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A comparison of *ad hoc* methods to account for non-cancer AIDS and deaths as competing risks when estimating the effect of HAART on incident cancer AIDS among HIV-infected men

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Abstract

Objective—We compared three *ad hoc* methods to estimate the marginal hazard of incident cancer AIDS in a highly active antiretroviral therapy (1996–2006) relative to a monotherapy/combination therapy (1990–1996) calendar period, accounting for other AIDS events and deaths as competing risks.

Study Design and Setting—Among 1911 HIV+ men from the Multicenter AIDS Cohort Study, 228 developed cancer AIDS and 745 developed competing risks in 14,202 person-years from 1990–2006. Method 1 censored competing risks at the time they occurred, method 2 excluded competing risks, and method 3 censored competing risks at the date of analysis.

Results—The age, race and infection duration adjusted hazard ratios (HRs) for cancer AIDS were similar for all methods (HR≅0.15). We estimated bias and CI coverage of each method with Monte Carlo simulation. On average across 24 scenarios, method 1 produced less biased estimates than methods 2 or 3.

Conclusions—When competing risks are independent of the event of interest, only method 1 produced unbiased estimates of the marginal HR, though independence cannot be verified from the data. When competing risks are dependent, method 1 generally produced the least biased estimates of the marginal HR for the scenarios explored; however, alternative methods may be preferred.

Keywords

Competing risks; epidemiology; HIV; highly active antiretroviral therapy; cancer

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What is new?

Key Findings

- While it is not possible to learn whether competing risks are dependent or independent from observed data, when competing risks are independent, censoring competing risks at the time that they occur produces unbiased estimates of the marginal hazard ratio, while excluding competing risks, or censoring at the date of analysis may bias results.
- When competing risks are dependent, censoring competing risks produced estimates of the marginal hazard that were less biased than those produced by excluding competing risks or censoring at the date of analysis. However, more formal competing risks methods may be preferred.

What this adds to what was known

- This paper highlights the use of informal competing risks methods that may be used by epidemiologists with the intention of estimating the marginal hazard ratio; and demonstrates when each method may be biased.

What is the implication?

- When epidemiologists are interested in estimating the marginal hazard ratio and have dependent competing risks, using the "ad hoc" methods presented here may induce bias, and more formal methods may be needed.

When estimating the effect of highly active antiretroviral therapy (HAART) on incident AIDS-defining cancers, often only the initial AIDS diagnosis is available or of interest, and other AIDS-defining events (e.g., opportunistic infections) and deaths are considered to be competing risks. "Formal" methods that account for competing risks, such as regression for cumulative incidence functions [1] or mixture models [2], are rarely used by epidemiologists. Of the over 700 original contributions that appeared in the Journal of Clinical Epidemiology, American Journal of Epidemiology, Epidemiology and the *International Journal of Epidemiology* in 2007, only three [3-5] used competing risks methods. When competing risks methods are used, the specific type of hazard ratio (HR) that is sought (i.e., the estimand) is often not clearly stated. For example, one may wish to estimate the ratio of the marginal hazards, the cause-specific hazards or the hazards of the subdistribution. Though these estimands are superficially similar, they are fundamentally different. We posit that epidemiologists conducting etiologic research are often interested in estimating the effect of exposure on the latent time to the event of interest, or the marginal hazards. Once the estimand is stated, there are often competing estimators. For example, when studying the effect of HAART on specific types of AIDS events, epidemiologists have: (i) censored individuals who incur a competing risk at the time of the competing risk [6], (ii) excluded individuals who incur a competing risk [7], or (iii) censored individuals who incur a competing risk at the date of analysis [8]. When the ratio of the marginal hazards is the desired estimand and the methods described above are used, they can be considered *ad hoc* methods for estimating the ratio of the marginal hazards.

It is unclear whether any or all of these *ad hoc* methods produce unbiased estimates of the marginal HR with appropriate confidence interval (CI) coverage. Below, we assessed the effect of HAART on AIDS-defining cancers using these three *ad hoc* methods to account for incident non-cancer AIDS and AIDS-free death as competing risks with observational data from the Multicenter AIDS Cohort Study. We also assessed the possible bias and CI coverage for these three *ad hoc* methods using Monte Carlo simulation.

METHODS

Study population

Since 1984, the Multicenter AIDS Cohort Study (MACS) has enrolled 6,972 homosexual and bisexual men in Baltimore, MD, Chicago, IL, Pittsburgh, PA, and Los Angeles, CA to study the natural and treated histories of HIV infection [9]. MACS participants complete semiannual physical examinations and questionnaires that include information on medication and treatments, and provide blood for laboratory measurements, including CD4 cell count.

This analysis included 1,911 men, 493 who seroconverted with HIV while under observation with dates of seroconversion known to within two years and 1,418 who were HIV seroprevalent at the time of enrollment. The MACS participants not included in this analysis were HIV-negative, and therefore were not at risk for AIDS,or had already developed AIDS, died or were lost to follow-up prior to 1990. MACS obtained institutional review board approval from participating institutions and all participants provided written informed consent.

Endpoint ascertainment

The outcome of interest was an incident (i.e., presenting) AIDS-defining cancer, either Kaposi's sarcoma or non-Hodgkin lymphoma. All other incident AIDS-defining events, including opportunistic infection, wasting syndrome, HIV-associated dementia and AIDS-free deaths were considered to be competing risks. Subsequent AIDS diagnoses that occurred after the presenting AIDS diagnoses were not considered to be events in this analysis. Clinical AIDS events were ascertained through participant self-report, and verified by medical record abstraction. Clinical AIDS was defined according to the 1993 Centers for Disease Control and Prevention criteria [10]. Individuals with only an immunologically-defined AIDS event (CD4 count <200 cells/μl or CD4% <14%) were not considered to have a clinical AIDS-defining illness for this analysis. Date of death was obtained through active and passive searches of death records and through the National Death Index.

Exposure assessment

Antiretroviral therapy exposure was assessed using calendar period as an instrument for HAART [11-23] to avoid the confounding that occurs when individual-level antiretroviral therapy use is used as exposure [13,16,24]. Calendar period meets the criteria of an instrument [25], because calendar period is (i) associated with antiretroviral therapy; (ii) independent of known confounders of the relationship between antiretroviral therapy and AIDS-free time; and (iii) independent of AIDS-free time, conditional on antiretroviral therapy [13,26]. Person-time was partitioned into the following calendar periods: monotherapy/combination therapy (1 January 1990–31 December 1995) and HAART (≥1 January 1996).

Statistical analysis

Seroconversion date—Among seroincident men, we defined seroconversion as one-third the time between the last negative and the first positive visits (median seroconversion window: 0.52 years; interquartile range (IQR): 0.48, 0.59). Among seroprevalent men, we imputed the unknown date of seroconversion 20 times. Imputations were drawn from a log-normal model for time from seroconversion to a given semiannual study visit conditional on age, type of event, CD4 cell count, race, and time from visit to event or censoring. Type of event (cancer AIDS/non-cancer AIDS/AIDS-free) and race (white/non-white) were treated as categorical variables. Age, CD4 cell count and time from visit to event or censoring were modeled as restricted cubic splines with knots at the 5^{th}, 50^{th} and 95^{th} percentiles [27]. Multiple imputations were combined using Rubin's method [28]. The earliest imputed seroconversion date was May 1978, and the distribution of imputed seroconversion dates reflected the known dynamics of

the HIV epidemic in the United States. The peak of HIV incidence in our study was 1983, consistent with a recent United States estimate of a peak between 1984 and 1985 [29]. Estimating dates of seroconversion was necessary, because infection duration was an important confounder in our analysis.

Data analysis—Person-time accrued for each participant from the latter of date of seroconversion (imputed in seroprevalent men), date of study entry or 1 January 1990 until the first of incident AIDS, death, loss to follow-up, or administrative censoring on 31 December 2006. HRs for AIDS-defining cancers and 95% confidence intervals (CI) were estimated with Cox proportional hazards regression [30], accounting for competing risks using the three methods described below. HRs for AIDS-defining cancers were estimated for the HAART calendar period, compared to the monotherapy/combination therapy calendar period. To control for confounding, the regression models were weighted by the inverse probability-of-exposure [31,32]. Weights were calculated using a logistic model, conditional on age at seroconversion, infection duration and race. Age at seroconversion and infection duration were modeled as restricted cubic splines with knots at the 5^{th}, 50^{th} and 95^{th} percentiles, to allow non-linear associations with calendar period [27]. Race (white/non-white) was modeled as an indicator variable. We used generalized estimating equations with an independent covariance structure to produce robust variance estimates to account for the weights. Data was analyzed with SAS version 9.1 (SAS Institute, Cary, NC).

Competing risk methods—Competing risks occur when there is more than one type of outcome, and experiencing one type of outcome precludes the other type of outcome from occurring or being observed. For example, experiencing a first AIDS-diagnosis of non-cancer AIDS precludes a participant from experiencing a first AIDS-diagnosis of cancer AIDS. Three *ad hoc* methods were employed here.

Method 1, the "censor method," estimates the cause-specific hazard, the probability of failure due to the event of interest, given that no failure of any type previously occurred [33-36]. When a single event type is of interest, method 1 censors each competing risk at the time at which it occurs, as shown in figure 1 panel B. Specifically, figure 1, panel A shows observed data for five individuals. Subject 1 has a competing risk at year 5, subject 2 has an event of interest at year 4, subject 3 has an event of interest at year 1, subject 4 has a competing risk at year 2, and subject 5 is censored at year 6. Figure 1, panel B shows implementation of method 1, where the competing risk of subject 1 and subject 4 are censored at the time of the competing risk. Method 1 is probably the most commonly employed method to handle competing risks [35-38]. Many investigators censor competing deaths during survival analysis, implementing method 1 without acknowledging this technique as a competing risks method. Additionally, investigators generally do not state the specific type of HR that they wish to estimate when using method 1; method 1 produces a cause-specific HR.

Method 2, the "exclude method," excludes all competing risks from the data set [7], as shown in figure 1 panel C. Specifically, in figure 1 panel C, data from subjects 1 and 4 are excluded from analysis. Thus, those who developed a first non-cancer AIDS event or who died prior to developing an AIDS event were excluded from the data prior to carrying out analysis. Method 2 produces an estimate of a conditional HR, where the HR applies to a subset of those who will incur the event of interest.

Method 3, the "extend method," extends the person-time to the date of analysis and then censors all competing risks [8,39,40], as shown in figure 1 panel D. Specifically, in figure 1 panel D, subjects 1 and 4 have their time at risk extended until 6 years. Thus, in our analysis, those who developed a first non-cancer AIDS event or who died prior to developing an AIDS event were censored at 31 December 2006. Method 3 produces an estimate of the subdistribution HR, the

probability of failing due to the event of interest given the absence of a previous failure due to the event of interest or the presence of a previous failure due to another event type [41]. However, without the inverse probability-of-censoring weights described by Fine and Gray [1]; method 3 does not necessarily provide a consistent estimator of the subdistribution HR.

Monte Carlo simulation—To compare the estimates and CI coverage of each *ad hoc* method, data were simulated for 24 scenarios [42]. Assuming that 1/3 of the subjects were exposed, 2,000 datasets of 500 subjects were simulated for each combination of the following parameters: an HR of the event of interest of 1 or 2; an HR of the competing event of 1, 1/2 or 2; 20% or 50% administrative censoring; and independent or dependent competing risks. Event and competing risk times were drawn from similar Weibull distributions with a common subject-specific normally-distributed frailty, and the earlier of the two times was assigned as the observed outcome. We take the true HR to be the ratio of the marginal hazards. To approximate the integration over the distribution of the frailty and obtain the marginal hazards we used the Kullback-Leibler information criteria [43] estimated on a sample of 1 million subjects weighted by the inverse probability-of-exposure given the frailty. An administrative censoring time was chosen to control the proportion administratively censored at 20% or 50%. The antilog of the absolute value of the difference between the log of the true HR and the mean log HR was used as a measure of bias. The mean standard error of log HR and the standard deviation of the log HR were used as measures of precision. The proportion of 95% CIs that included the true HR was used as a measure of the CI coverage. Simulation results are subject to Monte Carlo error; based on the 2,000 simulations, the 95% CI coverage estimates have a simulation standard error of ± 1/2%.

RESULTS

From 1 January 1990 to 31 December 2006, 745 clinical AIDS-defining events were diagnosed among 1911 men during 14 202 person-years of follow-up. Of the incident AIDS events, 228 were AIDS-defining cancers (175 Kaposi's sarcoma, 42 non-Hodgkin lymphoma and 11 central nervous system lymphomas). The 616 other AIDS-defining illnesses consisted predominantly of opportunistic infections (n=503), but also included wasting syndrome (n=83) and HIV-related dementia (n=30). An additional 129 men died without AIDS.

Seventy-seven percent of the men were white/non-Hispanic. The median date of seroconversion, age at seroconversion, and years of follow-up time from seroconversion to AIDS or censoring were August 1983 (IQR=September 1982, March 1986), 31 years old (IQR=26, 36), and 5.1 years (IQR=2.3, 14.4), respectively. On average, seroprevalent men had an earlier imputed median date of seroconversion, a younger median age at seroconversion, a shorter follow-up, a smaller proportion of white/non-Hispanic men, and a greater proportion of AIDS-defining events than seroincident men (table 1).

When the HAART calendar period was compared to the monotherapy/combination therapy calendar period, the HRs were similar for all three *ad hoc* methods. Method 1 (HR=0.164; 95% CI: 0.079, 0.340), method 2 (HR=0.127; 95% CI: 0.079, 0.203), and method 3 (HR=0.146; 95% CI: 0.071, 0.299) showed HRs ≅ 0.15 for incident cancer AIDS in the HAART era (table 2). No meaningful difference in the estimates was seen when the inverse-probability-of-exposure weights were truncated at the 1st and 99th percentile.

Appendix 1 shows a summary of the results of the simulation study conducted under 24 scenarios. When the events were dependent, the data were simulated with a correlation of 0.2 to 0.3 between events and competing risks. When the competing risks were independent, method 1 (the "censor method") produced valid estimates of the marginal HR, regardless of the HR of the association between the exposure and the event of interest, the HR of the

association between the exposure and the competing event or the proportion of participants censored. Methods 2 and 3 were only valid in 3 out of 12 scenarios under independent competing risks. When the competing risks were dependent, all three *ad hoc* methods produced relatively unbiased estimates only when the HR and competing risks HR were both null. In general, when the competing risks HR=1/2, method 2 (the "exclude method") underestimated the true marginal HR and method 3 (the "extend method") overestimated the true marginal HR, and when the competing risks HR=2, method 2 overestimated the true marginal HR and method 3 underestimated the true marginal HR. Additionally, the bias was greater in the presence of 20% censoring than 50% censoring. The precision of each method was approximately equal in each scenario.

In 24 scenarios, the estimates produced by method 1 (the "censor method") were generally less biased than those produced by methods 2 or 3. On average across all scenarios, the absolute relative bias for method 1 was 1.03, whereas the absolute relative bias for method 2 was 1.11 and the absolute relative bias for method 3 was 1.13 (table 3). 95% of 95% CIs included the true marginal HR when method 1 was applied, 88% of 95% CIs included the true HR when method 2 was applied and 83% of 95% CIs included the true marginal HR when method 3 was applied.

DISCUSSION

Three *ad hoc* methods for addressing competing risks produced similar HRs when estimating the effect of HAART on incident cancer AIDS, accounting for incident non-cancer AIDS and deaths as competing risks. Each method showed a reduction of approximately 85% in AIDS-defining cancers in the HAART era when compared to the monotherapy/combination therapy era.

Using Monte Carlo simulation, we compared the estimates of the marginal HR produced by each *ad hoc* method under 24 scenarios varying the HR of the event of interest, the HR of the competing risk, proportion censored and dependence of competing risks. When the true HR of the event of interest and the HR of the competing risk were both 1, regardless of the proportion censored or the dependence of events, each *ad hoc* method produced unbiased estimates. Overall, estimates were more biased when the HR of the competing risk was non-null and in the presence of light censoring (i.e. many competing events). The amount of data that is altered under *ad hoc* methods 2 and 3 (i.e., the number of participants that are either excluded in method 2 or have their person-time extended until date of analysis in method 3) is a function of the proportion of competing risks. Therefore, it is intuitive that studies with a large proportion of competing risks would produce more biased results.

The inferences that we are able to draw from our simulations are limited by examining the performance of each method in only 24 out of many possible scenarios. Future studies may wish to additionally alter the proportion exposed, the ratio of competing risks to events, the strength of the dependence between competing risks and events, and the effect of covariates. While investigators usually state that they are estimating the HR [7,8,36], it is usually not noted that method 1 estimates the cause-specific HR, method 2 estimates a conditional HR, and method 3 approximates the subdistribution HR. Our simulations take the marginal HR on the latent time to the event of interest as the true HR; the cause-specific HR is equivalent to the marginal HR in the case of independence [36,44].

Each *ad hoc* method addresses competing risks imperfectly, though epidemiologists have used each of these methods in past to address competing risks when estimating the effect of HAART on specific types of AIDS events [6-8]. When competing risks are independent, and method 1 is utilized, the survival experience of uncensored observations represents the unobserved

survival experience of the competing risks. Thus, this method is only a valid estimate of the marginal HR when the event of interest and the competing risk are independent, given covariates included in the regression model. In observed data it is not possible to assess the dependence between the event of interest and the competing risk [45]. However, the independence assumption can be relaxed to depend on a larger set of covariates by the use of inverse probability-of-censoring weights [46,47]. Methods 2 and 3 take different approaches to circumvent the biases associated with method 1 when the events are dependent. However, by excluding competing risks or extending competing risks to the date of analysis, the person-time at risk could be greatly under- or over-estimated. This may be of particular concern if the alteration in person-time is differential by exposure category. Finally, in all three methods, losses to follow-up are only redistributed to become events of interest, and not competing risks. This may induce bias when a study has a high rate of attrition.

Our results suggest that use of these *ad hoc* methods to estimate the marginal HR should be circumscribed. Though independence cannot be determined from the data, when the competing risks are thought to be independent of the event of interest, method 1 (the "censor method") may be used, as it produces unbiased estimates of both the marginal and cause-specific HRs. Second, when the competing risks are dependent, models for the cumulative incidence function [1] or mixture models [2,48] may be preferred; perhaps at the cost of altering the estimand. In the absence of such formal methods, method 1 (the "censor method" or a model for the cause-specific hazard) appears to be preferred over *ad hoc* methods 2 or 3 as estimates of the marginal HR. As epidemiologists rarely use competing risks methods, or identify the type of estimand that they are estimating when competing risks are present, there is a need for future work on applying competing risks in the epidemiologic literature.

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Appendix 1. Monte Carlo simulation results applying 3 ad hoc competing risks methods under 24 scenarios, varying the HR, the competing risks HR, the proportion censored and both independent (panel A) and dependent (panel B) competing risks

A. Independent Competing Risks						
Scenario		**Method**	**Bias**	**Mean SE of log(HR)**	**SD of log(HR)**	**95% CI Coverage**
Null (HR=1)						
	50% censoring					
1	Competing Risk HR=1	Method 1	1.01	0.191	0.190	96%
		Method 2	1.01	0.191	0.188	95%
		Method 3	1.00	0.191	0.197	95%

A. Independent Competing Risks						
Scenario		**Method**	**Bias**	**Mean SE of log(HR)**	**SD of log(HR)**	**95% CI Coverage**
2	Competing Risk HR=0.5	Method 1	1.01	0.179	0.166	97%
		Method 2	1.09	0.179	0.166	96%
		Method 3	1.10	0.179	0.167	91%
3	Competing Risk HR=2	Method 1	1.01	0.210	0.201	97%
		Method 2	1.17	0.210	0.204	86%
		Method 3	1.15	0.210	0.201	93%
	20% censoring					
4	Competing Risk HR=1	Method 1	1.01	0.150	0.163	94%
		Method 2	1.00	0.150	0.161	96%
		Method 3	1.01	0.150	0.162	92%
5	Competing Risk HR=0.5	Method 1	1.01	0.140	0.128	97%
		Method 2	1.22	0.140	0.131	77%
		Method 3	1.22	0.140	0.129	71%
6	Competing Risk HR=2	Method 1	1.03	0.171	0.162	97%
		Method 2	1.35	0.171	0.170	60%
		Method 3	1.39	0.170	0.167	55%
Alternative (HR=2)						
	50% censoring					
7	Competing Risk HR=1	Method 1	1.01	0.169	0.161	96%
		Method 2	1.01	0.169	0.159	97%
		Method 3	1.01	0.169	0.162	96%
8	Competing Risk HR=0.5	Method 1	1.01	0.163	0.169	94%
		Method 2	1.09	0.163	0.170	92%
		Method 3	1.08	0.163	0.170	95%
9	Competing Risk HR=2	Method 1	1.02	0.182	0.175	96%
		Method 2	1.14	0.181	0.171	90%
		Method 3	1.14	0.181	0.179	92%
	20% censoring					
10	Competing Risk HR=1	Method 1	1.00	0.136	0.138	94%
		Method 2	1.08	0.136	0.145	91%
		Method 3	1.07	0.136	0.135	92%
11	Competing Risk HR=0.5	Method 1	1.01	0.129	0.127	96%
		Method 2	1.22	0.130	0.127	67%
		Method 3	1.14	0.127	0.130	85%
12	Competing Risk HR=2	Method 1	1.01	0.148	0.163	94%
		Method 2	1.21	0.148	0.154	73%
		Method 3	1.40	0.146	0.158	36%
B. Dependent Competing Risks						

A. Independent Competing Risks						
Scenario		**Method**	**Bias**	**Mean SE of log(HR)**	**SD of log(HR)**	**95% CI Coverage**
Null (HR=1)						
	50% censoring					
13	Competing Risk HR=1	Method 1	1.00	0.101	0.184	97%
		Method 2	1.01	0.191	0.189	96%
		Method 3	1.00	0.191	0.183	97%
14	Competing Risk HR=0.5	Method 1	1.01	0.180	0.189	93%
		Method 2	1.08	0.180	0.189	95%
		Method 3	1.11	0.180	0.187	90%
15	Competing Risk HR=2	Method 1	1.05	0.212	0.204	97%
		Method 2	1.09	0.211	0.203	95%
		Method 3	1.19	0.211	0.209	89%
	20% censoring					
16	Competing Risk HR=1	Method 1	1.00	0.151	0.149	96%
		Method 2	1.00	0.151	0.156	95%
		Method 3	1.00	0.151	0.146	95%
17	Competing Risk HR=0.5	Method 1	1.07	0.139	0.139	91%
		Method 2	1.08	0.139	0.145	87%
		Method 3	1.28	0.139	0.135	55%
18	Competing Risk HR=2	Method 1	1.08	0.170	0.174	93%
		Method 2	1.09	0.170	0.177	80%
		Method 3	1.39	0.169	0.164	53%
Alternative (HR=2)						
	50% censoring					
19	Competing Risk HR=1	Method 1	1.01	0.170	0.190	94%
		Method 2	1.02	0.170	0.193	96%
		Method 3	1.00	0.170	0.188	94%
20	Competing Risk HR=0.5	Method 1	1.01	0.163	0.168	96%
		Method 2	1.08	0.163	0.166	93%
		Method 3	1.08	0.163	0.168	92%
21	Competing Risk HR=2	Method 1	1.02	0.184	0.183	95%
		Method 2	1.07	0.183	0.186	92%
		Method 3	1.17	0.183	0.181	88%
	20% censoring					
22	Competing Risk HR=1	Method 1	1.02	0.136	0.133	94%
		Method 2	1.08	0.136	0.132	93%
		Method 3	1.01	0.135	0.138	95%
23	Competing Risk HR=0.5	Method 1	1.02	0.136	0.133	93%

A. Independent Competing Risks						
Scenario		**Method**	**Bias**	**Mean SE of log(HR)**	**SD of log(HR)**	**95% CI Coverage**
		Method 2	1.23	0.130	0.132	68%
		Method 3	1.15	0.130	0.136	81%
24	Competing Risk HR=2	Method 1	1.01	0.148	0.153	96%
		Method 2	1.12	0.148	0.160	93%
		Method 3	1.32	0.147	0.151	56%

Glossary

AIDS	Acquired Immune Deficiency Syndrome
CI	confidence interval
HAART	highly active antiretroviral therapy
HIV	Human Immunodeficiency Virus
HR	hazard ratio
MACS	Multicenter AIDS Cohort Study

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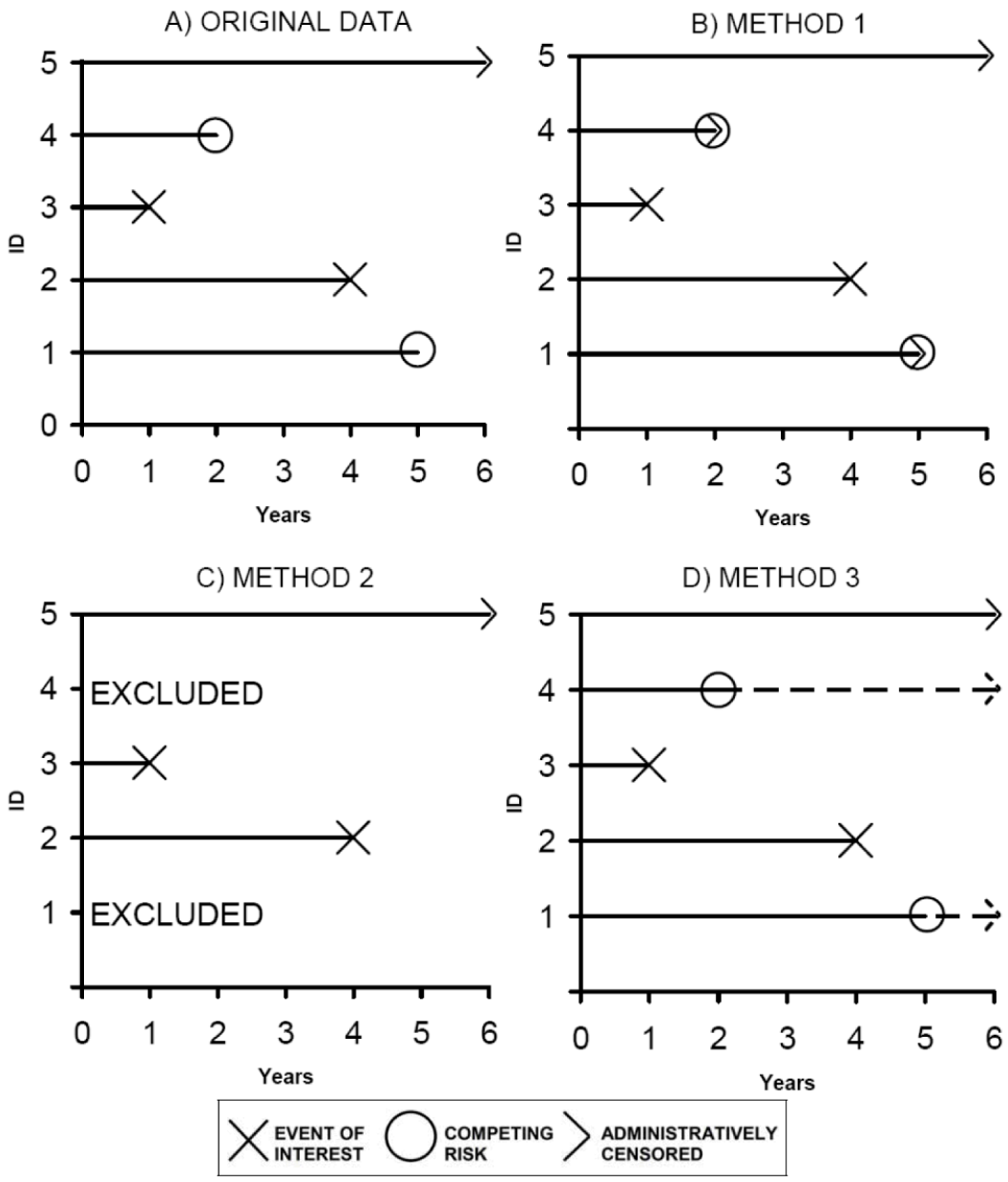

Figure 1.
Description of Four *Ad Hoc* Competing Risks Methods
Panel A: data for 5 individuals.
Panel B (method 1): the competing risk of subject 1 and subject 4 are censored at the time of the competing risk.
Panel C (method 2): data from subjects 1 and 4 are excluded from analysis.
Panel D (method 3): subjects 1 and 4 have their time at risk extended until 6 years

Table 1

Descriptive Characteristics of Seroincident and Seroprevalent Men in the Multicenter AIDS Cohort Study

	Seroincident	Seroprevalent	Total
N	493	1418	1911
Baseline visit date	1984.8 (1984.6, 1985.1)	1984.8 (1984.6, 1985.1)	1984.8 (1984.6, 1985.1)
Date of seroconversion*†‡	1988.0 (1985.5, 1992.1)	1983.1 (1982.4, 1985.0)	1983.6 (1982.7, 1986.2)
Age at seroconversion*	33.9 (28.5, 40.6)	29.7 (25.6, 34.3)	30.6 (26.3, 35.9)
Date of incident AIDS*†	1993.9 (1992.3, 1995.9)	1992.7 (1991.3, 1994.6)	1993.0 (1991.4, 1994.9)
Years of follow-up*	6.2 (3.2, 13.5)	4.6 (2.1, 14.9)	5.1 (2.3, 14.4)
White, non-Hispanic (n)	84% (413)	74% (1,052)	77% (1465)
Cancer AIDS (n)	9% (40)	13% (188)	12% (228)
Non-cancer AIDS (n)	29% (132)	34% (484)	33% (616)
AIDS-free deaths (n)	6% (28)	7% (101)	7% (129)

*Median (IQR)

†1992. 5=July 1, 1992

‡Date of seroconversion imputed among seroprevalent men

Table 2

The Effect of HAART Compared to Monotherapy/Combination Therapy on Progression to an AIDS-defining Cancer among HIV-infected Men in the Multicenter AIDS Cohort Study, Accounting for other AIDS-defining Events and AIDS-free Deaths as Competing risks with Three *Ad Hoc* Competing Risks Approaches

	Method 1 (Censors at competing risk)	**Method 2 (Excludes competing risk)**	**Method 3 (Censors at date of analysis)**
Monotherapy/Combination Therapy, 1990–95			
Person-years	7422	4906	9172
Cancer AIDS Events	197	197	197
Non-cancer AIDS Events	522	---	---
AIDS-free deaths	58	---	---
HAART, ≥ 1996			
Person-years	6780	6176	13 296
Cancer AIDS Events	31	31	31
Non-cancer AIDS Events	94	---	---
AIDS-free deaths	71	---	---
Adjusted Rate Ratio (95% CI)*	0.165 (0.079, 0.340)	0.127 (0.079, 0.204)	0.146 (0.071, 0.299)

CI: confidence intervals

*Adjusted for infection duration, age at seroconversion, race and cohort

Table 3

Average 95% confidence interval coverage (95% CI) and absolute bias for each method across 24 simulated scenarios

		95% CI Coverage			Bias	
	Independent Competing Risks	**Dependent Competing Risks**	**All Scenarios**	**Independent Competing Risks**	**Dependent Competing Risks**	**All Scenarios**
Method 1	96% (95, 96)	95% (94, 96)	95% (94, 96)	1.01 (1.01, 1.02)	1.04 (1.01, 1.07)	1.03 (1.02, 1.05)
Method 2	85% (78, 92)	90% (86, 95)	88% (83, 92)	1.13 (1.07, 1.18)	1.10 (1.06, 1.14)	1.11 (1.08, 1.15)
Method 3	83% (73, 93)	82% (73, 91)	83% (76, 90)	1.12 (1.06, 1.19)	1.13 (1.07, 1.21)	1.13 (1.08, 1.18)