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Cause-specific mortality among HIV-infected individuals, by CD4+ cell count at HAART initiation, compared with HIV-uninfected individuals

Nikolas Wada[a], **Lisa P. Jacobson**[a], **Mardge Cohen**[b], **Audrey French**[b], **John Phair**[c], and **Alvaro Muñoz**[a]

[a]Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland [b]Department of Medicine, Stroger Hospital of Cook County and Rush University, Chicago, Illinois, USA [c]Feinberg School of Medicine, Division of Infectious Diseases, Northwestern University, Chicago, Illinois, USA

Abstract

Objectives—To compare the proportion, timing and hazards of non-AIDS death and AIDS death among men and women who initiated HAART at different $CD4^+$ cell counts to mortality risks of HIV-uninfected persons with similar risk factors.

Design—Prospective cohort studies.

Methods—We used parametric mixture models to compare proportions of AIDS and non-AIDS mortality and ages at death, and multivariable Cox models to compare cause-specific hazards of mortality, across levels of $CD4^+$ cell count at HAART initiation (≤200 cells/μl: 'late', 201–350 cells/μl: 'intermediate', >350 cells/μl: 'early') and with HIV-uninfected individuals from the Multicenter AIDS Cohort Study and the Women's Interagency HIV Study. We used multiple imputation methods to address lead-time bias in sensitivity analysis.

Results—Earlier initiators were more likely to die of non-AIDS causes (early: 78%, intermediate: 74%, late: 49%), and at older ages (median years 72, 69, 66), relative to later initiators. Estimated median ages at non-AIDS death for each $CD4^+$ cell count category were lower than that estimated for the HIV-uninfected group (75 years). In multivariable analysis, non-AIDS death hazard ratios relative to early initiators were 2.15 for late initiators ($P < 0.01$) and 1.66 for intermediate initiators ($P = 0.01$); AIDS death hazard ratios were 3.26 for late initiators ($P < 0.01$) and 1.20 for intermediate initiators ($P = 0.28$). Strikingly, the adjusted hazards for non-AIDS death among HIV-uninfected individuals and early initiators were nearly identical (hazard ratio 1.01). Inferences were unchanged after adjustment for lead-time bias.

Correspondence to Nikolas Wada, Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, 615 North Wolfe Street, Room E7648, Baltimore, MD 21205, USA. Tel: +1 202 669 7739; fax: +1 410 955 7587; nwada@jhsph.edu.

Conflicts of interest

There are no conflicts of interest.

Conclusion—Results suggest the possibility of reducing the risk of non-AIDS mortality among HIV-infected individuals to approximate that faced by comparable HIV-uninfected individuals.

Keywords

antiretroviral therapy; bias; $CD4^+$ cell count; cohort studies; competing risks; mortality; statistical

Introduction

Treatment with HAART has increased life expectancies [1] and has lowered the share of AIDS-related mortality among HIV-infected populations [2]. Net effects of HAART on the hazards and timing of non-AIDS mortality in aggregate have been unclear. Associations between the degree of immune suppression and mortality from specific non-AIDS causes such as infections, myocardial infarctions and liver disease suggest that HAART, by restoring immune function, may reduce the risk of non-AIDS mortality.

Evidence has accumulated over time supporting HAART initiation at progressively higher $CD4^+$ cell counts [3–11], and guidelines for clinicians have followed suit [12]. All-cause mortality risks remain elevated among HAART-treated patients relative to HIV-uninfected individuals [2], but there is still a pressing question as to whether the lifespan of optimally treated HIV-infected individuals may approach that of HIV-uninfected individuals [13]. Although most studies consider mortality in aggregate, non-AIDS-related mortality risks may also decrease when HAART is initiated at higher $CD4^+$ cell counts [14]. Associations between $CD4^+$ cell count at HAART initiation and the competing risks of non-AIDS-related and AIDS-related mortality remain unclear.

Materials and methods

Study population

The Multicenter AIDS Cohort Study (MACS) and the Women's Interagency HIV Study (WIHS) are ongoing prospective cohort studies of HIV infection. Briefly, the MACS cohort is composed of homosexual and bisexual men from four sites in the United States, and the WIHS cohort is composed of women from six sites in the United States. The study population for this analysis included HIV-uninfected and HAART-exposed HIV-infected individuals. Only person-time after age 35 was included. The date of analysis was 1 January 2011 and those alive at that date were administratively censored. Studies were approved by the Committees of Human Research of participating institutions and the executive committees of MACS and WIHS.

Definition of time scale

Age was the time scale for the analysis, with the origin at 35 years old. To prevent sparse events from driving model estimates, we considered person-time and outcomes observed between the ages of 35 and 70 years. Individuals entering the study after age 35 were handled using left-truncation methods to avoid bias due to late entry into the analytical period. We chose age as the time scale to provide a meaningful time origin for both HIV-

uninfected and HAART-treated HIV-infected individuals and to provide the best possible control for age as a predictor of mortality.

We included both HIV-uninfected person-time and HIV-infected person-time following HAART initiation. Individuals could contribute person-time to both categories if they became infected with HIV during follow-up and were subsequently treated with HAART, with HIV-infected person-time prior to HAART initiation excluded from the analysis. Table 1 summarizes the treatment of person-time in the analysis.

Definition of outcomes and exposures

The two outcomes of interest were death from AIDS and death from non-AIDS causes. Deaths among WIHS and MACS members were classified through a review of death certificate and National Death Index (NDI) records; deaths were considered AIDS-related if AIDS, an AIDS-defining illness, pneumonia or sepsis was listed as a contributing cause of death on the death certificate or the NDI. Deaths resulting from injury or poisoning (43 from the MACS and 49 from the WIHS) were treated as right-censored observations at the time of death, because such deaths were unlikely to be related to $CD4^+$ cell count at HAART initiation and thus would have diluted effect estimates.

HAART initiators were classified into one of three categories defined by their $CD4^+$ cell count at initiation (≤200 cells/μl: 'late initiators', 201–350 cells/μl: 'intermediate initiators', >350 cells/μl: 'early initiators'). When the $CD4^+$ cell count at the time of HAART initiation was unavailable, we used the last measurement prior to the HAART initiation date, excluding those for whom the time window exceeded 1 year.

We defined baseline values for exposure variables that were applicable to both HIV-infected and HIV-uninfected individuals, and that have established associations with mortality [15–18]. Exposure variables were limited to those that were measured similarly between cohorts. Baseline was defined uniquely for each individual as the first study visit between ages 35 and 70 years as either HIV-uninfected or HAART-treated. Our interest was in controlling for differences in mortality across groups defined by time-fixed covariates at baseline, rather than in the acute effects of time-varying exposures. We considered a wide range of baseline variables; those included in the final analysis are described below.

All covariates were defined dichotomously. Hepatitis B virus (HBV) infection was defined by a positive test for hepatitis B surface antigen at initial study visit, and hepatitis C virus (HCV) infection was defined by a positive viral RNA test for HCVat baseline (MACS) or at the initial study visit (WIHS). At analytical baseline, depressive symptoms were defined as a CESD score of more than 16 [19]; hypertension was defined as either SBP at least 140 mmHg or DBP at least 90 mmHg; smoking and employment status (full-time, part-time or student) were measured by self-report. We also used cohort membership (MACS or WIHS) as a crude proxy variable to address sex and the other substantial differences in demographic, behavioural and socioeconomic traits between cohorts.

Statistical methods

Death from AIDS and death from non-AIDS causes are competing risks. To directly address the competing nature of these outcomes, we employed two statistical approaches. To obtain a fully parametric but minimally adjusted set of estimates, we fit mixture models [20] estimating both the proportion of individuals who experience each cause of death and the ages at death for each cause. We have previously described the details of this approach [2]. Let π be the proportion of HAART-treated individuals dying of non-AIDS causes by the upper limit of age (defined as 100), and $(1 - \pi)$ be the the proportion dying of AIDS. Let $S_1(t)$ be the survival function for the π% dying of non-AIDS, and $S_2(t)$ be the survival function for the $(1 - \pi)$% dying of AIDS. The models simultaneously estimate the mixture parameter π and the survival functions $S_1(t)$ and $S_2(t)$, employing Weibull distributions of survival times with location β and scale σ such that the pth percentile is $\exp[\beta + \sigma\{\log(-\log(1-p))\}]$ for each cause of death. The parameters β, σ and π were allowed to vary by exposure category. Right-censored observations were treated as interval-censored with an upper limit of 100 years of age to ensure realistic estimates for ages at death [2]. A key advantage of these models is that they allow estimation of probability density functions on the age scale that are cause-specific and that graphically reflect the proportion of individuals dying of each cause. We calculated percentile differences in ages at cause-specific death by exposure category. Confidence intervals (CIs) for percentiles and differences in percentiles were calculated using the delta method [21].

As multivariable mixture models were impractical owing to the infrequency of mortality, we used multivariable proportional cause-specific hazards (PCSH) models [22]. The efficiency afforded by assuming proportional hazards allowed us to estimate cause-specific hazard ratios by $CD4^+$ cell count category that were adjusted for important possible confounding variables. This approach also allowed testing for differential effects of an exposure across causes of death [22]. We started with a model containing only $CD4^+$ cell count categories and study cohort (MACS/WIHS) and added covariates in a stepwise fashion.

In the mixture models, the likelihood function incorporated uncertainty regarding cause of death among deaths classified as ‘unknown’ because of either missing or equivocal cause of death information from death certificates or the NDI; this approach does not require the assumptions of alternative approaches based on cause-specific hazards [23] or subhazards [24]. In the PCSH models, we used multiple imputation methods to reclassify unknown deaths into AIDS and non-AIDS categories, an approach we described previously [2].

Relative to a hypothetical clinical trial in which 35-year-old individuals are followed from a common $CD4^+$ cell count, these observational data are missing deaths and person-time that would have accrued prior to study entry in the intermediate and late initiator categories [25]. To address this lead-time bias, we employed a hybrid of two approaches [26,27]. For intermediate and late initiators with an observed HAART-naive $CD4^+$ cell count more than 350 cells/μl, we selected one such visit at random as the time at entry [26]. For those without such an observed visit, we multiply imputed the lead time using estimates from MACS data prior to HAART availability [27]. To derive these estimates, we fit mixtures of generalized gamma distributions, with the three outcomes defined as death from AIDS, death from non-

AIDS and transition to a lower $CD4^+$ cell count category. We then drew randomly from these conditional distributions to impute missing person-time for each individual. For the unseen events, we used estimates of π from the mixture models to determine the number of events, and random draws from the conditional distributions to determine the time to events. We performed 10 imputations, averaged the results, and appropriately adjusted the standard errors [28].

Statistical analyses were performed using SAS version 9.3 (SAS Institute Inc., Cary, North Carolina, USA) and R statistical software.

Results

Characteristics of the study population

Table 2 displays characteristics of the 6699 individuals who contributed person-time, stratified by HIV status and $CD4^+$ cell count category at HAART initiation. There were 165 deaths among HIV-uninfected individuals, and 341 AIDS deaths, 199 non-AIDS deaths and 32 unknown deaths among HAART initiators.

Leading primary causes of non-AIDS death among hepatitis-free individuals were cardiovascular disease (38%), non-AIDS cancers (27%), pulmonary disease (10%) and liver disease (5%). Among those with hepatitis infection, leading non-AIDS death causes were liver disease (28%), non-AIDS cancer (24%), cardiovascular disease (15%), renal disease (8%) and pulmonary disease (7%).

HIV-uninfected individuals were more likely to be younger, MACS members, of white race, high school and college graduates, employed, nonsmokers, heavy drinkers, not obese, hypertensive and not depressed ($P \leq 0.01$ for all comparisons) relative to HAART initiators. HBV ($P = 0.046$) and HCV were less prevalent ($P < 0.01$) among HIV-uninfected individuals relative to HAART initiators.

Results from mixture models

Those with HBV or HCV infection had substantially lower proportions of non-AIDS death (46 vs. 68%, $P < 0.01$) and lower median ages at non-AIDS death (HIV-uninfected: 67.0 vs. 75.0, $P < 0.01$; HAART initiators: 54.1 vs. 69.0, $P < 0.01$) relative to those without viral hepatitis. The following results from mixture models (Fig. 1) exclude those with HBV or HCV infection.

Figure 1 displays estimated probability density functions from mixture models for (a) non-AIDS death and (b) AIDS death stratified by HIV infection status and $CD4^+$ cell count at HAART initiation. The proportion of non-AIDS death (for early, intermediate, and late groups: 78%, 74%, 49%) and the median ages at non-AIDS death (72.0, 68.6, 65.7) decreased with lower $CD4^+$ cell counts at HAART initiation (Fig. 1a). All $CD4^+$ cell count categories had lower median ages at non-AIDS death relative to HIV-uninfected individuals (each $P < 0.01$). Similarly, the median ages at AIDS death (54.5, 52.4, 47.4) decreased with lower $CD4^+$ cell counts at HAART initiation (Fig. 1b).

Figure 1c and 1d use the conditional distributions from the mixture models to plot differences in age at non-AIDS death and AIDS death, respectively, by percentile (the reference category in Fig. 1c is HIV-uninfected individuals, and that for Fig. 1d is early initiators). Estimated median ages at non-AIDS death were lower than those for HIV-uninfected individuals by 3.0 years (95% CI 0.6–5.4) among early initiators; by 6.4 years (95% CI 3.7–9.2) among intermediate initiators; and by 9.3 years (95% CI 6.4–12.2) among late initiators. Estimated median ages at AIDS death were lower than those for early initiators by 2.1 years (95% CI −6.1 to 10.3) among intermediate initiators and by 7.0 years (95% CI 0.9–13.2) among late initiators.

Results from proportional cause-specific hazards model

Table 3 displays results from a multivariable PCSH model. In addition to the $CD4^+$ cell count category at HAART initiation, this model included study cohort (MACS/WIHS), HBV/HCV infection, smoking, depression, unemployment and hypertension. The estimated hazard ratio for non-AIDS death for the HIV-uninfected group relative to early initiators was 1.01 (P =0.95). Relative to early initiators, intermediate initiators had hazard ratios of 1.66 (P =0.01) for non-AIDS death and 1.20 (P =0.28) for AIDS death. Late initiators had higher hazard ratios: 2.15 (P <0.01) for non-AIDS death and 3.26 (P <0.01) for AIDS death. Estimated hazard ratios for all other covariates were above one, and all were statistically significant except WIHS membership for AIDS death. The hazard ratio for hepatitis was higher for non-AIDS death than for AIDS death (P <0.05).

To test the assumption that covariate effects were the same for HIV-uninfected individuals and for HAART initiators with respect to non-AIDS death, we also fit models with interaction terms between each exposure and HIV infection status; none of these interaction terms were statistically significant.

Adjustment for lead-time bias

Augmenting the data to address lead-time bias (via multiple imputation) with unobserved person-time and deaths resulted in an average additional 4666 person-years, 74 AIDS deaths and 35 non-AIDS deaths among late initiators, and an additional 2397 person-years, 17 AIDS deaths and seven non-AIDS deaths among intermediate initiators.

Table 4 compares results from this approach relative to those obtained without adjusting for lead-time bias. Among intermediate initiators, the proportion of non-AIDS death increased from 74 to 78%, the median age at non-AIDS death increased from 68.6 to 69.4 years and the median age at AIDS death decreased from 52.4 to 48.9 years. Among late initiators, the proportion of non-AIDS death increased from 49 to 51%, the median age at non-AIDS death decreased slightly from 65.7 to 65.3 years and the median age at AIDS death increased from 47.4 to 48.7 years.

Controlling for cohort and for hepatitis infection, adjustment for lead-time bias led to attenuation of hazard ratios among intermediate initiators from 1.69 to 1.54 (non-AIDS death) and from 1.21 to 1.15 (AIDS death). For late initiators, hazard ratios were attenuated from 2.15 to 2.08 (non-AIDS death) and from 3.30 to 2.83 (AIDS death).

Discussion

The results show a strong relationship between $CD4^+$ cell count at HAART initiation and cause-specific mortality. Earlier initiators were more likely to die of non-AIDS causes, and at older ages, than later initiators. Moreover, results suggest that non-AIDS mortality hazards among early initiators may approximate those faced by comparable HIV-uninfected individuals. Unadjusted results from mixture models show lower ages at non-AIDS death for even early HAART initiators relative to HIV-uninfected individuals. However, relative to HIV-uninfected study participants, HAART-treated individuals had characteristics associated with higher mortality. In multivariable PCSH models controlling for predictors of both non-AIDS and AIDS mortality, we observed that early HAART initiators and HIV-uninfected individuals had statistically indistinguishable hazards of non-AIDS death.

The results also highlight the substantially higher risks of mortality faced by individuals coinfected with HIV and hepatitis, as those infected with hepatitis B or C at baseline died of AIDS more frequently, and died of non-AIDS 15 years earlier than their hepatitis-free counterparts in both the MACS and WIHS cohorts. Disaggregating hepatitis infection in sensitivity analysis (not shown) showed remarkably similar hazard ratios in the multivariable model for HBV infection relative to HCV infection.

This study has several limitations. There were few deaths relative to the number of individuals surviving to the end of analysis, which testifies to the success of HAART. However, this fact precluded the use of multivariable mixture models and led to low statistical power. Infrequent mortality also limited the number of $CD4^+$ cell count categories for analysis. Estimates derived from observational data assume no unmeasured confounding, which may in fact be present. We attempted to minimize confounding by indication by controlling for covariates that affect disease progression, but if individuals who initiated HAART had a worse prognosis than those who did not initiate HAART at the same $CD4^+$ cell count and with the same values for measured covariates, results would likely underestimate any benefits of earlier initiation [29]. We were careful to interpret the results according to the baseline nature of covariates; in the absence of such interpretation, changes in covariate status after analytical baseline could result in some residual confounding.

Survival estimates conditioned on the type of outcome, as in median ages at death from the mixture models, apply to selected populations, as those who died of non-AIDS causes necessarily avoided AIDS death, and vice versa. Comparisons of these estimates are thus subject to selection. Nonetheless, they serve as a useful description of the distribution of cause-specific mortality in populations.

An important strength of the analysis lies in the comparison of HIV-infected individuals with an HIV-uninfected group drawn from the same population, rather than resorting to a comparison with the general population. For example, life expectancies in the United States stratified by hepatitis infection are not readily available. Even when data on important covariates in the general population are available, study participants may differ from the general population in determinants of mortality that are either unmeasured or measured imprecisely.

Another strength of the study was the inclusion of both men and women followed by parallel studies with a common data coordinating centre. It is notable that the adjusted hazard ratio for non-AIDS death among women was a statistically significant value of 1.4, indicating that residual effects of the lower socioeconomic status of WIHS members were powerful enough to remain after adjustment for several important covariates, despite the well-established longer lifespans of women in the general population.

Using age as the time scale provided strong control for this important mortality determinant, permitted comparison with HIV-uninfected individuals and allowed estimation of cause-specific life expectancies. The duration of follow-up time in the cohorts was considerable, allowing us to observe more long-term outcomes than would otherwise be possible. Although individuals contributed a maximum follow-up time of 26.7 years for MACS and 16.2 years for WIHS, we were able to use late entry methods to incorporate observed mortality between the ages of 35 and 70 years. Furthermore, using interval censoring methods on individuals who exited the study period alive allowed us to make realistic inferences beyond the observed age range.

The competing risks methods permitted a rich and detailed examination of mortality. Mixture models allowed parametric characterizations of cause-specific mortality, permitting meaningful summary measures (e.g. years by which exposures shorten life expectancies, as in Fig. 1). Cause-specific hazards models allowed multivariable analysis and formal tests for coefficient homogeneity across outcome types. Handling unknown deaths via multiple imputation in the semi-parametric models allowed us to use observed deaths to inform classification, rather than relying on exclusion or sensitivity analysis [24]. We are comforted by the fact that, in sensitivity analyses in which we assigned all unknown deaths to either of the causes, our effect estimates were not substantially altered and our qualitative conclusions were the same. This gives us reason to trust that any misclassification of mortality would not have altered our conclusions considerably.

Finally, we believe that the methods we used to address lead-time bias edged us closer to results that would be obtained in a randomized clinical trial. The direction of change in the estimates depends on the balance between the number of deaths and the amount of person-time added to each exposure category during adjustment. After adjustment, the results were similar both qualitatively and quantitatively, indicating that added lead time was largely compensated by the added deaths. This adjustment relies on the experience of MACS members from the pre-HAART era; if these are not representative of the MACS and WIHS cohorts in the HAART era, bias may be present. The approach also assumes that $CD4^+$ cell counts among the early initiators are representative of $CD4^+$ cell counts at the imputed entry times for intermediate and late initiators. Distributions were indeed similar, as the median $CD4^+$ cell count for early initiators was 488 cells/μl, compared with 544 cells/μl for later initiators with prior $CD4^+$ cell counts greater than 350 cells/μl, and 543 cells/μl for those relying on natural history estimates.

The similar hazards of non-AIDS death between HIV-uninfected individuals and early HAART initiators may be partially explained by the quality of healthcare received by early HAART initiators. Comprehensive healthcare delivery for HIV-infected individuals, where

effective, has been suggested as a model for even HIV-uninfected individuals [30]. The hazard ratio for AIDS death (1.2) was not significant for intermediate initiators relative to early initiators. This may be an issue of statistical power and/or confounding by indication, as previous work has demonstrated mortality benefits from initiating HAART prior to a $CD4^+$ cell count of 350 cells/μl [10,11].

The study population includes individuals on HAART regimens dating back to 1996 and individuals (some exposed to pre-HAART therapies) who lived with HIV prior to HAART availability. As therapies have become less toxic and more effective over time, and as therapy management strategies have improved, it may be expected that individuals initiating HAART today face lower risks of mortality than those estimated in this study.

These results suggest that early HAART initiation may diminish the elevated risks of non-AIDS mortality faced by HIV-infected individuals, risks that may be partly mediated by inappropriate immune activation and inflammation. There is reason to believe that the gap in non-AIDS mortality between HAART-treated individuals and HIV-uninfected individuals may continue to decrease, that is, that HIV-related non-AIDS death may decline further. Better therapy regimens and improved social support hold the prospect of improving the survival of all HAART initiators nearer to that of HIV-uninfected individuals.

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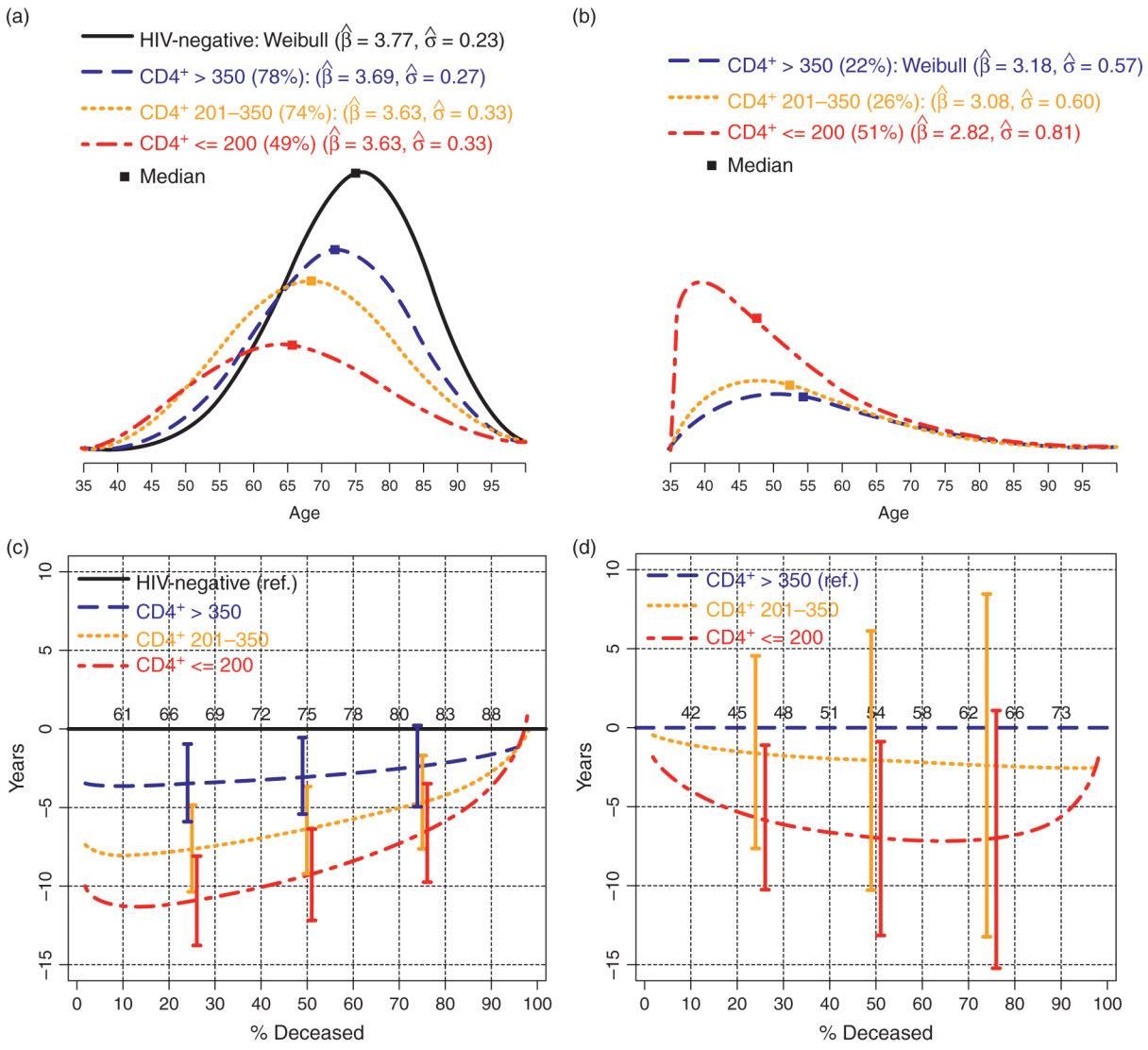

Fig. 1.

Cause-specific mortality by CD4$^+$cell count at HAART initiation, compared to HIV-negative individuals (a,b) Probability density functions for non-AIDS death (a) and AIDS death (b), stratified by CD4$^+$ cell count at HAART initiation. Percentages represent proportion of all-cause mortality. (c,d) Differences in age at non-AIDS death (c) and AIDS death (d) by percentile, stratified by CD4$^+$cell count at HAART initiation. Reference category for (c) is HIV-negative. Reference category for (d) is CD4$^+$ cell count >350 cells/μl at HAART initiation. For example, at 50% decreased in Fig. 1c, the value of the blue dashed line (−3.0) represents the median age at non-AIDS death for the early initiators (72.0) minus the median age at death for the HIV-negative reference (75.0). 95% confidence intervals at 25th, 50th and 75th percentiles calculated using the delta method. Numbers on x-axis are deciles (years of age at death) for the reference group.

Table 1

Description of person-time in study population.

Person-time category	Entry time	Exit time	Status at exit
HIV-negative	Years after age 35 first seen as HIV-negative (= 0 if first seen younger than age 35)	Years after age 35 last seen as HIV-negative	0 = right-censored: became HIV-positive, or alive as of 1 January, or turned 70 years of age, or died of accidental cause.
HIV-positive, HAART-experienced	Years after age 35 first seen after HAART initiation (= 0 if first seen younger than age 35)	Years after age 35 last seen	1 = died (of non-AIDS cause). 0 = right-censored: alive as of 1 January or turned 70 years of age, or died of accidental cause. 1 = died of non-AIDS cause. 2 = died of AIDS.

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Table 2

Characteristics of Multicenter AIDS Cohort Study and Women's Interagency HIV Study population at baseline.

	CD4$^+$ cell count ≤200 cells/μl at HAART initiation	CD4$^+$ cell count 201–350 cells/μl at HAART initiation	CD4$^+$ cell count >350 cells/μl at HAART initiation	HIV-negative	Total
Individuals	985	830	1138	3854	6699
Person-years	7502	6590	9203	44 991	68 287
Alive at exit of analysis	678	694	1009	3689	6070
Died of AIDS	202	67	72	n/a	341
Died of non-AIDS cause	87	65	47	165	364
Died of unknown cause	18	4	10	n/a	32
Median age (IQR)	41 (36–46)	41 (36–46)	40 (35–46)	35 (35–41)	38 (35–43)
HBV infection	5%	4%	3%	3%	4%
HCV infection	24%	22%	19%	7%	13%
MACS participants	40%	40%	41%	82%	64%
Nonwhite race	60%	61%	57%	27%	41%
No high school education	23%	24%	26%	9%	16%
No college education	78%	78%	76%	48%	61%
Unemployed	52%	45%	43%	18%	31%
Current smoker	44%	46%	41%	40%	42%
>13 alcoholic drinks/week	4%	5%	5%	13%	9%
Injection drug use	5%	5%	3%	5%	5%
Obese (BMI >30 kg/m^2)	25%	27%	34%	20%	24%
Hypertension	18%	19%	17%	22%	20%
Depressive symptoms	40%	38%	38%	25%	31%

HBV, hepatitis B virus; HCV, hepatitis C virus; IQR, interquartile range; MACS, Multicenter AIDS Cohort Study.

Table 3

Results from multivariable proportional cause-specific hazards model.

	Non-AIDS death			AIDS death	
	HR	**95% CI**		**HR**	**95% CI**
HIV-negative	1.01	(0.72–1.43)		n/a	n/a
$CD4^+$ cell count >350 cells/μl at HAART initiation (reference)	–	–		–	–
$CD4^+$ cell count 201–350 cells/μl at HAART initiation	1.66	(1.14– 2.40)		1.20	(0.86– 1.66)
$CD4^+$ cell count ≤200 cells/μl at HAART initiation	2.15	(1.52– 3.05)		3.26	(2.50– 4.25)
WIHS membership	1.41	(1.03– 1.94)	*a*	1.03	(0.76– 1.40)
Hepatitis B/C infection	2.23	(1.75– 2.84)		1.55	(1.23– 1.95)
Smoking	2.06	(1.62– 2.61)		1.52	(1.21– 1.91)
Depression	1.65	(1.32– 2.06)		1.58	(1.27– 1.97)
Unemployment	1.51	(1.11– 2.05)		1.89	(1.41– 2.55)
Hypertension	1.30	(1.03– 1.65)		1.42	(1.10– 1.82)

CI, confidence interval; HR, hazard ratio.

[a] Difference (P <0.05) between HR for non-AIDS death and HR for AIDS death.

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Table 4

Comparison of results from naive analysis vs. analysis adjusted for lead-time bias.

		Naive		Adjusted	
		Estimate	**95% CI**	**Estimate**	**95% CI**
$CD4^+$ cell count 201–350 cells/μl at HAART initiation	% non-AIDS death[a]	74%	(62–84)	78%	(72–85)
	Median age, non-AIDS death[a]	68.6	(66.1–71.3)	69.4	(67.2–71.8)
	Median age, AIDS death[a]	52.4	(47.2–59.7)	48.9	(44.9–54.5)
	Hazard ratio, non-AIDS death[b]	1.69	(1.17–2.45)	1.54	(1.07–2.20)
	Hazard ratio, AIDS death[b]	1.21	(0.87–1.68)	1.15	(0.84–1.57)
$CD4^+$ cell count ≤200 cells/μl at HAART initiation	% non-AIDS death[a]	49%	(41–58)	51%	(41–59)
	Median age, non-AIDS death[a]	65.7	(63.1–68.6)	65.3	(62.8–68.0)
	Median age, AIDS death[a]	47.4	(44.8–50.8)	48.7	(46.1–52.0)
	Hazard ratio, non-AIDS death[b]	2.15	(1.52–3.04)	2.08	(1.50–2.90)
	Hazard ratio, AIDS death[b]	3.30	(2.53–4.30)	2.83	(2.18–3.66)

CI, confidence interval.

[a] Estimates derived from mixture model of Weibull distributions.

[b] Hazard ratios relative to early HAART initiators (>350 cells/μl). Estimates derived from proportional cause-specific hazards model, adjusting for cohort (MACS/WIHS) and HBV/HCV infection.