Effectiveness of Potent Antiretroviral Therapy on Time to AIDS and Death in Men With Known HIV Infection Duration

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Context.—Time to development of acquired immunodeficiency syndrome (AIDS) and time to death have been extended with the increased use of combination therapy and protease inhibitors. Cohort studies following up persons with human immunodeficiency virus (HIV) infection in periods characterized by different therapies offer the opportunity to estimate therapy effectiveness at the population level.

Objective.—To assess the effectiveness of self-reported, long-term potent antiretroviral therapy in a cohort of 536 men whose duration of HIV infection was known (seroconverters).

Design.—Cohort study. The cohort was compared for time to development of AIDS and time to death in 1984 to 1990, 1990 to 1993, 1993 to July 1995, and July 1995 to July 1997 when the major treatments were no therapy, monotherapy, combined therapy, and potent antiretroviral therapy, respectively. Survival analysis methods with time zero set as the date of seroconversion and incorporating staggered entries into each period were used. Mean CD4 cell change, stratified by infection duration, was determined for each period using a random effects model.

Setting.—The Multicenter AIDS Cohort Study (MACS) in 4 urban areas (Baltimore, Md; Chicago, Ill; Los Angeles, Calif; and Pittsburgh, Pa).

Participants.—A total of 5622 men who were 18 years or older were enrolled into MACS. Of the 5622, there were 2191 HIV-positive individuals at enrollment. Of the 3431 men who were HIV-negative, 536 were observed to seroconvert and were followed up for up to 13 years. The group of 536 who seroconverted constituted the study population.

Main Outcome Measures.—Time from seroconversion to development of AIDS and to death and change in CD4 cell count.

Results.—A total of 231 seroconverters developed AIDS, and 200 men died. Using 1990 to 1993 as the reference period, the relative hazard of AIDS was 1.04 (95% confidence interval [CI], 0.73-1.48) during 1993 to July 1995 and 0.35 (95% CI, 0.20-0.61) during July 1995 to July 1997. Relative hazards of death were 0.87 (95% CI, 0.58-1.31) and 0.62 (95% CI, 0.38-1.01) for the same periods. The relative time (the factor by which times are contracted or expanded) to development of AIDS was 0.97 (95% CI, 0.86-1.09) for 1993 to July 1995 and 1.63 (95% CI, 1.40-1.89) for July 1995 to July 1997. Relative survival time for 1993 to July 1995 was 1.01 (95% CI, 0.91-1.12) and for July 1995 to July 1997 was 1.21 (95% CI, 1.07-1.36) relative to 1990 to 1993. The rate of CD4 cell count decline in July 1995 to July 1997 was significantly lower ($P<.05$) compared with the previous 2 periods.

Conclusions.—In the calendar period when potent antiretroviral therapy was introduced, the time to development of AIDS and time to death were extended, and rate of CD4 cell count decline was arrested.

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INCREASING USE of combination therapy in the treatment of human immunodeficiency virus (HIV) infection and acquired immunodeficiency syndrome (AIDS) began in the mid-1990s. In 1995, protease inhibitors were approved for treatment of HIV and AIDS, resulting in an increase in their use alone and in combination with other drugs. Clinical trials[1-8] have demonstrated the dramatic effect of combined therapies on levels of circulating HIV when treatment was initiated early in the course of HIV infection. It is likely, however, that the impact of potent antiretroviral therapy in the community setting may not be as successful as observed in clinical trials. Clinical trials select for compliant individuals and monitor the participants for compliance to the particular treatment regimen.

Recently, there have been reports of a decline in death due to AIDS in several major metropolitan areas of North America, including Vancouver, British Columbia, Los Angeles, Calif, and New York, NY.[9-12] Trends in AIDS incidence are more difficult to determine, especially in the absence of data on the number of infected persons in the population.

The actual effect of potent antiretroviral therapy on survival to AIDS and to

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death expected to occur outside the rigorous clinical trial setting may be approximated by studying uninfected persons enrolled in observational cohort studies who become infected with HIV and undergo treatment while under observation. Community experience with treatment includes such variables as compliance, access to care and drugs, use of other drugs, and physicians' decisions on treatment. The Multicenter AIDS Cohort Study (MACS) is a study of the natural history of HIV infection in men who have sex with men. The study began in 1984 with men who volunteered to participate[13] who are thus not representative of all men who have sex with men. The 5622 men in MACS have now been followed up for 12 to 13 years, representing an opportunity to observe changes in time to development of AIDS and time to death associated with increased use of combination therapy and protease inhibitors. Previous studies have compared incidence of AIDS and death in different calendar periods without adjusting for long-term survivors in later calendar periods who are not comparable with those experiencing a more rapid progression.[14,15] We restrict our analyses here to those in whom infection duration is known (ie, seroconverters). We compared changes in CD4 cell levels and incidence of AIDS and death in different time periods corresponding to different reported uses of therapy in persons with similar infection duration and age.

METHODS

Study Design and Follow-up

A cohort of 4954 men who were 18 years or older were recruited into MACS in 4 metropolitan areas of the United States from April 1984 through March 1985. To increase minority enrollment, an additional 625 men were recruited from 1987 to 1991. An additional 43 seroconverters from Pittsburgh, Pa, who were recruited at the same time, were followed up in a parallel study with the MACS protocol and added to these analyses.

The men were followed up at least every 6 months with repeat interviews, physical examinations, and blood sample collection. The interview included extensive questions about HIV or AIDS symptoms and use of specific antiretroviral drugs and prophylactic treatments for opportunistic infections in the 6 months preceding the semiannual visits. The men were given the opportunity to report use of other drugs. Serologic HIV antibody tests were routinely done on previously seronegative men at each visit. Confirmation of reported AIDS diagnosis was made via physician and/or hospital summaries. Deaths were monitored by follow-up of the men for vital status and by ongoing search of death records. Details of study design and method of follow-up have been published.[16,17]

Study Population

The study population consisted of MACS participants who were seronegative at enrollment (n = 3431) and seroconverted during follow-up (n = 536) before June 30, 1997. It has been documented that the seroconverters engaged in receptive intercourse more often and were younger than those remaining uninfected.[18] At time of recruitment neither participants nor investigators were aware of their HIV status.

Seroconversion date is defined by the last date an individual was known to be HIV seronegative and the first date known to be HIV positive. By study design, time lag between last negative and first HIV-positive visits should be 6 months, but some men missed visits while undergoing seroconversion. Of the 536 men with known dates of last negative and first positive visits, 50%, 75%, and 90% had a lag less than 6.2, 7.7, and 23.0 months, respectively. We have reported a significant downward trend of seroconversion over calendar time in the full cohort[19]; thus, we defined seroconversion as occurring at one third of the time interval between last negative and first positive visits, reflecting the true situation of declining incidence more accurately than using the midpoint between last negative and first positive visits (which assumes incidence is unchanging).

Outcome Variables

For each of the 536 seroconverters, we determined AIDS-free and survival times through June 30, 1997. Those AIDS-free or alive at the end of follow-up contributed with censored observations to the survival analysis of time to development of AIDS and time to death, respectively. Those seen from July 1, 1996, to June 30, 1997, with no report on outcomes of interest (ie, AIDS, death) were considered censored at date of analysis (ie, June 30, 1997).[20] For analysis of survival times we considered all deaths as events. Rate of CD4 cell count change was calculated from longitudinal counts concurrently measured at semiannual visits throughout the study.

Exposure Variables

The primary purpose of the analysis was to compare hazards of AIDS and death and rates of CD4 cell count change in those reaching the same duration of infection at different calendar periods corresponding to different types of therapy being used by the seroconverter cohort. Thus, this is an analysis of AIDS therapy effectiveness at the population level rather than efficacy at the individual level (ie, as prescribed by clinicians and used by patients) as in a clinical trial.[21,22]

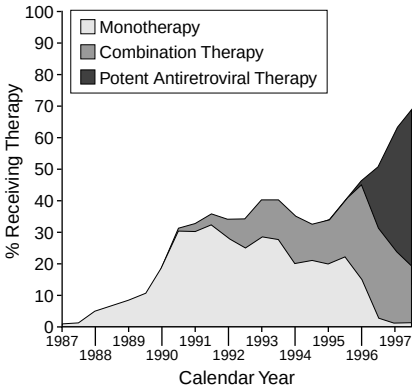

Figure 1.—Use of antiretroviral therapy by Multicenter AIDS Cohort Study seroconverters while free of AIDS (acquired immunodeficiency syndrome).

Therapy regimens were classified as monotherapy, combination therapy, and potent antiretroviral therapy groups. Monotherapy was defined as a single nucleoside reverse transcriptase inhibitor and included zidovudine, stavudine, zalcitabine, didanosine, and lamivudine. Combination therapy was defined as 2 or more nucleoside reverse transcriptase inhibitors. Potent antiretroviral therapy was defined according to 1997 US National Institutes of Health guidelines[23] as 2 or more nucleoside reverse transcriptase inhibitors with either a protease inhibitor, such as indinavir, saquinavir, ritonavir, or nelfinavir, or a nonnucleoside reverse transcriptase inhibitor, such as nevirapine or delavirdine. Men taking a protease inhibitor plus zidovudine and stavudine were not considered to be receiving potent antiretroviral therapy because that combination is antagonistic and should not be used (according to the National Institutes of Health guidelines) and, thus, were classified as receiving combination therapy. Conversely, those receiving 2 or more protease inhibitors were classified as receiving potent antiretroviral therapy. Those receiving only 1 protease inhibitor or 1 nucleoside reverse transcriptase inhibitor were classified as receiving monotherapy.

Prevalence of antiretroviral use by the seroconverters while free of AIDS is shown in Figure 1. On the basis of this analysis, follow-up has been divided into 4 periods corresponding to different therapy regimens: before 1990 (mostly

no therapy), 1990 to 1993 (monotherapy), 1993 to July 1995 (combined therapy), and July 1995 to July 1997 (potent antiretroviral therapy). These periods are used in subsequent analyses as proxies for the different regimens.

Data Analysis

Since it is crucial to compare hazards of AIDS and death in those with the same HIV infection duration, and since some of those contributing to later calendar periods enter with longer infection durations, we used survival analysis methods that incorporate staggering entries. Calendar period was treated as an external time-dependent covariate.[24] Individuals contributed as many records for data analysis as calendar periods in which they were observed at risk for events of interest. Each contribution was characterized by (1) infection duration the individual had when entering a given period, (2) infection duration when exiting a given period, and (3) the status with respect to events of interest at exit from the period (ie, if exit was due to event occurrence or if event free at exit). In the survival analysis, the individual only contributed to risk sets between entering and exiting and thus we compared hazards of events of interest in different calendar periods in men with the same infection duration.[22] Thus, the men seroconverting early in the study and contributing to the last calendar period have infection durations longer than other men in previous calendar periods. In the analysis, these men make no contributions to inferential statements about relative hazards (RHs) and relative times to event.

Estimation of survival curves was obtained using an extended (incorporating staggered entries) Kaplan-Meier method. Since in a given calendar period men entered with different infection durations, the method reconstructs survival function over the full range of values of years from seroconversion. The estimator is to be interpreted as the one to be obtained if conditions of that period are always present. Comparison of survival functions was done by estimating and testing RHs by using a Cox proportional hazards model with staggered entries.[22] Appropriate parametric regression methods were used to estimate and test relative times (ie, the factor by which times are expanded or contracted) with respect to a reference calendar period.[25,26] If therapies associated with a calendar period are more effective than those in the reference period, RH indicates the factor by which the event hazard is reduced, and relative times indicate the factor by which times are extended by more effective therapies.

To compare rate of CD4 cell count change in different calendar periods, we

Table 1.—Descriptive Statistics of 536 HIV Seroconverters Seen at Different Calendar Periods in the Multicenter AIDS Cohort Study From 1984 to 1997*

	Calendar Period			
Variable	Before 1990	1990-1993	1993-July 1995	July 1995-July 1997
No. seen while AIDS-free	367	414	370	288
Year of seroconversion†	1985.68	1986.76	1987.88	1989.15
Age at seroconversion†	32.3	32.7	33.0	33.4
Time between last negative and first positive visits†	0.52	0.52	0.52	0.52
Infection duration at beginning of calendar period†	0.34	3.41	5.12	6.35
No. of person-years while AIDS-free†	1152	961	761	491
No. of AIDS cases	48	78	82	23
No. of deaths	29	57	73	41

*HIV indicates human immunodeficiency virus; AIDS, acquired immunodeficiency syndrome.
†All values are median years unless otherwise noted.

Table 2.—Drug Therapy and Health Care Use in 4 Calendar Periods by HIV Seroconverters in the Multicenter AIDS Cohort Study From 1984 to 1997*

	Use During Calendar Period, %			
Variable	Before 1990 (n = 347)†	1990-1993 (n = 347)†	1993-July 1995 (n = 313)†	July 1995-July 1997 (n = 227)†
Nucleoside reverse transcriptase inhibitor (NRTI)				
Lamivudine	0	0	3.8	64.3
Zidovudine	17.0	49.1	44.1	53.7
Stavudine	0	0.9	8.6	37.9
Didanosine	0	9.8	20.4	15.9
Zalcitabine	0	8.1	17.9	14.1
Any NRTI usage	17.0	50.0	51.4	73.7
Protease inhibitor (PI)				
Indinavir	0	0	0	33.5
Saquinavir	0	0	0	18.1
Ritonavir	0	0	0	11.0
Nelfinavir	0	0	0	10.1
Any PI usage	0	0	0	46.7
Nonnucleoside reverse transcriptase inhibitor (NNRTI)				
Nevirapine	0	0	0	8.4
Delavirdine	0	0	0.3	0.9
Any NNRTI usage	0	0	0.3	8.4
Pneumocystis carinii pneumonia (PCP) prophylaxis and/or treatment				
Sulfamethoxazole	1.4	13.3	24.9	28.2
Dapsone	1.2	4.9	8.6	5.3
Aerosolized pentamidine	2.0	10.7	5.1	3.1
Trimethoprim	0	0.3	0.3	0
Intravenous pentamidine	1.2	0.6	1.0	0
Any PCP prophylaxis and/or treatment	4.6	22.5	31.9	32.6
Mycobacterium avium–intracellulare complex (MAC) prophylaxis				
Clarithromycin	0	1.2	3.2	5.3
Azithromycin	0	0	0.6	4.8
Rifabutin	0	0	4.5	2.2
Any MAC prophylaxis	0	1.2	8.0	9.3
Other prophylaxis and/or treatment				
Acyclovir for herpes	20.7	27.7	33.5	34.4
Acyclovir	2.3	15.3	19.5	22.0
Fluconazole	0	6.1	15.3	11.9
Health care usage				
Outpatient visit to physician's office, non–health maintenance organization (HMO)	NA	70.5	76.9	77.5
Outpatient visit to HMO	NA	22.9	26.3	37.0
Any health provider visit	NA	87.5	94.2	96.5

*HIV indicates human immunodeficiency virus; AIDS, acquired immunodeficiency syndrome; and NA, data not available for visits in this calendar period.
†Number of AIDS-free seroconverters for whom therapy could be assessed in the 4 calendar periods.

Calendar Period	No.	No. With Acquired Immunodeficiency Syndrome (AIDS)	Relative Hazards	95% Confidence Interval
Before 1990	367	48	1.51	(0.96-2.39)
1990-1993	414	78	1	NA
1993-July 1995	370	82	1.04	(0.73-1.48)
July 1995-July 1997	288	23	0.35	(0.20-0.61)

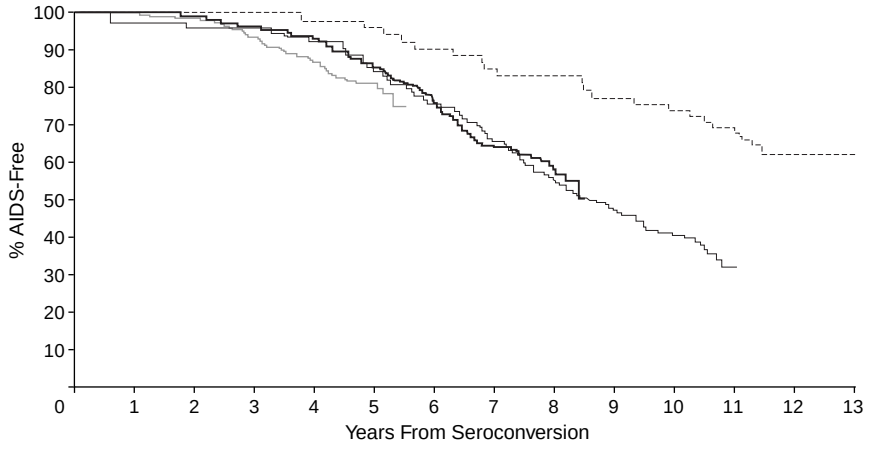

Figure 2.—Extended Kaplan-Meier curves and relative hazards for time to development of AIDS from human immunodeficiency virus seroconversion in calendar periods with different antiretroviral therapy use. NA indicates not applicable because this is the reference category.

Calendar Period	No.	No. Who Died	Relative Hazards	95% Confidence Interval
Before 1990	367	29	1.98	(1.07-3.66)
1990-1993	438	57	1	NA
1993-July 1995	421	73	0.87	(0.58-1.31)
July 1995-July 1997	354	41	0.62	(0.38-1.01)

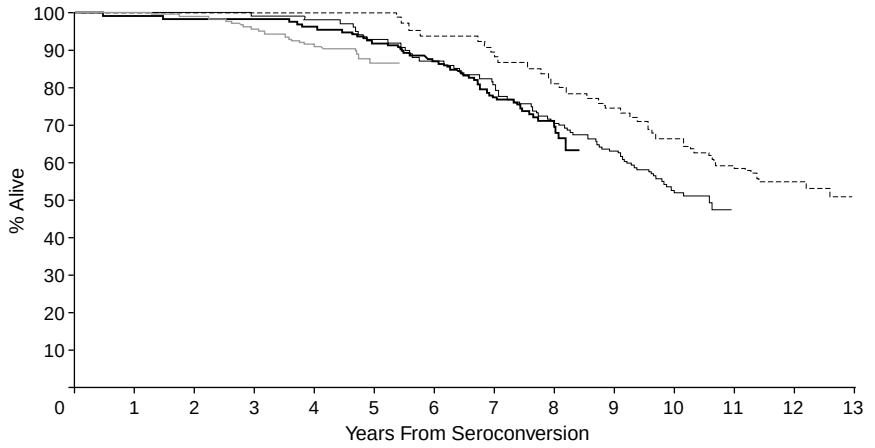

Figure 3.—Extended Kaplan-Meier curves and relative hazards for time to death from human immunodeficiency virus seroconversion in calendar periods with different antiretroviral therapy use. NA indicates not applicable because this is the reference category.

used a random-effects model[27] for cell count trajectories in those achieving similar infection durations at the beginning of each calendar period. For strata defined by infection duration at the beginning of a calendar period, we allowed intercepts and slopes to vary among individuals as a variable effect and we contrasted and tested for significance of differences between the average decline in each of the 3 calendar periods of interest. A slower CD4 cell count decline or even an increase in the latest period in those with similar infection durations would be indicative of therapy effectiveness.

RESULTS

Of the 536 HIV seroconverters in the MACS followed up to June 30, 1997, 50% seroconverted before December 1986. Median age at seroconversion was 33 years and median AIDS-free follow-up after seroconversion was 6.6 years. During the study's span of 13 years, only 67 (12.5%) were lost to follow-up while AIDS-free and 49 (9.1%) in follow-up to death. While AIDS-free, the 536 seroconverters were seen at 82.2% (5474) of possible 6-month visits. Table 1 presents descriptive statistics for AIDS-free seroconverters at each of the 4 calendar periods. The most striking difference between calendar periods was infection duration at the beginning of each period. Thus, we statistically adjusted for this difference in infection duration to compare men with similar infection duration at each calendar period. The appropriateness of such adjustment rests on the overlap between periods. Interquartile ranges of infection durations at entry were 0.3 to 0.4, 0.9 to 4.7, 2.3 to 7.1, and 3.7 to 9.2 years for the 4 calendar periods in Table 1, respectively. Thus, the last 3 periods, on which primary conclusions are based, have sufficient overlap to allow appropriate comparisons.

Table 2 shows the percentage of AIDS-free seroconverters using a given medication in the 4 calendar periods for each of the commonly prescribed medications. The table shows that the most striking change that occurred between the last 2 periods was the introduction of protease inhibitors with concomitant increases in use of lamivudine and stavudine. Marked increases were also noted in zidovudine use and *Pneumocystis carinii* pneumonia prophylaxis between the first 2 periods. There was a relatively small increase in the proportion of men with an outpatient visit in the last 3 intervals, from 87.5% in 1990 to 1993 to 96.5% in July 1995 to July 1997. Thus, most men have been under clinical care since 1990.

Figure 2 shows the Kaplan-Meier curves for AIDS-free time corresponding to estimates obtained by juxtaposing all contributions of different individuals seen in a given period since seroconversion. The percentage of those AIDS-free is highest for conditions of July 1995 to July 1997 (ie, availability of potent antiretroviral therapy), followed by those with conditions of the 2 middle periods (ie, monotherapy and combination therapy). The poorest AIDS-free survival was seen for conditions prior to 1990. With 1990 to 1993 as a reference, the RH of the period prior to 1990 was borderline significantly higher

(RH, 1.51; 95% confidence interval [CI], 0.96-2.39), the RH of 1993 to July 1995 was close to 1 (RH, 1.04, 95% CI, 0.73-1.48), and the RH of July 1995 to July 1997 was significantly lower and close to a third of the hazard in 1990 to 1993 (RH, 0.35; 95% CI, 0.20-0.61).

Figure 3 shows the corresponding analysis for survival times and the RHs of death. The inferences and directionalities were similar to those observed for AIDS occurrence, with the proviso that hazard of death during July 1995 to July 1997 relative to that for 1990 to 1993 was closer to 1 (ie, 0.62) and borderline significant (95% CI, 0.38-1.01).

To quantify relative times of different calendar periods we used log normal regression incorporating staggered entries. This parametric model provided an appropriate fit to the separate curves shown in Figures 2 and 3, and this parametric family has been shown to appropriately describe overall distribution of time to development of AIDS.[28] Since the last 3 periods have comparable ranges of follow-up and assessment of potent antiretroviral therapy effectiveness vs that of monotherapy and combination therapy is of central interest, we restricted analysis of relative times to the last 3 periods. Table 3 characterizes AIDS therapies received by the seroconverter cohort at later calendar periods. The second half of Table 3 provides estimates and 95% CIs of the relative AIDS-free times and survival times. The times for 1993 to July 1995 were similar to those for 1990 to 1993, indicating there was no major effect of combination therapy relative to monotherapy at the population level. In contrast, AIDS-free times for July 1995 to July 1997 were 63% longer than those for 1990 to 1993, and the extension of AIDS-free times was statistically significant. Similarly, survival times for July 1995 to July 1997 were significantly lengthened by 21%.

To determine the effect of potent antiretroviral therapy on rates of CD4 cell count change, we compared the mean change per year in the 3 calendar periods in men with similar HIV-infection durations at the beginning of the period. Table 4 shows the numbers of men and CD4 cell measurements, and mean CD4 cell count change per year by calendar period and infection duration. For example, there were 97 seroconverters who at the beginning of 1990 were infected for less than a year and provided, while AIDS-free, 342 CD4 cell measurements between 1990 and 1993. The mean change for those men was –81.2 cells per year. For all infection durations, the rate of change in July 1995 to July 1997 showed a CD4 cell count increase or decline of lesser magnitude than in the previous 2 periods. Except for those with infection duration between 4 and 5.5 years, rates of change in July 1995 to July 1997 were significantly ($P<.05$) different than those seen in 1993 to July 1995. Also, for those with infection duration between 1 and 3 years, rates in July 1995 to July 1997 were significantly different from those seen in 1990 to 1993. Rate of change in July 1995 to July 1997 for those with infection duration less than 1 year approached significance ($P = .09$) when compared with the corresponding rates in 1990 to 1993. Adjusted by infection duration, mean rate of CD4 cell count decline in 1990 to 1993 and 1993 to July 1995 was 80.9 and 94.2 cells faster than in July 1995 to July 1997 ($P<.05$). Consonant with inferences involving AIDS-free status and survival times, rate of CD4 cell count decline was not different when the periods of 1993 to July 1995 and 1990 to 1993 were compared.

Table 3.—Antiretroviral Therapy and Relative AIDS-Free and Survival Times by Calendar Periods*

	Calendar Period		
Variable	1990-1993	1993-July 1995	July 1995-July 1997
No. seen while AIDS-free	414	370	288
% of Patients who received†			
No therapy	50	49	27
Monotherapy only	36	25	3
Combination therapy	14	26	21
Potent antiretroviral therapy	0	0	49
Relative AIDS-free times (95% CI)‡	1	0.97 (0.86-1.09)	1.63 (1.40-1.89)
Relative survival times (95% CI)‡	1	1.01 (0.91-1.12)	1.21 (1.07-1.36)

*AIDS indicates acquired immunodeficiency syndrome; CI, confidence interval. Estimates of relative times are adjusted by infection duration and age at seroconversion and were obtained using log normal regression methods.
†Percentages of 347, 313, and 227 AIDS-free seroconverters for whom therapy could be assessed in the 3 calendar periods, respectively.
‡Relative time is the factor by which times are expanded or contracted.

COMMENT

The classic analysis involving an observational study measuring therapy efficacy is to divide groups by treatments actually taken and try to capture important confounding variables at an individual level. The major difficulty of such an approach is to ensure that there is no residual confounding. Although the approach presented herein does not determine efficacy, it does determine effectiveness at the population level by showing changes occurring in different calendar periods in persons with comparable infection duration. Also, it provides a characterization of therapies used by the cohort in these different calendar periods. Our observational study of potent an-

Table 4.—Mean CD4 Cell Count Change per Year Prior to AIDS in HIV Seroconverters by Calendar Period and Infection Duration at the Beginning of Calendar Period*

	Calendar Period								
	1990-1993			1993-July 1995			July 1995-July 1997		
No. of Years of Infection	No. of Individuals	No. of CD4 Cell Measurements	Mean Change in No. of Cells/y	No. of Individuals	No. of CD4 Cell Measurements	Mean Change in No. of Cells/y	No of Individuals	No. of CD4 Cell Measurements	Mean Change in No. of Cells/y
0.01-1.00†	97	342	−81.2	47	144	−115.1	14	40	−4.8
1.01-2.00†‡	32	151	−94.5	29	108	−79.4	15	52	49.0
2.01-3.00†‡	46	200	−42.9	25	89	−86.5	12	37	112.8
3.01-4.00†	48	208	−57.3	40	143	−77.3	27	90	−13.8
4.01-5.50	114	477	−74.0	38	140	−80.6	26	73	−28.9
5.51-7.00†	0	NA	NA	51	191	−65.3	35	114	34.1
7.01-8.50†	0	NA	NA	65	244	−62.5	27	88	12.8

*AIDS indicates acquired immunodeficiency syndrome; HIV, human immunodeficiency virus. The adjusted difference relative to July 1995 to July 1997 for 1990 to 1993 is −80.9 with a 95% confidence interval of −112 to −49; for 1993 to July 1995 it is −94.2 with a 95% confidence interval of −118 to −70.
†The calendar period of July 1995 to July 1997 in comparison with 1993 to July 1995 has a value of $P<.05$.
‡The calendar period of July 1995 to July 1997 in comparison with 1990 to 1993 has a value of $P<.05$.

tiretroviral therapy in the MACS does not provide as accurate an assessment of biologic efficacy as a clinical trial, nor can it easily take into account frequent drug regimen changes and dose variations in individual drugs, or concurrent use of other drugs. Finally, it provides only self-reported adherence information, possibly subject to bias. These misclassification problems would tend to reduce the likelihood of observing a difference in time to development of AIDS and to death attributable to potent antiretroviral therapy. Nonetheless, this study provides an assessment of potent therapy effect in a setting where rigorous monitoring of adverse effects, vigorous promotion of drug regimen adherence, and observation of the use of other drugs is not possible. A drug therapy showing efficacy in a clinical trial may have little public health impact under the less stringent conditions existing in the community. Drug effectiveness in the community, therefore, also needs to be evaluated.

Cohort studies offer not only data to characterize which therapies are received by cohort members, but also data for comparing incidences of events of interest (eg, AIDS, death) for those having the same infection duration at different calendar times. The RHs, AIDS-free times, and survival times presented herein are in men with similar infection duration who were infected at the same ages. Comparisons provided by national registries of persons with unknown infection duration[14,15,29] cannot be directly adjusted by infection duration. Arbitrary CD4 cell levels used to approximate time since infection do not adequately adjust for the effect of long-term survivors being more prevalent in later cohorts.

Direct measures of the relative time interval by which AIDS-free and survival times have been lengthened (Table 3) provide data useful in conducting cost-effectiveness analyses. Such analyses will need to include the increased expense resulting from cost of potent antiretroviral therapy, earlier therapy initiation, and prolonged survival. Hospitalization cost reductions and productive work prolongation counterbalance these expenses.

Autran et al[29] noted CD4 cell count increases with potent antiretroviral therapy in a clinical trial. Our findings show a consistent increase in CD4 cell counts in seroconverters with infection durations varying from less than 1 year to 8.5 years. This reduction in CD4 cell loss was not seen during 1990 to 1993 and 1993 to July 1995 when monotherapy and combined therapy were the dominant therapy modes. These findings further support the beneficial effect of potent therapy as used in the community, especially since the CD4 cell count increase in the study by Autran et al[29] was accompanied by an increase in memory CD4 cell counts, reduction in T-cell activation, improved CD4 cell reactivity to recall antigens, and a late rise in naive CD4 cells. Although we have not yet completed HIV RNA measurements in these men, the reported decrease in T-cell activation[29] suggests that the CD4 cell count increase seen herein is associated with concurrent HIV RNA load decrease.

Although we do not provide care for MACS subjects, we did obtain data on physician and/or health care facility visits during the last 3 periods (Table 2). We observed only a small (9%) increase in the proportion visiting a health care facility between 1990 to 1993 and July 1995 to July 1997.

The proportion taking either monotherapy or combined therapy in the first 2 periods (1990 to 1993 and 1993 to July 1995) was about the same (50% and 51%; Table 3), but fell to 24% in July 1995 to July 1997. The proportion not taking any therapy was similar in the first 2 time periods, 50% and 49%, respectively, but decreased to 27% in July 1995 to July 1997 because 49% of the men began taking potent antiretroviral therapy. Thus, increased survival to AIDS and death in July 1995 to July 1997 was probably due to some men taking potent therapy (the proportion taking it during this time rose steeply). Of the 49% reporting use of potent therapy for the entire July 1995 to July 1997 period, most reported receiving it for about one half of the period. The majority, 74 (66%) of the 112 men reporting potent therapy use in July 1995 to July 1997, reported taking no therapy (n = 41, 37%) or monotherapy (n = 33, 29%) in the previous calendar period. Only 1 (2%) of 41 men having no prior treatment developed AIDS whereas 5 (7%) of 67 men with prior monotherapy or combined therapy developed AIDS. It has been reported that potent therapy response is better in previously untreated persons,[5] so this may have contributed to its apparently high effectiveness despite only 49% of the entire cohort taking it.

The lack of difference in apparent efficacy of monotherapy vs combined therapy may reflect the fact that some men in 1990 to 1993 were already receiving combined therapy. The difference in the proportion reporting combination therapy use between this earlier period and 1993 to July 1995 was only 12% (Table 3). Similarities between the 2 periods in the early 1990s are in agreement with a recent report[30] in which the same methods were used to analyze a seroconverter cohort in Vancouver, British Columbia, where event of interest was survival time after seroconversion, but these findings did not include the calendar period when protease inhibitors were introduced.[30] Hogg et al[15] recently ascribed mortality declines in 1996 to introduction of lamivudine and stavudine, introduced concurrently with protease inhibitors, which may have been the more likely explanation for the decline. We observed a protease inhibitor use increase during the same period that lamivudine and stavudine use increased (Table 2). Our results complement those from an observational HIV outpatient study[31] in which a decrease was shown in overall mortality and incidence of *Pneumocystis carinii* pneumonia, *Mycobacterium avium* complex disease, and cytomegalovirus retinitis in those with less than 100 $CD4^+$ cells per mL with increasing use of combination antiretroviral therapy. The addition of protease inhibitors augmented therapy benefits. The study included women, people of color, and injection drug users.

An unexpected finding was that the reported increasing use of potent antiretroviral therapy appeared to have greater effect on extending time to development of AIDS than time to death. This relative difference in delaying AIDS and death is similar to that seen with zidovudine use.[32,33] It is not clear why the effect is greater for delaying AIDS onset vs death, but it may reflect lower efficacy of antiretroviral therapy given to individuals with very advanced HIV disease.

The results strongly suggest that potent antiretroviral therapy use by HIV-infected persons in the community will have a substantial beneficial effect on prolonging time to development of AIDS and time to death, and arresting CD4 cell count decline. While comparisons made here are of calendar periods and, therefore, reflect all differences from previous calendar periods, the most likely cause for improved survival was introduction and use of potent antiretroviral therapy in the last calendar period. Although the magnitude of its impact on seroconverters appears large given that only 49% were taking this therapy during the last period, it is probable that those with advanced disease were more likely to have been offered, or have chosen to take potent therapy. It is these men, and not those in earlier disease stages, who would have been most likely to develop AIDS and die in the last calendar period had they not received potent therapy. Further follow-up of this cohort and of cohorts of women, persons of color, and injection drug users,[34] as prevalence of potent antiretroviral use increases, will provide a clearer picture of its long-term effect, as well as of treat-

ment failures and less than optimal levels of adherence.

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