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The effect of combined antiretroviral therapy on the overall mortality of HIV-infected individuals

The HIV-CAUSAL Collaboration*

Abstract

Objective—To estimate the effect of combined antiretroviral therapy (cART) on mortality among HIV-infected individuals after appropriate adjustment for time-varying confounding by indication.

Design—A collaboration of 12 prospective cohort studies from Europe and the United States (the HIV-CAUSAL Collaboration) that includes 62,760 HIV-infected, therapy-naïve individuals followed for an average of 3.3 years. Inverse probability weighting of marginal structural models was used to adjust for measured confounding by indication.

Results—2039 individuals died during the follow-up. The mortality hazard ratio was 0.48 (95% confidence interval: 0.41, 0.57) for cART initiation versus no initiation. In analyses stratified by CD4 cell count at baseline, the corresponding hazard ratios were 0.29 (0.22, 0.37) for <100 cells/μL, 0.33 (0.25, 0.44) for 100-<200 cells/μL, 0.38 (0.28, 0.52) for 200-<350 cells/μL, 0.55 (0.41, 0.74) for 350-<500 cells/μL, and 0.77 (0.58, 1.01) for ≥500 cells/μL. The estimated hazard ratio varied with years since initiation of cART from 0.57 (0.49, 0.67) for <1 year since initiation to 0.21 (0.14, 0.31) for ≥ 5 years (p-value for trend<0.001).

Conclusions—We estimated that cART halved the average mortality rate in HIV-infected individuals. The mortality reduction was greater in those with worse prognosis at the start of follow-up.

Keywords

HIV infection; antiretroviral therapy; mortality; marginal structural models; inverse probability weighting

Introduction

The introduction of combined antiretroviral therapy (cART) in 1996 ushered in a new era for HIV-infected individuals in countries where this therapy was available. cART increases CD4 count, decreases HIV RNA level, and extends AIDS-free survival, at least in the short-term.[1–5] However, surrogate markers like CD4 cell count and HIV RNA are not fully adequate to infer the effect of cART on clinical endpoints. [6–10] In the current cART era, AIDS-free survival is less relevant than mortality alone because HIV-infected individuals often survive with acceptable quality of life following their first AIDS diagnosis, and death is often the result of non AIDS-defining causes.[11] Therefore, it would be highly desirable to have a reliable estimate of the effect of cART on overall survival for public health planning and to inform HIV modeling and cost/effectiveness calculations.

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Unfortunately, after twelve years of cART use in developed countries, the magnitude of the effect of cART on all-cause mortality remains unclear. The available effect estimates have been inferred from comparisons of mortality rates between the pre-cART era and the late-cART era.[12–18] These ecological comparisons may result in treatment misclassification (not all patients in the late-cART era take cART, and some pre-cART patients took monotherapy or dual therapy), may be confounded by temporal trends in health care quality, and do not appropriately adjust for important confounders like CD4 cell count and HIV RNA. Although a prospective cohort design can be used to mitigate, or eliminate, these problems, few cohort studies include sufficient antiretroviral-naïve HIV-infected individuals to provide precise effect estimates of cART on all-cause mortality. Even fewer cohort studies can explore potential effect modification by key covariates such as CD4 cell count, HIV RNA viral load, transmission group, and sex.

Here we present estimates of the effect of cART on all-cause mortality among HIV-1-infected individuals included in a large multinational collaboration of cohort studies from Europe and the United States. We also present these effect estimates stratified by clinical and demographic characteristics. Because unbiased estimation of the effect of cART requires appropriate adjustment for time-dependent confounding by indication (e.g., due to CD4 cell count and HIV RNA), we used inverse probability weighting of marginal structural models.[19,20]

Methods

Study Population

The HIV-CAUSAL Collaboration comprises 12 prospective cohort studies from five European countries and the United States. All cohorts in the collaboration are based on data collected for clinical purposes within national health care systems with essentially no barriers to access. The individual cohort studies are UK CHIC (United Kingdom),[21] ATHENA (Netherlands),[22] FHDH-ANRS CO4 (France),[23] SHCS (Switzerland),[24] PISCIS (Spain),[25] CoRIS/CoRIS-MD[26, 27] (Spain), VACS-VC (United States veterans),[28] UK Register of HIV Seroconverters[29] (United Kingdom), ANRS PRIMO (France),[30] ANRS SEROCO (France),[31] and GEMES (Spain).[15,32] The last four studies include individuals for whom it was possible to estimate the time of HIV seroconversion (known as seroconverters). Individuals participating in both FHDH-ANRS CO4 and ANRS PRIMO/SEROCO were removed from FHDH-ANRS CO4, those in both CoRIS and PISCIS were removed from CoRIS, and those in UK CHIC and the UK Register of HIV Seroconverters were removed from UK CHIC. See the Appendix for a description of each individual cohort.

The date of start of follow-up was cohort-specific and ranged from January of 1996 to January of 1998. Our analyses were restricted to HIV-1-infected individuals that met the following criteria at the start of follow-up: age 18 years or older, antiretroviral therapy-naive, no history of AIDS (defined as the onset of any Category C AIDS-defining illness[33]), no pregnancy (when information was available), HIV-RNA >500 copies/mL (in cohorts in which it could not be confirmed that the patient was therapy-naive), and CD4 cell count and HIV-RNA measurements within 6 months of each other. For each patient, follow-up ended at death, 12 months after the most recent lab measurement, pregnancy (if known), or the cohort-specific administrative end of follow-up (ranging between December 2003 and September 2007), whichever occurred earlier.

cART initiation was defined as the date at which a patient initiated treatment with either three or more antiretroviral drugs, or two ritonavir-boosted protease inhibitors, or one non-nucleoside reverse transcriptase inhibitor plus one boosted protease inhibitor. The date of

death was identified independently by the cohorts using a combination of national and local mortality registries and clinical records (see Appendix for details).

Statistical methods

We fit a pooled logistic model[34] to estimate the average mortality hazard ratio for cART initiation versus non initiation. The model included a time-varying indicator for ever use of cART, month of follow-up (restricted cubic splines with 5 knots) and the following baseline covariates: CD4 cell count (<100, 100-<200, 200-<350, 350-<500, ≥500 cells/μL), HIV RNA level (<10,000, 10,000–100,000, >100,000 copies/mL), sex, transmission group (heterosexual, homosexual/bisexual, injection drug use, other or unknown), calendar year (1996–1998, 1999–2000, 2001–2006), age (<35, 35–50, >50 years), geographic origin (Western developed countries, other or unknown), race (white, black, other or unknown), years since HIV diagnosis (<1 year, 1-<5 years, 5+ years, or unknown), and cohort. We fit a separate model with the cART indicator replaced by the variable "years since cART initiation" (<1, 1-<2, 2-<3, 3-<4, 4-<5, and 5+ years).

Because cART is more likely to be initiated in individuals with higher mortality risk (e.g., with low CD4 cell count and high HIV RNA levels), the estimates from the above regression model need to be adjusted for this time-dependent confounding by indication. To do so, one could add the time-varying confounders, CD4 cell count and HIV RNA, as covariates in the logistic regression model. However, this standard approach may introduce bias because the confounders are affected by prior cART use and are on the causal pathway between cART and mortality.[35] We therefore used inverse probability weighting to adjust for measured time-dependent confounders that are affected by prior cART use. Formally, under the assumption that all time-varying predictors of both cART and mortality were included in the analysis, our weighted model estimates the parameters of a marginal structural Cox model[19, 36] and can be used to mimic a sequentially randomized trial in which subjects were assigned to initiate cART at different times.

Each patient in the above logistic models received a time-varying weight inversely proportional to the estimated probability of having his/her own observed history of cART initiation, as described elsewhere.[19, 20] To estimate each patient's probability of cART initiation in each month, we fit a pooled logistic model that included the covariates listed above for the mortality model plus the most recent measurement of the following time-varying covariates: CD4 cell count (restricted cubic splines with 5 knots), HIV RNA level (3 categories), AIDS (yes, no), and time since last lab measure (5 categories). To better adjust for cohort-specific factors, the weight models also included product terms between cohort and time of follow-up, time-varying CD4 cell count, and HIV RNA level. Inverse probability weights were also computed to adjust for potential selection bias due to censoring. Both the cART and censoring weights were stabilized as described elsewhere,[19, 20] and their product was used to fit the weighted regression model. To avoid undue influence of outliers on the variance of the estimates, we truncated the weights at a maximum value of 10. Truncation did not materially change the point estimates (non-truncated estimates not shown). The estimated weights used in the analysis had mean 1.05 (1st percentile: 0.10, 99th percentile: 5.3). We computed 95% confidence intervals (CI) by using variance estimators that take into account the procedure of weight estimation.[36] Subset analyses were performed according to the following baseline characteristics: sex, age, HIV RNA levels, CD4 cell count, transmission group, and baseline year.

Several sensitivity analyses were also performed: (i) in addition to censoring individuals at 12 months without a lab measurement, we conducted separate analyses in which individuals were censored at 6, 18, and 24 months, (ii) the start of follow-up was delayed by 3 months, (iii) the weights were re-estimated by adding rate of CD4 count and HIV RNA change to the

models, (iv) the weights were re-estimated by lagging the CD4 count and HIV RNA level 7 and 14 days to ensure that cART initiation was predicted using prior lab measurements, (v) women starting cART with HIV RNA <500 were censored to reduce the probability that pregnant women were included in the analysis, (vi) individuals (mostly from the early-cART era) were censored if they did not start cART after having initiated some form of antiretroviral therapy, (vii) alternate definitions of cART were used, (viii) individuals were considered untreated during their first month on cART to allow for a lag period between cART initiation and its potential effect on mortality, and (ix) patients with AIDS at baseline were included in the analysis.

Because hazard ratios are not always simple to interpret and can be affected by selection bias, we also estimated absolute risks by cART status. To do so, we fit a weighted model that included linear and quadratic terms for the variable "years since cART initiation." We then used the predicted values from this model to estimate the 5-year survival curves that would have been observed if all individuals had initiated cART at baseline and if no individuals had initiated cART during the follow-up period. All analyses were conducted with SAS 9.1.3.

Results

Our study included 62,760 HIV-infected individuals who met the eligibility criteria. Of these, 26% initiated cART during the first 3 months, and 55% during the entire follow-up. The average follow-up was 3.3 years. There were 2039 deaths during the follow-up, which yielded an overall mortality rate of 10 cases per 1,000 person-years (Table 1). The mortality rate ranged from 6/1000 person-years in the seroconverters cohorts to 40/1000 person-years in the study of U.S. veterans.

The mortality hazard ratio for cART initiation versus no cART initiation ranged from 0.22 in the cohorts of seroconverters to 0.62 in the study of U.S. veterans (p-value for heterogeneity across cohorts: 0.21). The overall mortality hazard ratio (95% CI) was 0.48 (0.41, 0.57) in the pooled dataset (Table 1), but this estimate varied by the individuals' baseline characteristics (Table 2). By CD4 cell count at baseline, the hazard ratio ranged from 0.29 (0.22, 0.37) among those with <100 cells/μL to 0.77 (0.58, 1.01) among those with ≥500 cells/μL. The mortality hazard ratio estimate also varied by time since cART initiation (Table 3). Compared with no cART initiation, the mortality hazard ratio ranged from 0.57 (0.49, 0.67) for less than 1 year since cART initiation to 0.21 (0.14, 0.31) for 5 or more years since cART initiation (p-value for trend <0.001).

We also estimated the 5-year survival curves under cART initiation at baseline and under no cART initiation during the follow-period. Overall, the estimated probability of surviving 5 years if cART had been initiated at baseline was 96%, compared with 92% if cART had not been initiated (Figure 1). These estimates, however, varied by CD4 cell count at baseline (Figure 2) and transmission group (Figure 3). The 5-year survival for cART vs. no cART was 89% vs. 43% for <100 cells/μL, 94% vs. 76% for 100 to <200 cells/μL, 97% vs. 91% for 200 to <350 cells/μL, 97% vs. 94% for 350 to <500 cells/μL, and 97% vs. 96% for ≥500 cells/μL. The 5-year survival for cART vs. no cART was 97% vs. 92% for heterosexuals, 97% vs. 95% for homo/bisexuals, 92% vs. 83% for injection drug users, and 95% vs. 94% for others.

The sensitivity analyses described in the previous section did not materially change or suggest a weaker effect of cART (data not shown). For comparison purposes, we also fit unweighted models that (1) did not include any covariates except cART initiation, (2) included only baseline covariates, and (3) included baseline and time-varying covariates. As

expected, conventional adjustment via unweighted models led to hazard ratios closer to the null value (Figure 4). The mortality hazard ratio for cART initiation vs. no initiation was 0.79 when no adjustment for time-varying confounding was attempted and 0.83 when conventional adjustment was used, versus 0.48 when inverse probability weighting was used.

Discussion

We estimated that initiation of cART reduced the overall incidence of mortality of HIV-infected individuals by 50%. In absolute terms, this mortality reduction was translated into a 5% increase in 5-year survival for cART initiation compared with no initiation. However, the absolute benefit depended on the baseline CD4 cell count: the survival increase ranged from about 46% in individuals with less than 100 cells/μL to about 1% in those with more than 500 cells/μL. Similarly, the absolute benefit was greatest in injection drug users compared with other transmission groups.

Because our collaboration includes a wide range of HIV-infected individuals living in Europe and the United States—including representative clinical cohorts, seroconverters, and U.S. veterans—we could confirm that cART initiation was followed by 40–60% mortality reduction in all of these groups, with perhaps an even greater reduction among seroconverters. The survival benefit was clear even among U.S. veterans, who experienced a higher mortality rate (40 deaths per 1000 person-years) than the other cohorts (6–13 deaths per 1000 person-years). The high mortality rate among U.S. veterans—partly explained by their older age, predominantly male sex, and different death ascertainment procedures—is in line with those reported in similar populations.[16, 37, 38]

Previous studies reported mortality hazard ratios for cART vs. no cART in the range 0.1 to 0.5. However, most previous studies on cART and mortality have been based on ecological comparisons and/or did not appropriately adjust for time-dependent confounders,[12–18] which makes the estimates hard to interpret. Lack of appropriate adjustment for time-varying CD4 cell count and HIV RNA levels may result in either underestimation or overestimation of the effect of cART. In contrast to previous studies, we used a prospective cohort design and inverse probability weighting to appropriately adjust for measured confounders. It has been previously shown that effect estimates obtained from observational HIV cohorts via inverse probability weighting, but not those obtained via conventional adjustment methods, can replicate the findings of randomized clinical trials on cART and time to AIDS.[3, 20] In the current analysis, we found empirical proof of the bias of conventional methods in that further adjustment for the strong time-varying confounding by indication resulted in a weaker (from 0.79 to 0.83), rather than stronger, effect estimate.

The validity of our effect estimates, however, relies on the untestable assumption that the measured covariates were sufficient to adjust for confounding by indication. We believe this assumption may approximately hold here because the most important clinical information used by physicians as indications for cART initiation (i.e., CD4 cell count and HIV-RNA) was collected and used in the analysis. An incomplete or imperfect measurement of confounders would result in attenuation of the effect because the bias due to confounding by indication is upwards in this setting. As a further protection against unmeasured confounding, we estimated the effect of cART initiation rather than the effect of continued cART use. This strategy makes it unnecessary to adjust for joint determinants of treatment discontinuation and death, which are less well-measured in most observational studies. The price to pay for this strategy is again an attenuation of the effect estimate towards the null (as it would happen in the intention to treat analysis of a placebo-controlled randomized clinical trial) if a substantial proportion of individuals stopped taking cART during the

follow-up. Thus, our effect estimates could be viewed as conservative estimates of the effect of continuous cART. Note, however, that the effect of continuous cART use would not be clinically interesting if most subjects who discontinue cART do so for toxicity-related reasons.

Other studies have used surrogate biological markers, like HIV RNA and CD4 cell count, in hopes of rapidly inferring the effect of cART on death. Several randomized studies, however, suggest that surrogate markers may not be good proxies for clinical endpoints like death.[6–9] In the MRC Delta Trial, CD4 cell count and HIV RNA changes overestimated clinical benefit (defined as survival or no disease progression).[9] HIV RNA may be an inadequate surrogate for death because death may be caused mainly by immune system damage or unintended harmful effects via other mechanisms;[39] CD4 cell count may be inadequate due to biological and assay-based variability, differences between peripheral blood and lymphatic levels, and the existence of other important markers of immune function that are affected by treatment, like CD8 cells.[9] Even if surrogate biological markers provide some indication of short-term clinical endpoints, it is debatable whether these surrogate effects translate into long-term clinical effects, which depend on the interplay among immune factors, drug resistance, and toxicities that may not be evident in the short-term. For example, a regime might be perceived to be favorable in the short-term because its potency allows patients to maintain higher CD4 count and lower viral load, but over the long-term, this same potency might cause toxicities that lead to death more quickly. It is best to directly evaluate the effect of cART on mortality in large follow-up studies as we did here. An alternative would be to evaluate the effects of cART on cause-specific morbidity and mortality, but this information is not available in all HIV cohorts.

In summary, in the absence of data from long-term randomized clinical trials, appropriate adjustment for time-varying confounding in observational cohorts provide the best available evidence on the effects of cART on the overall mortality of HIV-infected individuals. We estimated that cART initiation halved the mortality rate of HIV-infected individuals in developed countries, and that the absolute reduction in mortality was stronger in those with worse prognosis at the start of follow-up. Thus the 46% survival increase estimated for individuals who start cART at CD4 cell count less than 100 cells/μL demonstrates the benefits of being treated even at the most advanced stages of immunosupression. This finding, however, does not imply one should delay cART initiation until the CD4 cell count drops below 100 because, besides the possibility of dying during the waiting period, the 5-year mortality risk of treated individuals with less than 100 cells/μL at baseline (11%) was almost 4 times greater than that of treated individuals with more than 500 cells/μL (3%).

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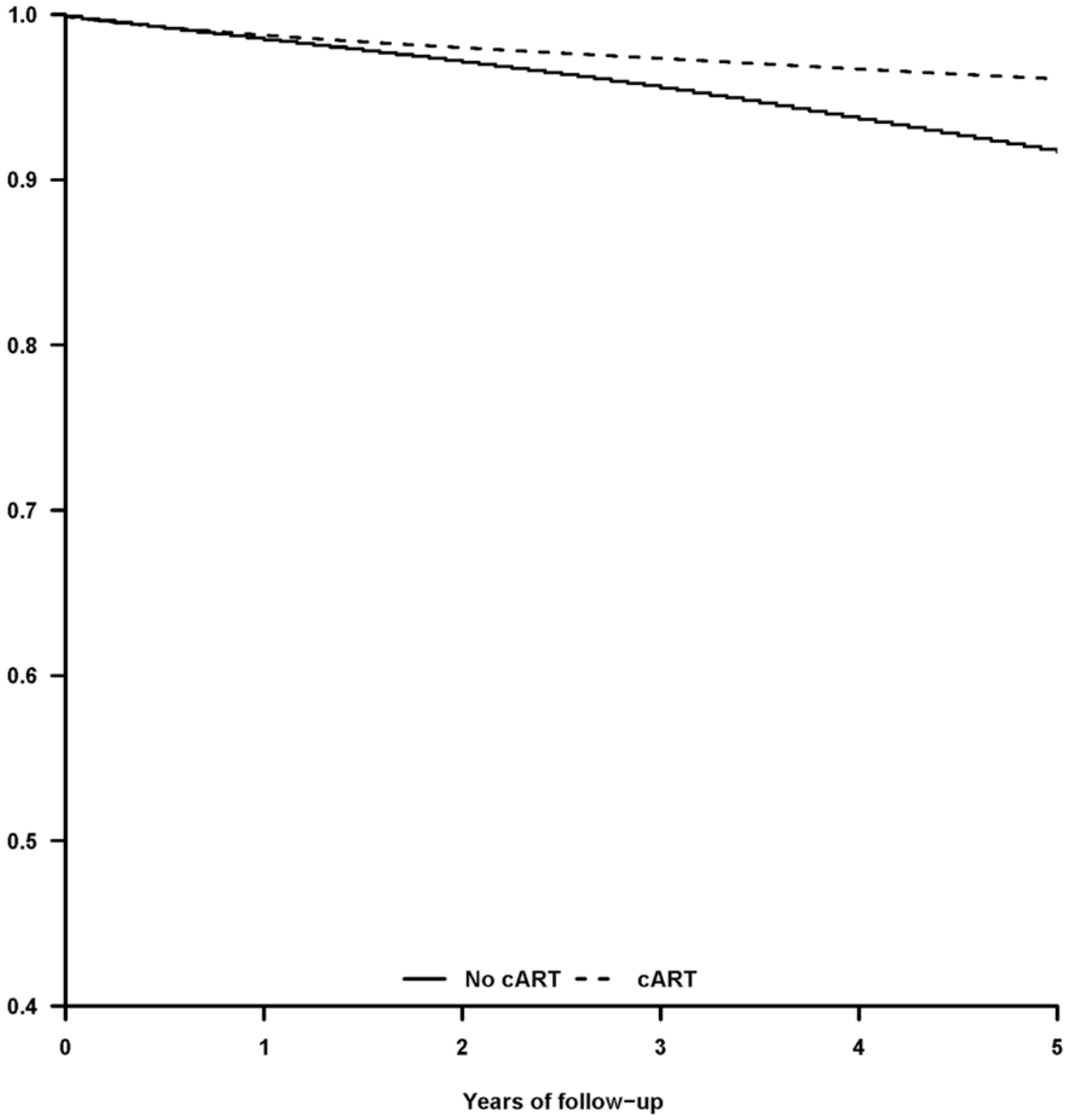

Fig 1.
Estimated survival curves under the regimes ‘initiate cART at baseline’ and ‘never start cART,’ HIV-CAUSAL Collaboration

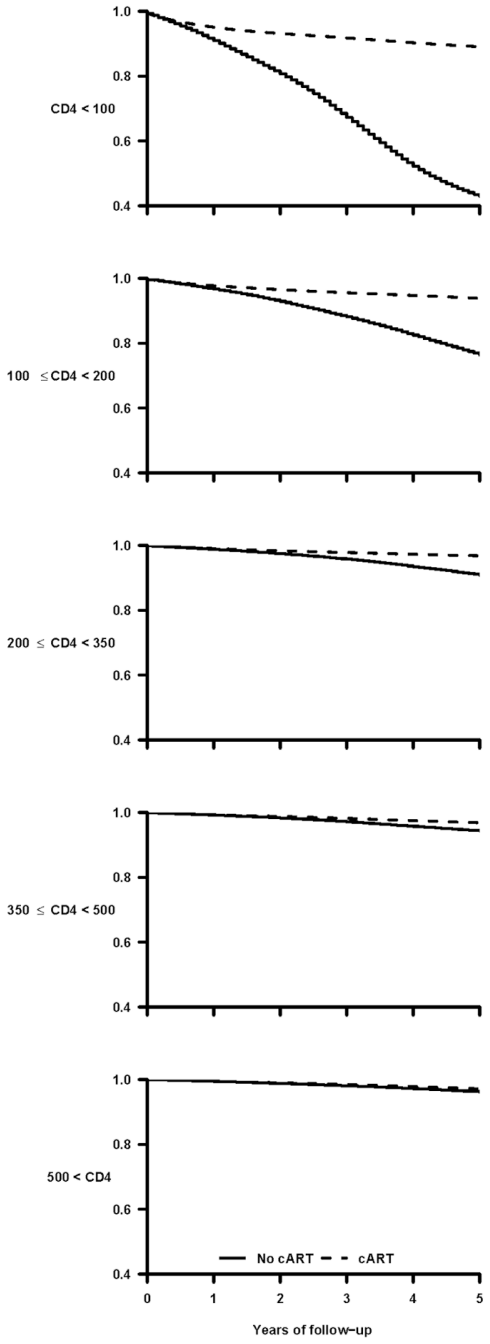

Fig 2.

Estimated survival curves under the regimes ‘initiate cART at baseline’ and ‘never start cART’ by CD4 cell count at baseline, HIV-CAUSAL Collaboration.

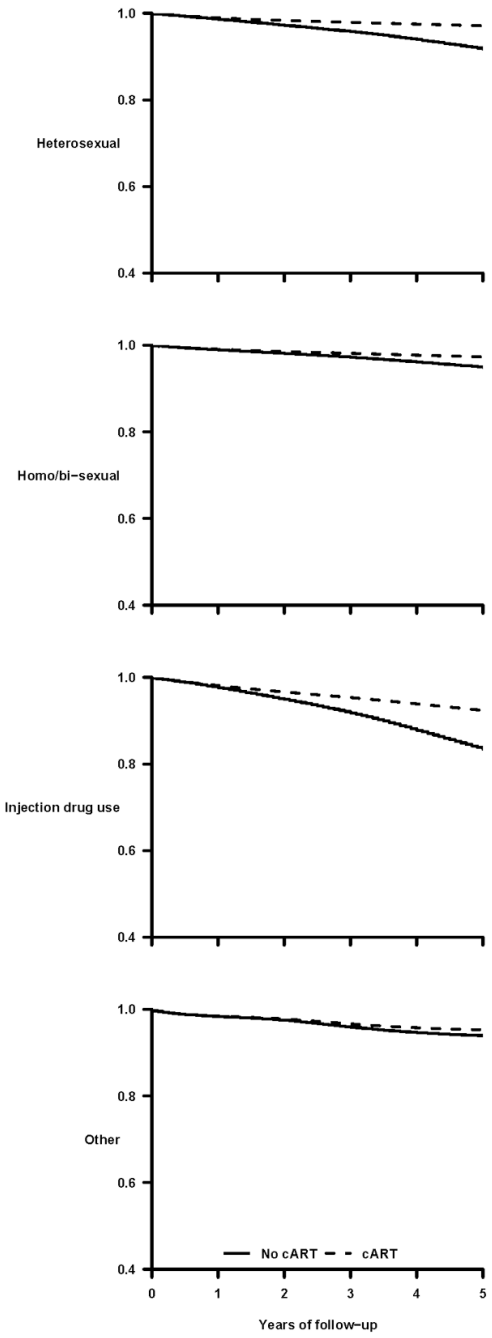

Fig. 3.
Estimated survival curves under the regimes ‘initiate cART at baseline’ and ‘never start cART’ by transmission group, HIV-CAUSAL Collaboration.

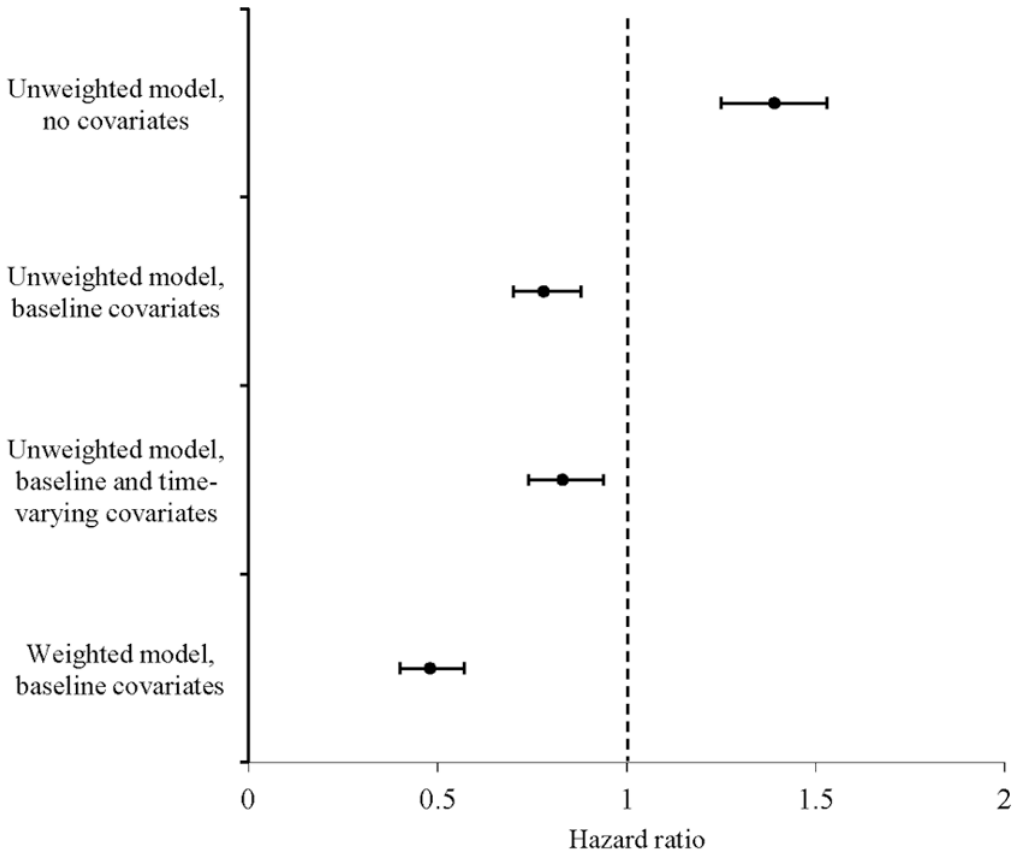

Fig. 4.
Comparison between weighted and unweighted estimates of the mortality hazard ratio, HIV-CAUSAL Collaboration.

Table 1

Characteristics of study participants and mortality hazard ratio for cART initiation versus non initiation, HIV-CAUSAL Collaboration

Study*	Country	Eligible Individuals	Women, %	Injection drug users, %	Median CD4 cell count at baseline, per μL	Median HIV RNA level at baseline, copies/mL	Person-years of follow-up	Median follow-up time, months	Initiators of cART during follow-up, %	No. of deaths	Mortality rate, per 1000 person-years	Mortality hazard ratio† (95% CI)
UK CHIC	U.K.	12,388	22.8	3.9	365	35,253	42,995	30	53	324	7.3	0.55 (0.37, 0.83)
ATHENA	Netherlands	5,055	20.9	2.9	410	24,127	13,524	27	52	101	7.5	0.48 (0.22, 1.03)
FHDH-ANRS CO4	France	26,360	33.7	13.0	395	27,300	87,669	28	53	654	7.5	0.46 (0.34, 0.61)
SHCS	Switzerland	4,160	32.7	27.2	380	26,000	19,206	46	61	248	12.9	0.48 (0.30, 0.75)
PISCIS	Spain	3,961	23.4	30.9	350	43,600	11,912	26	64	137	11.5	0.43 (0.28, 0.66)
CoRIS	Spain	4,087	24.8	28.9	385	31,623	8,870	21	56	84	9.5	0.61 (0.36, 1.05)
VACS-VC	U.S.A.	3,730	2.8	Unknown	387	20,900	10,480	26	60	418	39.9	0.62 (0.48, 0.82)
Sero-converters	UK, France, Spain	3,019	13.8	12.5	491	40,000	12,515	39	52	73	5.8	0.22 (0.11, 0.44)
Pooled		62,760	26.4	12.7	390	29,700	207,171	29	55	2039	9.8	0.48 (0.41, 0.57)

*CoRIS includes the cohorts CoRIS and CoRIS-MD; Seroconverters includes the cohorts UK Register of HIV Seroconverters, ANRS PRIMO, ANRS SEROCO, and GEMES.

†Adjusted for baseline CD4 cell count, baseline HIV RNA level, sex, transmission group, calendar year, age, geographic origin, race, years since HIV infection, cohort, time-varying CD4 cell count and HIV RNA, and time since last lab measurement. Inverse probability weights were truncated at a maximum of 10.

Table 2

Mortality hazard ratio for cART initiation versus non initiation by baseline characteristics, HIV-CAUSAL Collaboration

Baseline characteristic		Eligible individuals	Person-years	No.of deaths	Mortality rate, per 1,000 person-years	Mortality hazard ratio	95% CI
CD4 cell count, per μL	<100	5,319	18,130	507	28.8	0.29	(0.22, 0.37)
	100-<200	6,521	22,013	339	15.4	0.33	(0.25, 0.44)
	200-<350	14,886	49,798	435	8.7	0.38	(0.28, 0.52)
	350-<500	15,360	51,416	362	7.0	0.55	(0.41, 0.74)
	≥500	20,674	65,815	396	6.0	0.77	(0.58, 1.01)
HIV RNA, copies/mL	<10,000	18,929	58,261	415	7.1	0.82	(0.64, 1.05)
	10,000–100,000	27,981	93,508	775	8.3	0.46	(0.36, 0.60)
	>100,000	15,850	55,403	849	15.3	0.36	(0.28, 0.45)
Sex	Female	16,589	51,823	331	6.4	0.32	(0.21, 0.50)
	Male	46,171	155,349	1708	11.0	0.52	(0.44, 0.62)
Age, years	<35	30,990	101,404	514	5.1	0.60	(0.46, 0.78)
	35–50	25,743	85,819	1036	12.1	0.47	(0.36, 0.60)
	>50	6,027	19,948	489	24.5	0.41	(0.31, 0.53)
Transmission group	Heterosexual	22,254	70,454	496	7.0	0.31	(0.21, 0.46)
	Homo/bi-sexual	24,342	87,558	502	5.7	0.66	(0.50, 0.89)
	Injection drug use	7,964	25,619	489	19.1	0.45	(0.36, 0.56)
	Other/Unknown*	4,470	13,060	552	42.3	0.73	(0.45, 1.18)
Calendar year	1996–1998	19,964	93,696	1038	11.1	0.47	(0.38, 0.58)
	1999–2000	9,936	38,245	440	11.5	0.48	(0.35, 0.66)
	2001–2006	32,860	75,231	561	7.5	0.46	(0.34, 0.62)

*Other or unknown included all VACS-VC participants

Table 3

Mortality hazard ratio for cART initiation versus non initiation by time since initiation, HIV-CAUSAL Collaboration

Time since initiation of cART	Person-years	No. of deaths	Mortality Hazard ratio	95% CI
Non initiation	86,068	758		
<1 year	29,768	428	0.57	(0.49, 0.67)
1 to <2 years	25,852	282	0.49	(0.39, 0.62)
2 to <3 years	19,441	191	0.42	(0.31, 0.57)
3 to <4 years	14,651	139	0.31	(0.22, 0.44)
4 to <5 years	11,035	96	0.26	(0.18, 0.38)
≥5 years	20,358	145	0.21	(0.14, 0.31)