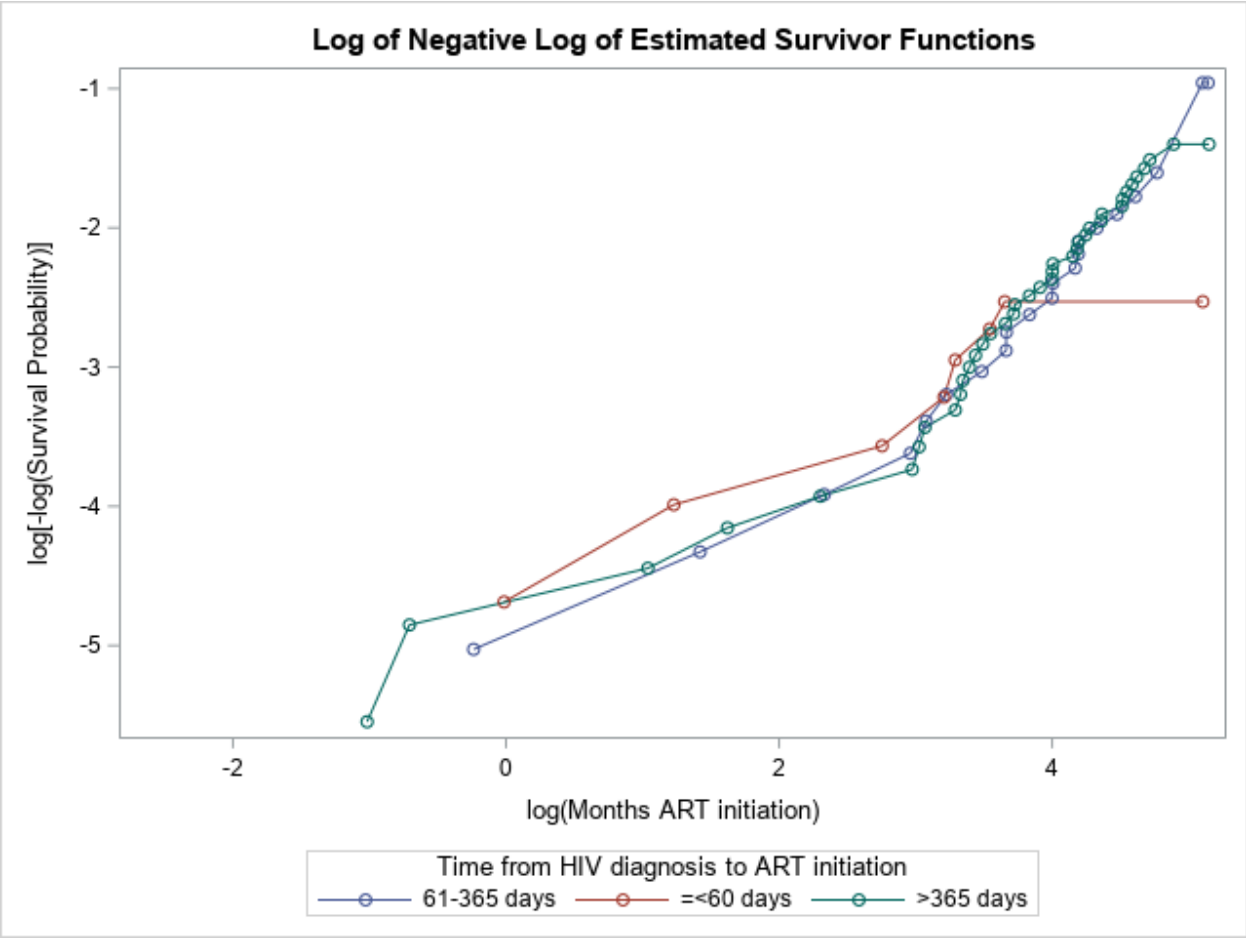

Figure 4: Log(-Log) of Estimate Survivor Function for All-Cause Mortality

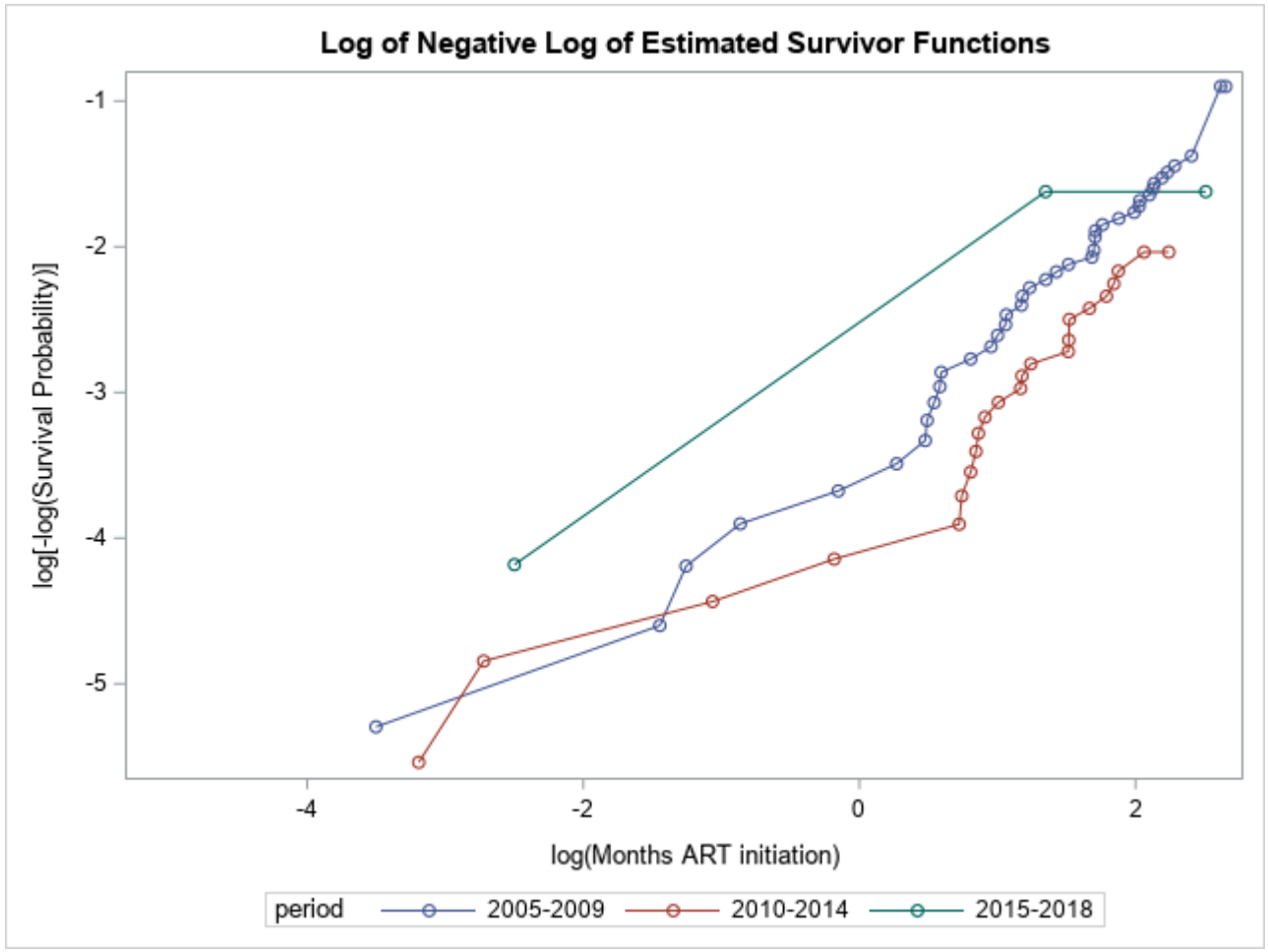

Table 5: Pearson Correlation Coefficients

	Any event	Death
Time from HIV diagnosis to ART initiation	0.89	0.55
VACS Index	0.17	0.38
VACS Index at 1 year	0.33	0.74

*Table 6: Unadjusted and adjusted hazard ratios of primary outcomes by time between HIV diagnosis and ART initiation**

	61-365 days						>365 days						Wald Chi-Square p value	
	Unadjusted HR	95% HR CL		Adjusted HR	95% HR CL		Unadjusted HR	95% HR CL		Adjusted HR	95% HR CL		Unadjusted HR	Adjusted HR
Any event	0.97	0.58	1.60	1.27	0.76	2.12	1.36	0.87	2.14	1.81	1.15	2.87	0.12	0.02
Death	1.62	0.68	3.84	2.49	1.05	5.94	1.80	0.80	4.04	2.81	1.24	6.33	0.36	0.05

* Using ≤60 days as referent group

Figure 5: Unadjusted and adjusted hazard ratios plots

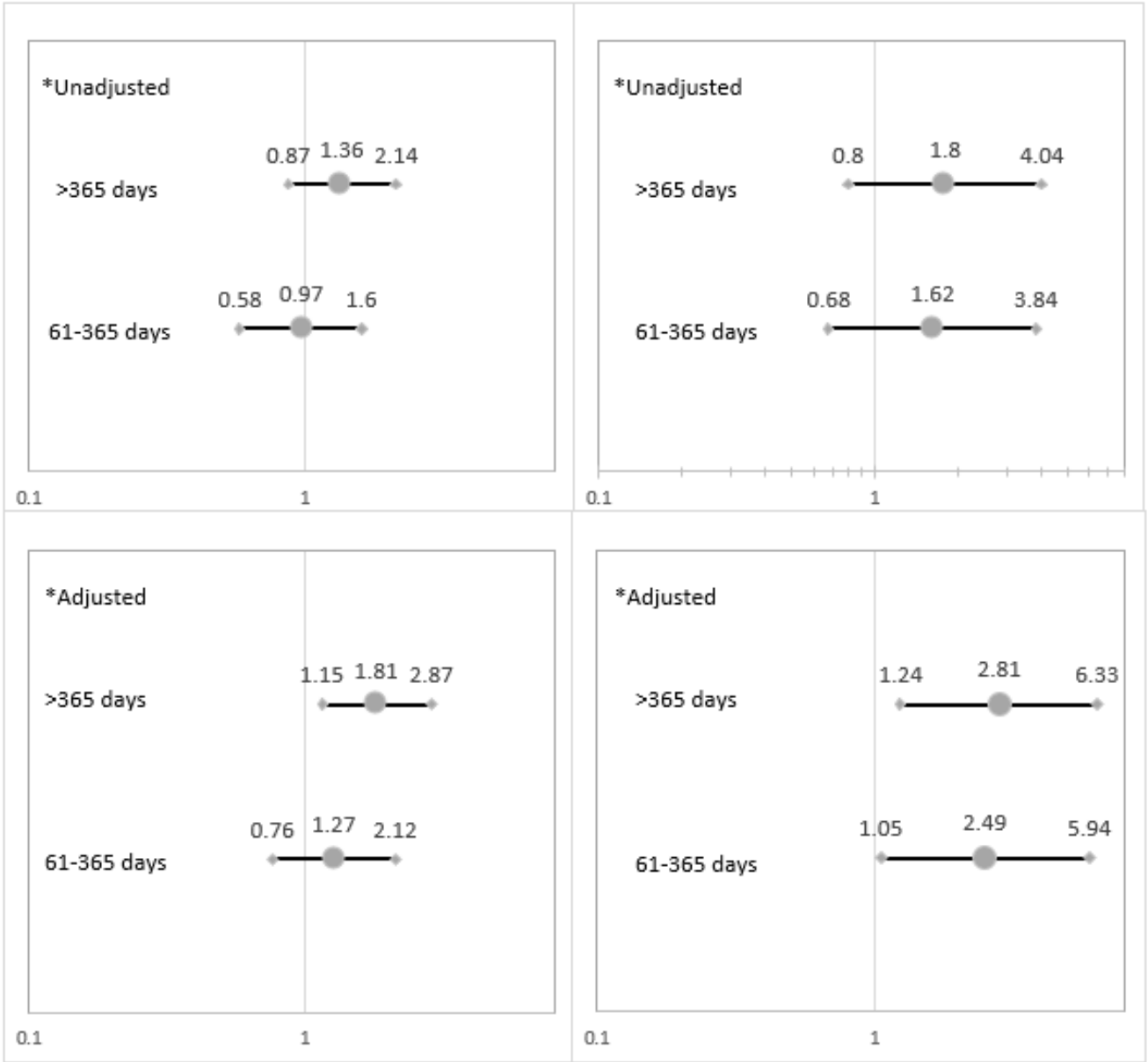

Figure 6: Unadjusted Cox Proportional Hazards Model for Composite Outcome

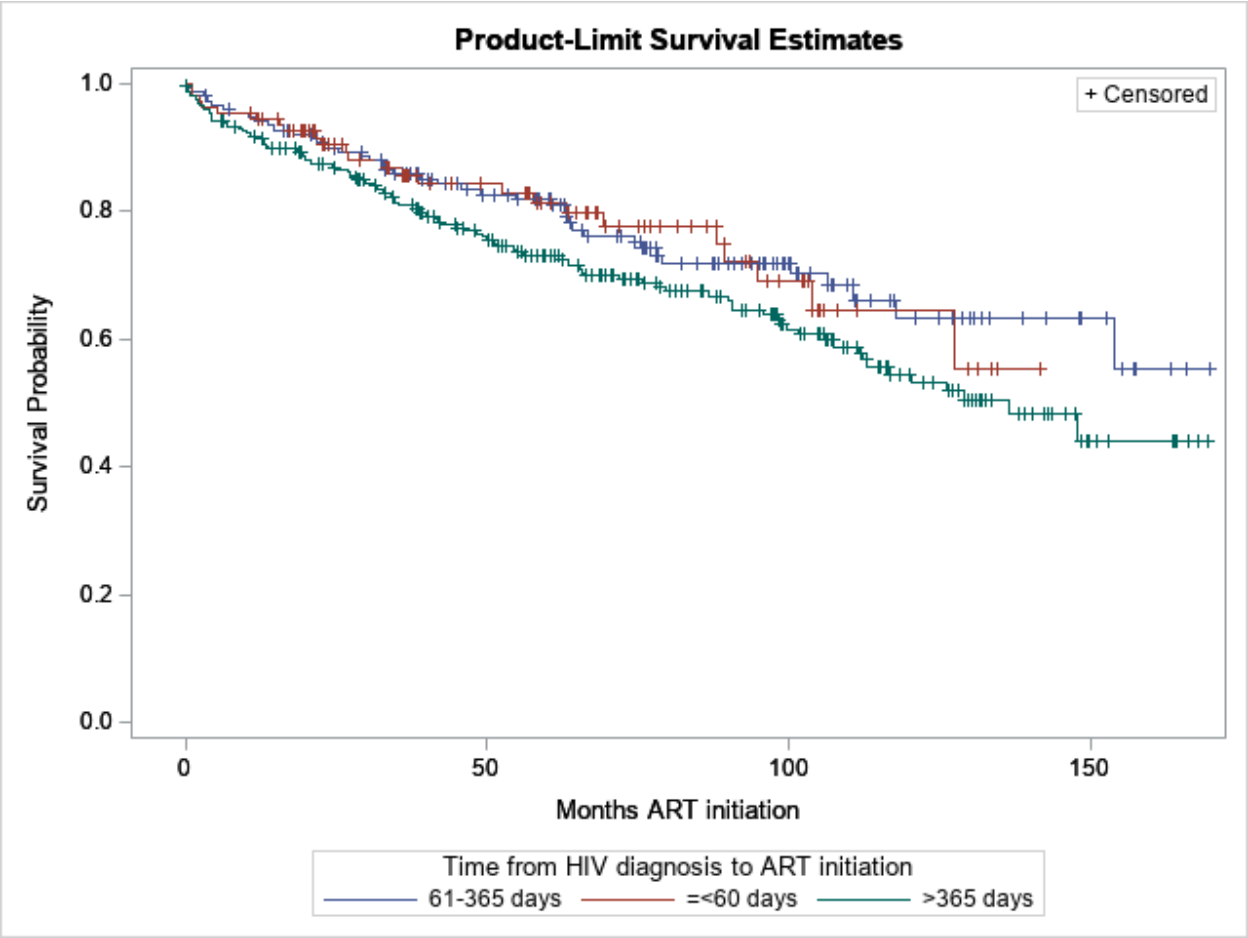

Figure 7: Unadjusted Cox Proportional Hazards Model for All-Cause Mortality

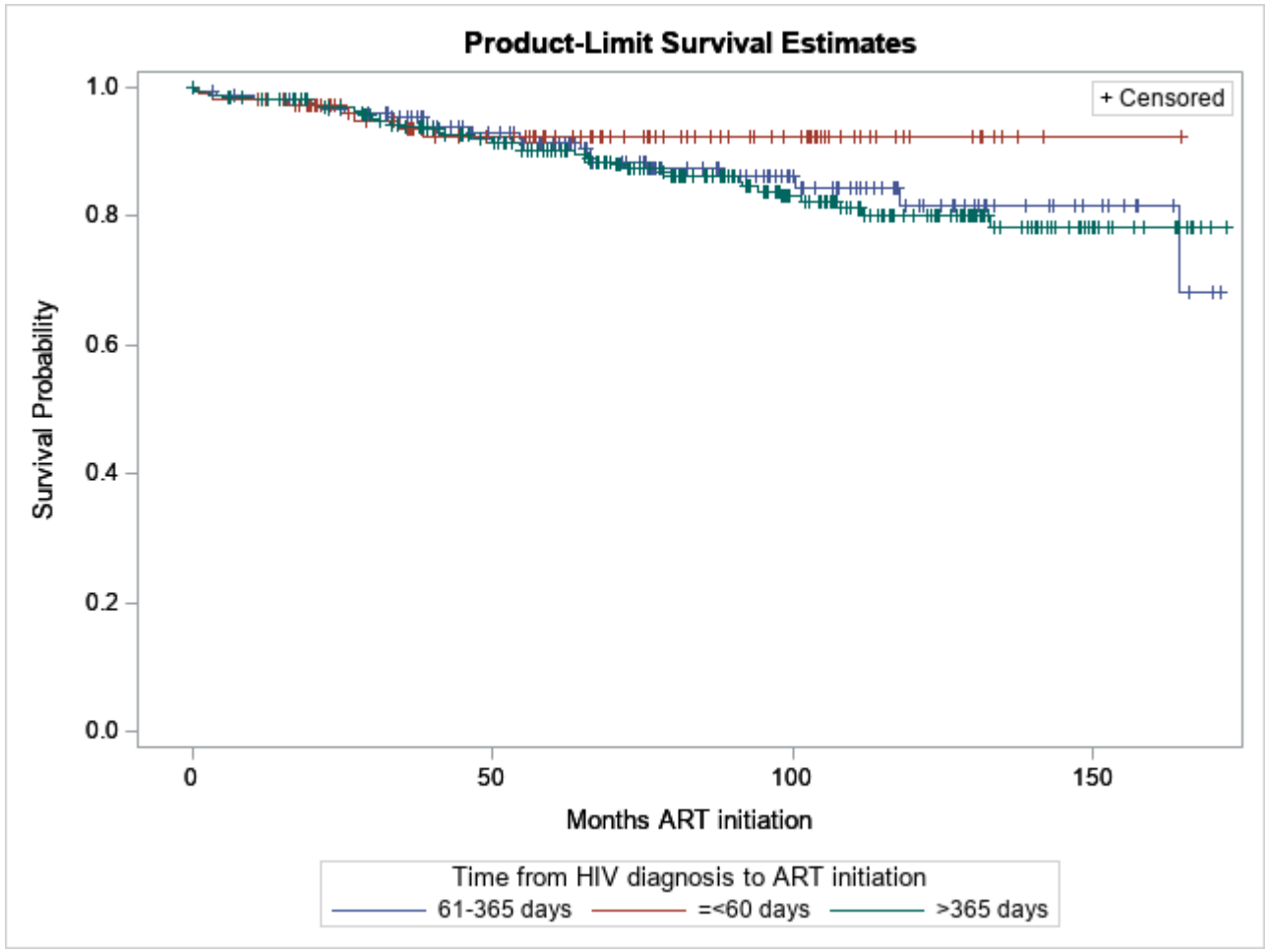

Table 7: Subdistribution hazards model for competing events by time between HIV diagnosis and ART initiation

	61-365 days						>365 days						Wald Chi-Square p value	
	Unadjusted HR	**95% HR CL**		**Adjusted HR**	**95% HR CL**		**Unadjusted HR**	**95% HR CL**		**Adjusted HR**	**95% HR CL**		**Unadjusted HR**	**Adjusted HR**
AIDS-defining illness	UD*	--	--	UD	--	--	UD	--	--	UD	--	--	--	--
ASCVD	0.96	0.38	2.42	1.07	0.41	2.80	0.90	0.37	2.16	1.01	0.39	2.59	0.97	0.98
Death	1.80	0.58	5.57	2.85	0.89	9.07	1.73	0.59	5.04	2.69	0.90	8.06	0.57	0.18
Invasive infection	1.54	0.30	7.92	1.61	0.32	8.02	2.54	0.58	11.17	2.70	0.67	10.98	0.35	0.28
Malignancy	1.32	0.33	5.28	0.38	0.33	5.77	1.41	0.40	5.04	1.47	0.39	5.58	0.87	0.85
Severe liver disease	0.18	0.04	0.86	0.18	0.04	0.86	0.56	0.21	1.50	0.58	0.21	1.63	0.10	0.10
Severe renal disease	UD	--	--	UD	--	--	0.49	0.09	2.67	0.77	0.14	4.35	--	--

UD*=undefined

Figure 8: Cumulative Incidence Function of Subdistribution Model of Composite Outcome

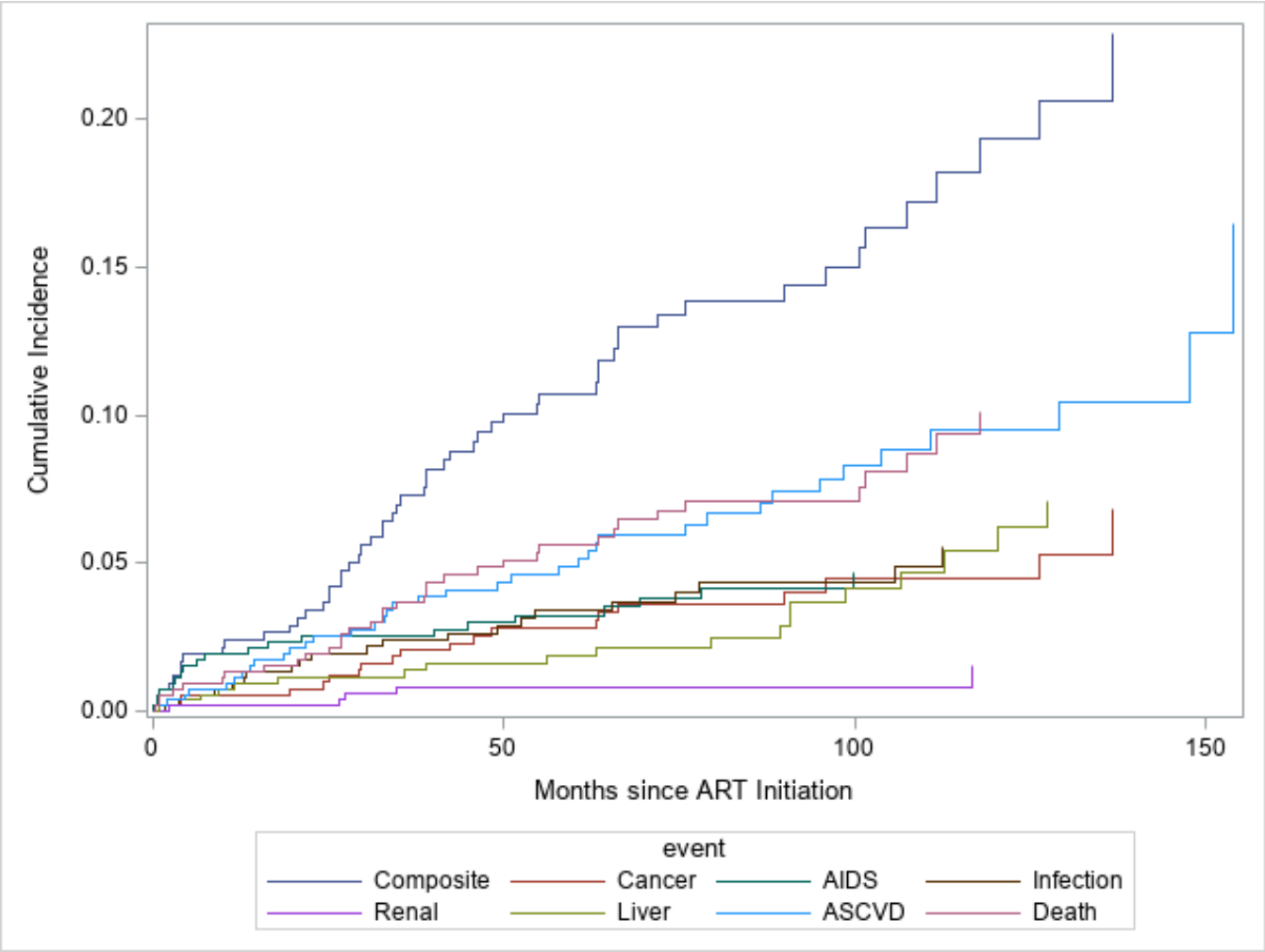

*Table 8: Adjusted hazard ratios of primary outcomes by time from HIV diagnosis to ART initiation, adjusted by VACS Index at ART initiation and VACS Index at 1 year**

	61-65 days			>365 days			Wald Chi-Square p value
	Adjusted HR	95% HR CL		Adjusted HR	95% HR CL		Adjusted HR
Any event	1.30	0.76	2.22	1.67	1.03	2.70	0.08
Death	2.80	1.01	7.64	2.90	1.12	7.52	0.09

* Using ≤60 days as referent group

Appendix A

RCTs included in Cochrane Review [30]*				
Study	**Study Design**	**Location**	**Number of participants**	**Outcomes**
Amanyire, 2016 [70]	Cluster-RCT	20 clinics in Uganda	15,000 treatment-naïve adults	ART initiation, viral suppression, retention in care, others
Elul, 2017 [71]	Cluster-RCT	10 clinics in Mozambique	5327 treatment-naïve adults	Mortality and viral suppression at 12 months, time to ART initiation, linkage to care at 1 month, retention in care at 6 months, others
Koenig, 2017 [72]	Open-label RCT	Haiti	762 treatment-naïve adults with WHO stage 1 or 2 disease	Retention in care and viral suppression at 12 months, same-day initiation, others
Labhardt, 2018 [73]	Open-label RCT	Household-based study in Lesotho	278 treatment-naïve adults without WHO stage 4 disease or TB	Mortality, virological suppression and retention in care at 12 months, others
McNairy, 2017 [74]	Open-label RCT	10 clinics in eSwatini	2550 treatment-naïve adults	Linkage to care at 1 month, retention at 12 months, time to ART initiation, death and LTFU at 12 months, others
Rosen, 2016 [75]	Open-label RCT	2 clinics in South Africa	463 treatment-naïve adults	Viral suppression and retention at 10 months, initiation of treatment within 3 months, others
Stevens, 2017 [76]	Individual RCT	3 clinics in South Africa	717 treatment-naïve adults with CD4 <350 cells/mm^3	Retention in care at 6 and 12 months, time to ART initiation, others

* Table created from data from review article

Summary of findings in Cochrane Review for Rapid ART compared to standard care for people living with HIV [30]*

Rapid ART compared to standard care for people living with HIV

Patient or population: people living with HIV
Setting: any
Intervention: rapid ART
Comparison: standard care

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with standard care	Risk with rapid ART				
Mortality at 12 months	44 per 1000	32 per 1000 (22 to 44)	RR 0.72 (0.51 to 1.01)	5451 (7 RCTs)	⊕◯◯◯ Very low[a,b,c]	We do not know if rapid ART has an effect on mortality after one year of follow-up
Virological suppression at 12 months	506 per 1000	597 per 1000 (556 to 642)	RR 1.18 (1.10 to 1.27)	2719 (4 RCTs)[d]	⊕⊕⊕◯ Moderate[e,f,g,h]	Rapid ART probably increases the likelihood of individuals being virally suppressed after 12 months
Retention in care at 12 months	538 per 1000	656 per 1000 (597 to 726)	RR 1.22 (1.11 to 1.35)	5001 (6 RCTs)	⊕⊕◯◯ Low[g,h,i,j]	Rapid ART may improve retention in care at 12 months.
Uptake of ART at 90 days	719 per 1000	942 per 1000 (848 to 1000)	RR 1.31 (1.18 to 1.45)	11,404 (4 RCTs)	⊕⊕◯◯ Low[h,k,l]	Rapid ART may improve uptake of ART at 90 days.
Uptake of ART at 12 months	870 per 1000	948 per 1000 (922 to 975)	RR 1.09 (1.06 to 1.12)	3713 (4 RCTs)	⊕⊕⊕◯ Moderate[h,k]	Rapid ART probably improves uptake of ART at 12 months.

* Table courtesy of review article

APPENDIX B

Diagnoses and Associated ICD-9/ICD-10 Codes		
Diagnosis	**ICD-9m Codes**	**ICD-10 Codes**
Depression	V60; 296.20; 296.21; 296.21; 296.22; 296.23; 296.24; 296.25; 296.30; 296.31; 296.32; 296.33; 296.34; 296.35; 296.5; 296.6; 296.82; 296.90; 300.4; 309.01; 309.1; 309.28; 311	F31.3; F31.4; F31.5; F31.6; F32; F33.0; F33.1; F33.2; F33.3; F33.8; F33.9; F34.1; F34.8; F34.9; F38.0; F38.1; F38.8; F39; F99; F41.2
Homeless	V60; 296.20; 296.21; 296.21; 296.22; 296.23; 296.24; 296.25; 296.30; 296.31; 296.32; 296.33; 296.34; 296.35; 296.5; 296.6; 296.82; 296.90; 300.4; 309.01; 309.1; 309.28; 311	Z59
Tobacco use	305.1	F17.21
Hypertension	401.9; 401.0; 401.1; 402.; 403.; 404.; 405.; 437.2	I10.; I11.9; I12.9; I12.0; I13.0; I13.2; I13.10; I13.11
Cancer	140.; 141.; 142.; 143.; 144.; 145.; 146.; 147.; 148.; 150.; 151.; 152.; 153.; 154.; 155.; 156.; 157.; 158.; 160.; 161.; 162.; 163.; 164.; 170.; 171.; 172.; 185.; 186.; 187.; 188.; 189.; 190.; 191.; 192.; 193.; 194.; 200.; 201.; 202.; 203.; 204.; 205.; 206.; 207.; 208.	C00.; C01.; C02.; C03.; C04.; C05.; C06.; C07.; C08.; C09.; C10.; C11.; C12.; C13.; C15.; C16.; C17.; C18.; C19.; C20.; C21.; C22.; C23.; C24.; C25.; C30.; C31.; C32.; C33.; C34.; C35.; C36.; C37.; C38.; C40.
ASCVD	410.; 402.; 404.; 428.; 433.01; 433.11; 433.21; 433.31; 433.81; 433.91; 434.01; 434.11; 434.91; 436.; 438.	I21.; I11.; I13.; I50.; I63.; I67.89; I69.99
AIDS	112.5; 112.81; 112.82; 112.83; 112.84; 112.85; 112.86; 112.87; 112.88; 114.1; 114.2; 114.3; 115.01; 115.02; 115.03; 115.04; 118.; 321.0; 117.5; 007.4; 176.; 007.2; 031.2; 136.3; 046.3; 003.1; 130.; 078.5; 010.; 011.; 012.; 013.; 014.; 015.; 016.; 017.; 018.	B37.7; B37.6; B37.84; B37.5; B37.82; B37.81; B45.; B38.3; B38.4; B38.89; B25.9; B48.8; B45.1; A07.2; A07.3; A31.2; B59; A81.2; B58.2; A02.1; C46.1; C46.2; C46.4; C46.4; C46.7; C46.9; C46.0; B58.2; B58.09; B58.01; B58.81; B58.3; B58.1; B58.1; B58.89; B58.0
Infection	320.0; 320.1; 320.2; 320.3; 421.; 481.; 482.; 483.; 485.; 487.; 488.	G00.0; G00.3; I33.0; I39.; I33.9; J13.; J15.0; J15.1; J18.1; J15.9; J15.7; J16.0; J16.8; J18.0; J11.0; J12.9; J10.1; J11.1; J11.2; J11.81; J11.89; J18.0
Renal disease	585.6	N18.6
Liver disease	570.; 571.5	K72.00; K76.2; K74.0; K74.60; K74.69

APPENDIX C

Veterans Aging Cohort Study Index		
Characteristic	**Value**	**Score**
Age (years)	<50	0
	50-64	+12
	≥65	+27
CD4 count (cells/mm^3)	≥500	0
	350-499	+6
	200-349	+6
	100-199	+10
	50-100	+28
	<50	+29
HIV-1 RNA (copies/ml)	<500	0
	500-99,999	+7
	≥100,000	+14
Hemoglobin (g/dL)	≥14.0	0
	12.0-13.9	+10
	10.0-11.9	+22
	<10.0	+38
FIB-4 Index	<1.45	0
	1.45-3.25	+6
	>3.25	+25
eGFR	≥60.0	0
	45.0-59.9	+6
	30.0-44.9	+8
	<30.0	+26
Hepatitis C co-infection	No	0
	Yes	+5

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