



Original Contribution

Effect of Highly Active Antiretroviral Therapy on Multiple AIDS-defining Illnesses among Male HIV Seroconverters

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The effect of highly active antiretroviral therapy (HAART) on *multiple* acquired immunodeficiency syndrome (AIDS)-defining illnesses remains unclear. Between 1984 and 2005, 573 male human immunodeficiency virus seroconverters in four US urban centers were followed for a median of 9.7 years. During follow-up, 345, 113, 50, and 65 men incurred 0, 1, 2, and >2 AIDS-defining illnesses, respectively. The authors extend the Cox proportional hazards model to determine whether the effect of HAART, as measured by calendar periods, persists beyond the first AIDS-defining illness. After adjustment for race and age at seroconversion, the hazards of a first through third AIDS-defining illness in the HAART calendar period (beyond July 1995) were 0.31 (95% confidence interval (CI): 0.21, 0.46), 0.39 (95% CI: 0.22, 0.74), and 0.33 (95% CI: 0.14, 0.79), respectively, relative to the monotherapy and combination therapy reference calendar period (January 1990–July 1995) and therefore did not attenuate with the number of prior AIDS-defining illnesses (p for homogeneity = 0.83). After the authors averaged over multiple AIDS-defining illnesses, the hazard of an AIDS-defining illness in the HAART calendar period was 0.34 (95% CI: 0.25, 0.45) relative to the reference calendar period. HAART protects against initial and subsequent AIDS-defining illnesses, whose inclusion in analysis markedly increased the precision of the estimated hazard ratio.

AIDS; antiretroviral therapy, highly active; HIV; survival analysis

Abbreviations: AIDS, acquired immunodeficiency syndrome; CI, confidence interval; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus.

Randomized trials have documented the protective effect of highly active antiretroviral therapy (HAART) on time to *first* acquired immunodeficiency syndrome (AIDS)-defining illness or death among persons infected with human immunodeficiency virus (HIV) (1–3). For example, in 1997, the AIDS Clinical Trial Group 320 conducted a randomized

controlled trial of HAART (defined as a protease inhibitor in addition to two nucleoside analogues) versus a standard therapy comprising two nucleoside analogues in patients who were HIV positive with CD4+ T-lymphocyte counts of less than 200 cells/mm³ at random assignment. In this study, the hazard of AIDS or death in patients assigned to

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HAART was one half (hazard ratio = 0.50, 95 percent confidence interval (CI): 0.33, 0.76) that in patients assigned to the less potent standard therapy (3).

In addition to randomized evidence, several observational studies support the protective effect of HAART on time to first AIDS-defining illness (4–6). Using observational cohort data from the Multicenter AIDS Cohort Study, Detels et al. (6) found the hazard of an initial AIDS-defining illness in the calendar period associated with HAART (i.e., beyond July 1995) to be approximately one third (hazard ratio = 0.35, 95 percent CI: 0.20, 0.61) that for the calendar period associated with monotherapy (i.e., January 1990–January 1993).

Relatively little randomized or observational research has been conducted to explore the effect of HAART on multiple sequential (as opposed to multiple concurrent) AIDS-defining illnesses. We therefore addressed the question of whether the protective effect of HAART persists beyond the first AIDS-defining illness. We hypothesized that the magnitude of the hazard ratios for second and third AIDS-defining illnesses would decrease compared with the hazard ratio for the first AIDS-defining illness. In other words, the relative protective effect of HAART would diminish with worsening clinical status.

MATERIALS AND METHODS

Study population

The Multicenter AIDS Cohort Study is an ongoing prospective cohort study of the natural and treated history of HIV infection (7). Beginning in 1984, the study enrolled 5,622 homosexual men in four US urban centers: Baltimore, Maryland/Washington, DC; Chicago, Illinois; Pittsburgh, Pennsylvania; and Los Angeles, California. The results presented here are limited to the 573 of the 4,089 seronegative participants who seroconverted before the August 2005 date of analysis.

Participants were seen semiannually. During their study visit, they completed an extensive interviewer- or computer-administered questionnaire, underwent a physical examination, and provided biologic specimens, including a blood sample for CD4+ T-lymphocyte count, levels of plasma HIV RNA, and serologic HIV antibody tests on HIV-seronegative men. The questionnaire gathered information about medication use, medical history, health services, and behaviors. Institutional review boards approved all protocols, and written informed consent was obtained for all Multicenter AIDS Cohort Study participants.

Endpoint ascertainment

The endpoints of interest were the times from HIV seroconversion to the first AIDS-defining illness and the times between successive AIDS-defining illnesses. The date of HIV seroconversion was taken to be the midpoint between the date of a participant's last HIV-negative and first HIV-positive visits. The median interval between these two visits was 0.52 (interquartile range: 0.49, 0.69) years.

Twenty men had multiple diagnoses of *Pneumocystis carinii* (or *Pneumocystis jirovecii*) pneumonia. To handle the potential problem that two or more reports of the same *P. carinii* pneumonia infection within a short time period may represent a single underlying illness, a second or third *P. carinii* pneumonia diagnosis within 6 months of an earlier such diagnosis was disregarded. As a result, seven *P. carinii* pneumonia diagnoses were excluded. In addition, instances in which a patient was diagnosed with more than one AIDS-defining illness on the same day were taken as a single event. Otherwise, all types of recurrent AIDS-defining illnesses were included in the analyses. Because of the small number of men who had more than three AIDS-defining illnesses ($n = 31$), only the first three AIDS-defining illnesses were analyzed. As a result, those with more than three AIDS-defining illnesses were censored immediately after their third event. Men were also censored at death, loss to follow-up (defined as neither dead nor seen within the last 12 months of study), or administratively censored if still alive at the end of the study period in August 2005.

Exposure assessment

Each participant's person-time was partitioned into four calendar periods corresponding to different antiretroviral therapy regimens, as defined by Detels et al. (6): 1) before January 1990 (i.e., no therapy), 2) January 1990 to December 1992 (i.e., monotherapy), 3) January 1993 to July 1995 (i.e., combination therapy), and 4) beyond July 1995 (i.e., HAART). On the basis of prior work (6, 8) that found no significant differences between the monotherapy and combination therapy periods, we collapsed these two calendar periods into one. Indicator variables for the resulting three calendar periods combined to act as an instrument that proxies for exposure to antiretroviral therapies.

Greenland (9) describes how instrumental variables can be used to circumvent confounding. Calendar periods appear to fulfill the requirements of an instrumental variable (9) for antiretroviral therapy use and have been used in such a fashion previously (6). First, calendar periods are associated with antiretroviral therapy use because therapies were introduced over time. Second, calendar periods represent an external time-dependent covariate, which cannot be affected by indications for treatment with antiretroviral therapy. Third, we assume that calendar periods are independent of AIDS diagnosis given indications for and actual use of antiretroviral therapy based on the results of Detels et al. (6).

Statistical methods

For each stratum of calendar period (i.e., before January 1990, January 1990 to July 1995, and beyond July 1995) and AIDS-defining illness (i.e., first, second, and third), the number of AIDS events and the total amount of person-time were tabulated. We fit a population-averaged proportional hazards model with staggered entries that counted gap time and had event-specific baseline hazards (10). Alternatively, one could handle the statistical dependence incurred by multiple AIDS-defining illnesses by using a subject-specific approach leading to random-effects (i.e., frailty) models

TABLE 1. Descriptive statistics for 573 human immunodeficiency virus seroconverters in four US urban centers between 1984 and 2005

	No. of AIDS*-defining illnesses								Total (n = 573)	
	0 (n = 345)		1 (n = 113)		2 (n = 50)		>2 (n = 65)			
	Value	IQR* or %	Value	IQR or %	Value	IQR or %	Value	IQR or %	Value	IQR or %
Median date of seroconversion	1989.1†	86.1, 92.4	1986.1	85.3, 89.0	1986.4	85.1, 88.8	1985.7	85.2, 87.8	1987.5	85.4, 91.0
Median age (years) at seroconversion	35	30, 41	33	28, 39	32	28, 38	32	28, 39	34	29, 40
No. of White, non-Hispanic men	294	85	97	86	48	96	54	83	493	86
No. of deaths	80	23	74	65	43	86	52	80	249	43

* AIDS, acquired immunodeficiency syndrome; IQR, interquartile range.

† 1989.1 = February 6, 1989 (i.e., 0.1 = 36.5 days).

(11). Here, we concentrated on the population-averaged approach because we were interested in making an inference about the population-averaged effect (12). We used time since HIV seroconversion as the time scale by allowing staggered entries into the risk set, which engenders implicit nonparametric control for possible confounding effects of the duration of HIV infection by comparing men at the same time since HIV seroconversion. We counted the gap time (13, 14) between successive AIDS-defining illnesses rather than total time (15, 16) because the latter approach counts immortal person-time (17) in the denominators of associated rates. The gap-time approach appeared to better reflect the biologic process of multiple sequential AIDS-defining illnesses, while the total-time approach seemed more appropriate for multivariate survival times (e.g., time to first cancer diagnosis and first myocardial infarction). Finally, we allowed the baseline hazard to vary with AIDS-defining illness (i.e., first, second, and third).

We estimated the hazard of AIDS-defining illnesses in each of the three calendar periods. We compared relative hazards by using the monotherapy and combination therapy calendar period as the reference group throughout. We adjusted for two covariates: age at seroconversion and race. Age at seroconversion was thought to be a potential confounder because age is associated with calendar period, and older persons are known to progress to AIDS faster than younger persons. Age at seroconversion was modeled by using a restricted cubic spline with four knots located at 23, 30, 37, and 49 years, which were the 5th, 35th, 65th, and 95th percentiles, respectively (18). The restricted cubic spline creates a smoothly joined piecewise polynomial that allows for a flexible, nonlinear association between age at seroconversion and AIDS-defining illnesses. Race was modeled as an indicator variable of White versus non-White.

We calculated robust 95 percent confidence intervals based on the sandwich estimator (16) as a measure of precision. Accounting for the dependence between multiple AIDS-defining illnesses by resampling the 573 men 200 times to create bootstrap variance estimates yielded similar confidence intervals. All models used Efron's method (19) for handling ties. Summary results were plotted by using

extended Kaplan-Meier curves (20). Cox's proportionality assumption was assessed by adding an interaction between calendar period and time (p for homogeneity = 0.19) as well as log of time (p for homogeneity = 0.59). All analyses were conducted by using SAS version 9.1 software (SAS Institute, Inc., Cary, North Carolina).

RESULTS

The median date of seroconversion was July 1987 (interquartile range: May 1985, January 1991), the median age at seroconversion was 34 (interquartile range: 29, 40) years, and 493 of the 573 participants (86 percent) were White, non-Hispanic (table 1). The group with no AIDS-defining illnesses during follow-up had a slightly later median date of seroconversion and a somewhat older age at seroconversion compared with the group who had more than two AIDS-defining illnesses, reinforcing the need to account for time since seroconversion and age at seroconversion in analyses. Racial composition was similar across groups defined by number of AIDS-defining illnesses with the exception of a higher percentage of White, non-Hispanic men in the group with two AIDS-defining illnesses.

Participants were followed for a median of 9.7 (interquartile range: 6.5, 14.6) years. At the end of follow-up, 249 of 573 or 43 percent had died, 84 of 573 or 15 percent had dropped out of the study, and 240 of 573 or 42 percent were administratively censored. Also at the end of follow-up, 345 of 573 or 60 percent did not have an AIDS-defining illness, while 113 (20 percent), 50 (9 percent), and 65 (11 percent) men had one, two, or more than two AIDS-defining illnesses, respectively. As expected, the percentage of deaths in the group with no AIDS-defining illnesses (23 percent) was markedly lower than the percentage in the other three groups (one: 65 percent, two: 86 percent, more than two: 80 percent). The proportion of person-time on no therapy, monotherapy or combination therapy, and HAART in the calendar periods associated with each of these treatment regimens (i.e., prior to January 1990, January 1990 to July 1995, and beyond July 1995) was 96 percent, 29 percent, and 58 percent, respectively (figure 1).

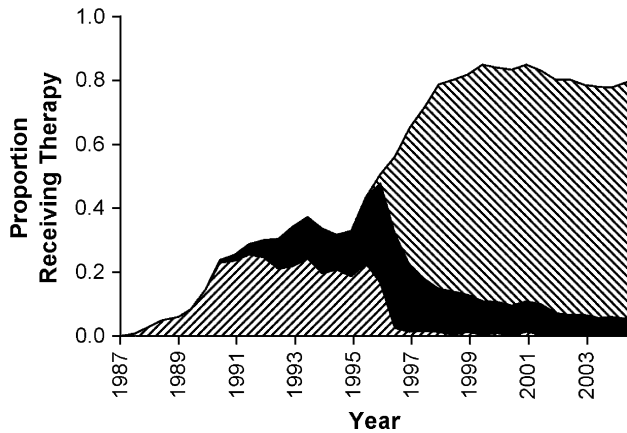


FIGURE 1. Use of antiretroviral therapy by 573 human immunodeficiency virus seroconverters in the Multicenter AIDS Cohort Study, United States, 1987–2004. Forward-slashed area, proportion receiving monotherapy; solid area, proportion receiving combination therapy; backward-slashed area, proportion receiving highly active antiretroviral therapy; remaining area, proportion not receiving therapy.

When only the first AIDS-defining illness was used, the hazard for the HAART calendar period was 0.29 (95 percent CI: 0.19, 0.44; standard error = 0.21) relative to the monotherapy and combination therapy reference calendar period. When we allowed for multiple AIDS-defining illnesses and enabled the hazard ratios to vary by the number of prior AIDS-defining illnesses, the hazards of first through third AIDS-defining illnesses in the HAART calendar period were 0.31 (95 percent CI: 0.21, 0.46), 0.39 (95 percent CI: 0.22, 0.74), and 0.33 (95 percent CI: 0.14, 0.79), respectively, relative to the reference calendar period (table 2).

The hazard of AIDS in the HAART calendar period relative to the reference calendar period did not vary substantially with number of prior AIDS events (Wald p for homogeneity = 0.83). Therefore, a model that averaged over AIDS event number was fit. In this model, the hazard for the HAART

calendar period was about one third that for the reference calendar period (hazard ratio = 0.34, 95 percent CI: 0.25, 0.45; standard error = 0.15; table 2 and figure 2). The addition of second and third AIDS-defining illnesses reduced the standard error of the log hazard ratio corresponding with the HAART calendar period by 29 percent ($1 - 0.15/0.21$) compared with restricting analyses to the first AIDS-defining illness.

DISCUSSION

We estimated the hazard of AIDS in the calendar period associated with HAART compared with the calendar period associated with monotherapy and combination therapy using data from the Multicenter AIDS Cohort Study. We used extended Cox proportional hazards regression models to allow for multiple events with staggered entries and event-specific baseline hazards. Contrary to our hypothesis that the effect of HAART would wane over subsequent AIDS-defining illnesses, our results indicate a protective effect of HAART of about one third for the first as well as for subsequent AIDS-defining illnesses.

The protective effect of HAART that we found is stronger than the one half reported by Hammer et al. (3), yet it is consistent with the findings of Detels et al. (6), who compared the same HAART calendar period with the calendar period associated with only monotherapy. The estimated treatment effect found in the randomized controlled trial by Hammer et al. is subject to moderate (~20 percent) non-compliance (3). Noncompliance in a randomized controlled trial analyzed using intent-to-treat analysis provides a null-biased estimate of the biologic effect of treatment. Cole and Chu (21) found that even 10 percent noncompliance can appreciably bias a hazard ratio of size one half. Therefore, the stronger protective effect presented here should be closer to the biologic effect of HAART than that reported by Hammer et al., assuming that calendar periods fulfill the criteria of an instrumental variable.

The limitations of the present analysis include 1) a lack of specificity due to commingling of disparate AIDS-defining

TABLE 2. Relative hazards of AIDS* by calendar period and event number for 573 human immunodeficiency virus seroconverters in four US urban centers between 1984 and 2005

Calendar period	AIDS event no.	No. of events	No. of person-years	RH ^{*,†}	95% CI [*]
<1990	1st = 2nd = 3rd‡	55	1,335.0	1.32	0.93, 1.87
1990–1995.5§	1st = 2nd = 3rd‡	254	2,064.1	1	
>1995.5	1st = 2nd = 3rd‡	99	2,266.2	0.34¶	0.25, 0.45
>1995.5	1st	49	1,914.6	0.31	0.21, 0.46
	2nd	29	252.3	0.39	0.22, 0.74
	3rd	21	99.3	0.33	0.14, 0.79

* AIDS, acquired immunodeficiency syndrome; RH, relative hazard; CI, confidence interval.

† Adjusted for age at seroconversion and race.

‡ Relative hazards were assumed to be homogeneous across the 1st, 2nd, and 3rd AIDS events.

§ 1990 = January 1, 1990 (i.e., 0.1 = 36.5 days).

¶ p for homogeneity across AIDS event no. = 0.83.

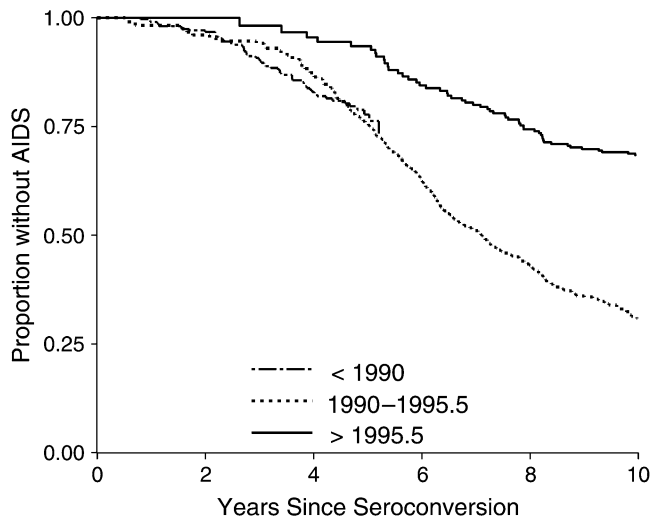


FIGURE 2. Proportion of the 573 human immunodeficiency virus seroconverters in the Multicenter AIDS Cohort Study between 1984 and 2005 without acquired immunodeficiency syndrome (AIDS). Extended Kaplan-Meier curves for the time from seroconversion to the first AIDS-defining illness or between successive AIDS-defining illnesses in calendar periods of antiretroviral therapy use are plotted. The period from January 1990 to July 1995 (i.e., 1995.5) served as the reference category.

illnesses, 2) restrictions on the possible number of AIDS-defining illnesses in the first calendar period, 3) possible selection bias due to loss to follow-up, 4) the treatment of death as a censoring event, and 5) the assumption of constant adherence levels.

All AIDS-defining illnesses were analyzed unless more than one such illness was diagnosed on the same day or unless two or more diagnoses of the same *P. carinii* pneumonia infection occurred within 6 months of each other. Besides the problem that some repetition among AIDS-defining illnesses may well represent a single underlying illness, particular AIDS-defining illnesses may not lend themselves to multiple events (i.e., a report of a second event may be erroneous). Regardless, multiple AIDS-defining illnesses are a common clinical occurrence (22) and therefore should not be ignored.

The time scale used in our analysis was years since HIV seroconversion to ensure that men with similar durations of infection were being compared. Using time since seroconversion as the time scale is indicated for analyses of first AIDS-defining illnesses and is appropriate, but not necessary, for analyses of subsequent AIDS-defining illnesses. For subsequent AIDS-defining illnesses, if one were willing to not use time since seroconversion as the time scale, then precision could be improved by combining data on seroconverting and seroprevalent men. Nonetheless, men contributing person-time to the first calendar period were less likely to have AIDS-defining illnesses, particularly second and third AIDS-defining illnesses, during the first calendar period because of the time necessary to seroconvert, incur

a first AIDS-defining illness, and be at risk for subsequent AIDS-defining illnesses.

Eighty-four or 15 percent of the 573 men were lost to follow-up. Emigrative selection bias (i.e., informative dropout) could markedly alter our inferences only if loss to follow-up was strongly differentially associated with AIDS-defining illnesses. If the worst-case scenario is considered, in which all 68 men lost to follow-up in the HAART calendar period had an AIDS-defining illness at the date last seen and all 16 men lost to follow-up in the calendar periods before HAART was introduced did not have another AIDS-defining illness by the end of follow-up in August 2005, the estimated effect of HAART is still strongly protective (hazard ratio = 0.52).

Death was treated as a censoring event in this analysis, which may not always be appropriate (23). Specifically, since the large majority of deaths are due to AIDS, one may wish to decompose the effect of calendar periods on survival and incident AIDS-defining illnesses among those who survive.

If a constant biologic effect of antiretroviral therapy is assumed, the observed effect of antiretroviral therapy will wax or wane with adherence or lack of adherence, respectively. We assumed a constant level of adherence to antiretroviral therapy over follow-up. If, in fact, the biologic effect of antiretroviral therapy wanes but adherence improves with the diagnosis of additional AIDS-defining illnesses, the observed association may be falsely constant over multiple sequential AIDS-defining illnesses.

The strengths of this study include 1) a large study population of 573 seroconverters, yielding relatively precise estimates; 2) confirmation of the large majority of AIDS-defining illnesses by medical record abstraction, reducing the likelihood of information bias due to outcome misclassification (7); and 3) use of calendar periods as an instrument for exposure to antiretroviral therapies. Use of calendar periods as an instrument to proxy for exposure to antiretroviral therapies circumvents the problem of confounding by indication.

Multiple events survival analysis is rarely used in epidemiologic applications (24), particularly HIV/AIDS applications (25). Methods for repeated events in survival analysis may have important advantages when informed by the underlying biology of the process under study. For instance, if we had observed our hypothesized waning effect of HAART, examination of multiple AIDS-defining illnesses may have guided therapeutic innovation (e.g., development of new pharmacologic agents targeted at specific disease stages). Alternatively, under the persistent homogeneous protective effect of HAART that we observed, analysis of multiple AIDS-defining illnesses improves the precision of the estimated hazard ratio.

In conclusion, this study estimated the effect of HAART on multiple AIDS-defining illnesses as opposed to limiting analyses to the first AIDS-defining illness. Results indicate that the relative effect of HAART appears to be both protective and stable over multiple AIDS-defining illnesses. This finding bolsters the current practice of sustained use of HAART by persons with an initial or repeated AIDS-defining illness.

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