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Effect of HAART on Incident Cancer and Non-Cancer AIDS Events among Male HIV Seroconverters

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Abstract

Objective—To explore the impact of highly active antiretroviral therapy (HAART) on the prevention of AIDS-defining cancers relative to other AIDS-defining events.

Design—Prospective cohort study using 2,121 HIV+ male seroconverters (median age: 28, 51% white/non-Hispanic) in the Tri-service AIDS Clinical Consortium (n=1,694) and the Multicenter AIDS Cohort Studies (n=427).

Methods—Poisson regression models, with calendar periods to represent antiretroviral therapy, were extended to analyze first incident AIDS-defining cancers and other first AIDS-defining events as competing risks.

Results—81 AIDS-defining cancers (64 Kaposi's sarcoma; 17 non-Hodgkin lymphoma) and 343 other AIDS events occurred during 14,483 person-years in 1990-2006. The rate ratio of AIDS-defining cancers during the HAART calendar period was 0.26 (95% confidence limits [CL]: 0.15, 0.46) and of other AIDS-defining events was 0.28 (95% CL: 0.21, 0.36) compared to the monotherapy/combotherapy calendar period, adjusting for age, infection duration, race and cohort. The association of HAART with decreased AIDS incidence appeared to be equal (interaction ratio=0.95 (95% CL: 0.51, 1.74) for AIDS-defining cancers and other AIDS-defining events.

Conclusion—In HIV-infected men, HAART appears equally protective against first AIDS-defining cancers and other first AIDS-defining events.

Keywords

Highly Active Antiretroviral Therapy; Cancers; Kaposi's sarcoma; AIDS-Associated Lymphoma; Opportunistic infections; Epidemiology

INTRODUCTION

The protective effect of highly active antiretroviral therapy (HAART) on the incidence of AIDS or death has been well established via randomized trials^{1, 2} and observational studies.³⁻⁷ Previous research has focused primarily on the effect of HAART on incident AIDS, although HAART has also been shown to reduce the incidence of specific AIDS-defining events, namely AIDS-defining cancers,⁸⁻¹⁷ opportunistic infections^{15, 18, 19} and recurrent AIDS events.⁷ However, it is unclear whether the protective effect of HAART on prevention of AIDS is as potent for AIDS-defining cancers as other AIDS-defining events.

Among men, AIDS-defining cancers include Kaposi's sarcoma (KS) and non-Hodgkin lymphoma (NHL), specifically Burkitt's, immunoblastic and central nervous system lymphomas. Among those with AIDS in the United States (US), the incidence rates of KS and NHL were 1,150 and 760 events per 100,000 person-years between 1990 and 2002.¹⁶ Several studies have compared the incidence of KS and NHL among those who have and have not been treated with HAART, measured directly by HAART use,^{11, 12} and indirectly by calendar period as an instrumental variable for HAART use.^{8-10, 13, 17} The majority of observational studies suggest that HAART provides strong protection against KS^{8, 9, 11-17, 19} and NHL.^{8, 9, 11-13, 15-17} However, two studies reported an increase in the incidence of NHL in the HAART calendar period.^{14, 19} HAART may also be less effective at delaying mortality among those with AIDS-defining cancers than for other AIDS-defining events.^{20, 21} Despite the totality of evidence supporting a protective effect of HAART on the incidence of KS and NHL, it remains unclear whether HAART is as effective at reducing the incidence of AIDS-defining cancers as it is for other AIDS-defining events. Refined estimates of the association of HAART with AIDS-defining cancers are critical to understanding the treated history of HIV infection. Efforts

to alter the constituents of HAART may be required if heterogeneities between AIDS-defining cancers and other AIDS-defining events are uncovered.

We used calendar period as an instrumental variable for HAART exposure and applied statistical methods to estimate the effect of HAART on AIDS-defining cancers relative to the effect of HAART on non-cancer AIDS-defining illnesses using the Tri-service AIDS Clinical Consortium and Multicenter AIDS Cohort Study observational data. We hypothesized that the protective effect of HAART on AIDS-defining cancers would be less than the effect of HAART on non-cancer AIDS-defining illnesses.

METHODS

Study Population

Data from two well-established prospective cohort studies were combined for this analysis: the Tri-service AIDS Clinical Consortium (TACC) and the Multicenter AIDS Cohort Study (MACS). TACC has enrolled 4,566 HIV-infected participants since 1988²² who are active duty US military personnel or beneficiaries, as part of the US Military Natural History Study. US military personnel who tested HIV positive at mandatory screenings, and had a documented conversion window of less than two years, were included in this study. Participants are evaluated at one of seven medical centers across the US: Wilford Hall Medical Center, San Antonio, TX; Brooke Army Medical Center, Fort Sam, Houston, TX; Walter Reed Army Medical Center, Washington, D.C.; Naval Medical Center, San Diego, CA; National Naval Medical Center, Bethesda, MD; Portsmouth Naval Hospital, Portsmouth, VA and Tripler Army Medical Center, Honolulu, HI. Since 1984, MACS has enrolled 6,972 homosexual men in Baltimore, MD, Chicago, IL, Pittsburgh, PA, and Los Angeles, CA to study the natural and treated histories of HIV infection.²³ In both study cohorts, participants complete semiannual physical examinations, questionnaires that include information on medication and treatments, and provide blood for the measurement of CD4 cell count and HIV-1 RNA viral load.

This analysis included 1,694 of 4,566 participants in the TACC and 427 of 6,972 participants from the MACS with dates of seroconversion known to within two years prior to December 31, 2006. Active duty members of the US military were at risk of seroconversion in the TACC and 4,088 men who were HIV-negative at baseline were at risk for seroconversion in the MACS. The MACS and TACC participants not included in the analysis were either HIV-seroprevalent at baseline, remained HIV-negative throughout follow-up, had seroconversion windows greater than two years or had already developed AIDS, died or were lost to follow-up prior to 1990. Additionally, the small proportion of women in TACC (9%) was excluded from the analysis. Both studies obtained institutional review board approval from participating institutions and all participants provided written informed consent.

Endpoint Ascertainment

The outcome of interest in this study was a first incident AIDS-defining illness. Clinical AIDS was defined according to the 1993 Centers for Disease Control and Prevention clinical criteria.²⁴ Individuals with only an immunologically-defined AIDS event (CD4 count <200 cells/ μ l or CD4% <14%) were not considered to have a clinical AIDS-defining illness for this analysis. In TACC, AIDS events were ascertained from medical records, and in the MACS, AIDS events were ascertained through self-report, and were confirmed with medical records. The first AIDS illness was either an AIDS-defining cancer or another clinical AIDS-defining event. AIDS-defining cancers included KS and NHL, and other AIDS-defining illnesses included opportunistic infections, wasting syndrome and HIV-associated dementia. The date of AIDS onset was defined as the midpoint between the last AIDS-free visit and the first visit when AIDS was reported. Participants who did not develop AIDS while under observation were

censored due to drop out at the date of their last visit (n=911), or administratively censored on December 31, 2006 (n=718). 40 participants who died without progressing to AIDS were censored at the date of death. Finally, 28 participants who developed AIDS, but were missing a specific AIDS diagnosis were censored at the last visit prior to diagnosis.

Exposure Assessment

Antiretroviral therapy exposure was assessed by using calendar period as an instrumental variable for HAART to avoid the confounding by indication that occurs when individual-level antiretroviral therapy use is used as an exposure variable.⁵ Briefly, sicker individuals (e.g., low CD4 cell counts) are typically treated with antiretroviral therapy and therefore those with antiretroviral therapy exposure have poorer prognoses, thus inducing confounding by indication.²⁵ Participant person-time was partitioned into the following two calendar periods: monotherapy/combination therapy (1990-95) and HAART (≥ 1996). Therefore, a participant may contribute person time at risk for AIDS in the monotherapy/combination therapy calendar period, the HAART calendar period, or both calendar periods. Calendar period meets the criteria to be an instrumental variable for HAART,²⁶ because calendar period is 1) associated with antiretroviral therapy; 2) independent of known confounders of the relationship between antiretroviral therapy and AIDS-free time; and 3) independent of AIDS-free time, conditional on antiretroviral therapy. Previous studies have used calendar period as an instrumental variable for antiretroviral therapy.^{3, 4, 7, 27-36}

Statistical Methods

Date of seroconversion was estimated from the dates of the last seronegative and first seropositive visits. We defined the date of seroconversion as one-third the time period between the last negative visit and the first positive visit to reflect the decline in HIV seroconversion over time.³ The median seroconversion window was 0.9 years (interquartile range [IQR]: 0.5, 1.3 years). Median values (IQRs) and percentages for selected participant characteristics were compared by cohort and event type.

To compare the effect of HAART on incidence of AIDS-defining cancers versus other AIDS-defining events, methods to account for competing risks were used. 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 NHL or KS precludes a participant from having a first AIDS-diagnosis of non-cancer AIDS. In this analysis, independent competing risks methods were used to compare the effect of HAART on AIDS-defining cancers to other AIDS-defining events.³⁷ This method is an extension of standard survival analysis techniques, using data augmentation to simultaneously provide estimates for all competing events under study. Poisson regression was carried out on the augmented data set. Specifically, let j be an event type indicator, where $j = 0$ for a non-cancer AIDS event and $j = 1$ for a cancer AIDS event. A duplicate data set is created to produce one record for each type of event with the event type indicator swapped (i.e. $j = 1$ for a non-cancer AIDS event and $j = 0$ for a cancer AIDS event). Each outcome is alternately treated as a non-event in the duplicated data set. The number of clinical AIDS cases is assumed to be Poisson distributed with rate λ_j , estimated on the original data set augmented with the duplicated data set. Rate ratios were used as the measure of association with 95% confidence limits (CL) as the measure of precision. Rate ratios for cancer and non-cancer AIDS were estimated for the HAART calendar period, compared to the monotherapy/combination therapy calendar period. Additionally, an interaction ratio was estimated to assess whether the effect of the HAART calendar period compared to the monotherapy/combination therapy calendar period was modified by type of AIDS event. We used generalized estimating equations with an independent covariance structure to produce robust variance estimates, correcting for the dependence imparted by the augmented data.^{37, 38}

To control for confounding, the regression models were weighted by inverse probability of exposure weights, conditional on age at seroconversion, infection duration, race and cohort.^{39,40} Age at seroconversion and infection duration were modeled as restricted cubic splines with knots at the 5th, 50th and 95th percentiles (20, 28 and 43 years and 0, 0.8 and 8.7 years, respectively), to allow non-linear associations with calendar period.⁴¹ Race (white/non-Hispanic, black/non-Hispanic or other) and cohort (TACC or MACS) were modeled as indicator variables. Inverse probability weights were well-behaved with a mean/median of 1.0/0.9 and minimum/maximum values of 0.5/8.5. Effect modification by study was explored with the inclusion of an interaction term. Sensitivity of the results to the calendar period definition was assessed by use of one, two and three year lag periods. Data was analyzed with SAS version 9.1 (SAS Institute, Cary, NC).

RESULTS

From January 1, 1990 to December 31, 2006, 424 clinical AIDS-defining events were diagnosed among 2,121 men during 14,483 person-years of follow-up. Of the AIDS events, 82 were AIDS-defining cancers, of which 64 (79%) were KS, 16 (20%) were NHL and one (1%) was a central nervous system lymphoma. The 343 other AIDS-defining illnesses consisted predominantly of opportunistic infections (n=281, 82%), but also included wasting syndrome (n=46, 13%) and HIV-related dementia (n=16, 5%).

Fifty-one 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 November 1991 (IQR=June 1988, July 1997), 28 years old (IRQ=23, 34), and 6.6 years (IQR=4.0, 10.5), respectively. MACS participants had an earlier median date of seroconversion, a greater median age at seroconversion, a longer follow-up and a greater proportion of white/non-Hispanic men than the TACC participants. No notable differences were seen between those with AIDS-defining cancers and other AIDS-defining illnesses (table 1).

Antiretroviral therapy use (no therapy, monotherapy, combination therapy and HAART) among participants from both TACC and MACS is presented in figure 1 by calendar year, demonstrating the rationale for the definition of the monotherapy/combination therapy calendar period as 1990-95 and the HAART calendar period as ≥ 1996 .

With the monotherapy/combination therapy calendar period as the referent group, the rates of both AIDS-defining cancers (rate ratio (RR)=0.26; 95% CL 0.15, 0.46) and non-cancer AIDS diagnoses (RR=0.28; 95% CL 0.21, 0.36) were reduced in the HAART calendar period (table 2). HAART, measured by calendar period, was observed to be equally effective at reducing the incidence of both cancer AIDS and non-cancer AIDS (interaction ratio=0.95 (95% CL 0.51, 1.74). Allowing for modification by cohort with the inclusion of an interaction term, the rate ratios for cancer AIDS in the HAART versus monotherapy/combination therapy period were similar in the TACC (RR=0.27) and MACS (RR=0.24) studies; likewise, the rate ratios for non-cancer AIDS in the HAART versus monotherapy/combination therapy period were similar in the TACC (RR=0.29) and MACS (RR=0.25) studies.

It may not be reasonable to assume the effect of HAART on preventing AIDS begins immediately at HAART initiation, or at the beginning of the HAART calendar period (i.e. 1996), particularly for KS or NHL, which may have long latency periods. We therefore assessed the sensitivity of the results to the calendar period definition, using lag periods of one, two and three years for each calendar period (i.e. monotherapy/combination therapy period redefined as ≥ 1991 , ≥ 1992 and ≥ 1993 and HAART calendar period redefined as ≥ 1997 , ≥ 1998 and ≥ 1999 , respectively). Of the 24 AIDS-defining cancers in the HAART calendar period, 8

occurred in 1996-98, 8 occurred in 1999-2002 and 7 occurred in 2003-2006. With a one-year lag period, rate ratios of 0.23 (95% CL 0.12, 0.42) and 0.23 (95% CL 0.17, 0.30) were observed for AIDS-defining cancers and other AIDS-defining events, respectively (interaction ratio=1.00 (95% CL 0.51, 1.97)). With a two-year lag period, rate ratios of 0.24 (95% CL 0.13, 0.45) and 0.22 (95% CL 0.16, 0.31) were observed for AIDS-defining cancers and other AIDS-defining events, respectively (interaction ratio=1.10 (95% CL 0.55, 2.19)). With a three-year lag period, rate ratios of 0.29 (95% CL 0.15, 0.55) and 0.23 (95% CL 0.16, 0.33) were observed for AIDS-defining cancers and other AIDS-defining events, respectively (interaction ratio=1.26 (95% CL 0.61, 2.58)).

DISCUSSION

We estimated the incidence rates of AIDS-defining cancers and other AIDS-defining events in the HAART calendar period compared to the monotherapy/combination therapy calendar period, and the effect of the HAART calendar period on the rate of AIDS-defining cancers relative to the rate of other AIDS-defining events. Though we hypothesized that the effect of HAART on AIDS-defining cancers would be attenuated when compared to other AIDS-defining events, we observed the calendar period associated with HAART had an equally protective effect on the rate of both cancer and non-cancer AIDS events among HIV-infected men.

There appeared to be a trend of an attenuated effect of HAART on AIDS-defining cancers compared to other AIDS-defining events across lag periods of one, two and three years. However, even with a three year lag period, the interaction ratio was both practically and statistically non-significant, and was imprecise due to being based on very few cancer cases (n=15). This potential delayed effect of HAART should be explored further in future studies with a larger number of AIDS-defining cancers in the HAART calendar period.

The dramatically reduced rate of non-cancer and cancer AIDS events that we observed in the HAART calendar period is consistent with published research. When the HAART and pre-HAART calendar period were compared, Detels et al.¹⁸ observed an 80 percent decline in opportunistic infections in MACS and the CASCADE collaboration¹⁵ observed a 58 to 96 percent risk reduction of several AIDS-defining opportunistic infections, dementia and wasting syndrome. A rate ratio of 0.21 (95% CL 0.07, 0.60) for AIDS-defining cancers was reported in the Women's Interagency HIV Study,⁸ and a rate ratio of 0.31 (95% CL 0.22, 0.42) was reported in the Studies of HIV/AIDS Longitudinal Outcome Metrics cohort when the HAART calendar period was compared to the pre-HAART calendar period.¹³ These estimates are similar to the results in our study (RR=0.26; 95% CL 0.15, 0.46). An inverse variance weighted average of these three estimates yields a precise summary estimate of RR=0.29 (95% CL: 0.22, 0.38). As 64 of the 81 cancer occurrences in our study were KS, the associations presented were primarily based on the effect of HAART on KS. Thus the effect of HAART on NHL could not be specifically addressed.

In our analysis, we used calendar period as an instrumental variable for antiretroviral therapy use.²⁶ To the degree that calendar period acts as a proper instrument, our results are valid. Additionally, the utilization of independent competing risks methods assumes that the probability of developing an AIDS-defining cancer is independent of the probability of developing another AIDS-defining event.⁴² This assumption cannot be directly assessed as, by definition, both a first AIDS-defining cancer and another first AIDS-defining event are not observed in the same person. This independence assumption may be violated as both types of AIDS events have a shared etiology related to HIV-associated immune suppression. However, a previous study found that independent and dependent competing risks methods produced similar estimates for the reduction of specific AIDS-defining events in the HAART calendar

period.¹⁵ Another option for analysis is the use of mixture models that allow for dependence between competing events.^{43, 44} However, the mixture model approach requires the estimation of an additional parameter, namely the proportion of participants who will eventually develop a first AIDS-defining cancer. With the present data pooling two large US cohorts, there were an insufficient number of cancer AIDS events in the HAART calendar period to accurately estimate this additional parameter. Future work with further follow-up, and perhaps pooling of additional international cohorts, will explore the possible dependent competing risks of AIDS-defining cancer and other non-cancer AIDS-defining events.

A main strength of this analysis was the use of two of the largest, well-characterized cohorts of seroconverters in the US with medically-confirmed AIDS diagnoses. The use of men with a known date of HIV seroconversion allowed us to carefully control for duration of HIV infection, an important confounder due to its strong association with both calendar period and progression to AIDS. Additionally, the combination of the two cohorts enhances the generalizability of our results to men of a broad age range and racial composition. However, as our analysis only included men, it is questionable whether the results presented here are generalizable to HIV-infected women, especially since cervical cancer is also considered to be an AIDS-defining cancer among women.

In conclusion, HAART appears to be as effective at preventing AIDS-defining cancers as other AIDS-defining events among male seroconverters in the Tri-service AIDS Clinical Consortium and the Multicenter AIDS Cohort Study. This study provides reassurance that antiretroviral therapies targeted at enhancing the immune system and preventing AIDS diagnoses in general are equally protective against various types of AIDS-defining events among HIV-infected men.

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Figure 1.

Antiretroviral therapy use by calendar year among participants in the Tri-service AIDS Clinical Consortium and the Multicenter AIDS Cohort Study, 1987-2006.

Table 1
Descriptive characteristics of seroconverters in the Tri-service AIDS Clinical Consortium and the Multicenter AIDS Cohort Study

	TACC	MACS	Censored	TACC and MACS combined	
				AIDS-defining Cancers	Non-cancer AIDS-defining Events
N	1694	427	1697	81 [‡]	343 [‡]
Date of seroconversion* [‡]	1992.9 (1989.5, 1998.3)	1987.5 (1985.4, 1991.6)	1993.3 (1989.6, 1998.8)	1987.6 (1986.3, 1990.3)	1988.0 (1986.5, 1990.4)
Age at seroconversion*	26.0 (23.0, 31.0)	34.6 (29.0, 41.3)	28.0 (23.0, 33.6)	29.0 (24.0, 34.6)	28.3 (24.0, 35.0)
Date of incident AIDS* [‡]	1995.2 (1993.4, 1997.7)	1994.0 (1992.4, 1995.6)	---	1994.5 (1993.1, 1996.3)	1994.7 (1992.6, 1996.7)
Years of follow-up*	6.1 (3.7, 9.9)	8.5 (5.9, 14.8)	6.9 (3.8, 11.3)	6.7 (5.2, 8.4)	6.2 (4.6, 8.2)
White, non-Hispanic (n)	43% (734)	83% (353)	49% (822)	68% (55)	61% (210)

* Median (IQR)
[‡] 1992.5=July 1, 1992
[‡] Of the 343 non-cancer AIDS-defining illnesses, 220 were in TACC and 123 were in MACS. Of the 81 AIDS-defining cancers (64 Kaposi's sarcoma and 17 non-Hodgkin lymphoma), 43 were in TACC and 39 were in MACS.

Rate ratios for AIDS-defining cancer and other AIDS-defining events in the HAART versus the monotherapy/combination therapy eras, and the interaction ratio between HAART and type of AIDS event among 2,121 male seroconverters in the Tri-service AIDS Clinical Consortium and the Multicenter AIDS Cohort Study, followed between 1990 and 2006

Table 2

	Person-years	AIDS-defining cancers		Other AIDS-defining events		Interaction Ratio (95% CL) *
		AIDS Events	Adjusted Rate Ratio (95% CL) *	AIDS Events	Adjusted Rate Ratio (95% CL) *	
Mono/Combination Therapy, 1990-95	5,752	58 [†]	1	229	1	1
HAART, ≥ 1996	8,732	23 [†]	0.26 (0.15, 0.46)	114	0.28 (0.21, 0.36)	0.95 (0.51, 1.74)

* Adjusted for infection duration, age at seroconversion, race and cohort; CL, confidence limits

[†] 58 = 49 KS, 9 NHL; 23 = 15 KS, 8 NHL