

ORIGINAL ARTICLE

Cardiovascular and Cerebrovascular Events in Patients Treated for Human Immunodeficiency Virus Infection

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ABSTRACT

BACKGROUND

Metabolic abnormalities associated with human immunodeficiency virus (HIV) infection, including dysglycemia and hyperlipidemia, are increasingly prevalent, and there is concern about the possibility of an association with accelerated cardiovascular and cerebrovascular disease.

METHODS

We conducted a retrospective study of the risk of cardiovascular and cerebrovascular disease among the 36,766 patients who received care for HIV infection at Veterans Affairs facilities between January 1993 and June 2001.

RESULTS

For antiretroviral therapy, 70.2 percent of the patients received nucleoside analogues, 41.6 percent received protease inhibitors, and 25.6 percent received nonnucleoside reverse-transcriptase inhibitors for a median of 17 months, 16 months, and 9 months, respectively. Approximately 1000 patients received combination therapy with a protease inhibitor for at least 48 months, and approximately 1000 patients received combination therapy with a nonnucleoside reverse-transcriptase inhibitor for at least 24 months. Between 1995 and 2001, the rate of admissions for cardiovascular or cerebrovascular disease decreased from 1.7 to 0.9 per 100 patient-years, and the rate of death from any cause decreased from 21.3 to 5.0 deaths per 100 patient-years. Patient-level regression analyses indicated that there was no relation between the use of nucleoside analogues, protease inhibitors, or nonnucleoside reverse-transcriptase inhibitors and the hazard of cardiovascular or cerebrovascular events, but the use of antiretroviral drugs was associated with a decreased hazard of death from any cause.

CONCLUSIONS

Use of newer therapies for HIV was associated with a large benefit in terms of mortality that was not diminished by any increase in the rate of cardiovascular or cerebrovascular events or related mortality. Fear of accelerated vascular disease need not compromise antiretroviral therapy over the short term. However, prolonged survival among HIV-infected patients means that longer-term observation and analysis are required.

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WIDESPREAD USE OF POTENT combination antiretroviral therapy dramatically improves survival among patients infected with the human immunodeficiency virus (HIV) but introduces questions about long-term management.^{1,2} HIV-associated abnormalities of lipid and insulin metabolism have been recognized, and there is an increasing prevalence of fat redistribution, frank diabetes, and hyperlipidemia.³⁻¹⁰ There are reports of premature cardiovascular and cerebrovascular disease and of endothelial dysfunction, possibly linked to both effects of the drugs and HIV infection itself.¹⁰⁻¹⁸ These reports have aroused concern about highly active antiretroviral therapy.

We used anonymous data bases of the Department of Veterans Affairs (VA) to construct a large, retrospective cohort of patients who received care for HIV infection or the acquired immunodeficiency syndrome (AIDS). We used data on that cohort to evaluate trends in the rates of cardiovascular and cerebrovascular disease and the relation between the risk of disease and the use of antiretroviral therapy.

METHODS

STUDY BACKGROUND

Our study was conducted under the auspices of the Oversight Committee for the Evaluation of the Metabolic Complications of Highly Active Antiretroviral Therapy, convened by the European Agency for the Evaluation of Medicinal Products, but final decisions regarding this research and report rested with the authors. The study was approved by the Committee on Human Subjects at the University of California, San Diego, and the VA San Diego Healthcare System, which did not require informed consent.

SOURCES OF DATA

Our source of data was the Quality Enhancement Database for HIV (QED-HIV), which we developed using anonymous information obtained from the Master Veteran Record National Database and VA National Patient Care (utilization) data bases, and the Immunology Case Registry of the VA AIDS Service.¹⁹ This registry is formed through the "sweeping" of data on patients with HIV from local registries at each VA facility into a central data base, which contains no patient identifiers except an encrypted number used to link and "unduplicate" data that appear in more than one local registry. Coding

schemes executed by off-site persons not affiliated with our study group were used to augment the data on vital status by the addition of information from VA death-benefit claims, Social Security records, and (through 1999) the National Death Index. We classified the cause of death by scanning the individual causes available from the National Death Index. We calculated the use of medications by estimating the number of days covered by each prescription.

Overall, we believe that the records we used describe care received by these veterans well, because the VA data systems are relatively uniform, and because services are comprehensive and usually free, including direct provision of all antiretroviral drugs approved by the Food and Drug Administration. Evidence of the completeness of the records includes the facts that primary diagnoses were available for 96 to 99 percent of admissions and that less than 5 percent of deaths were found only in non-VA sources.

OUTCOMES

We report on five outcomes: admission for cardiovascular disease, admission for cardiovascular or cerebrovascular disease, admission for or death from cardiovascular or cerebrovascular disease, death from any cause, and admission for cardiovascular or cerebrovascular disease or death from any cause. In order to convert codes from the *International Classification of Diseases, Ninth Revision (ICD-9)* or *Tenth Revision (ICD-10)*²⁰ to the dependent variables listed above, we reviewed the literature and convened a panel including senior coder-abstracters and researchers in infectious diseases, neurology, and cardiology. We included the following ICD-9 codes for cardiovascular disease when they appeared as one of the first three listed discharge diagnoses and for cerebrovascular disease when they appeared as one of the first five listed discharge diagnoses: 410, "acute myocardial infarction," except with a fifth digit of 2; 411, "other acute and subacute forms of ischemic heart disease"; 413, "angina pectoris," except 413.1; 414, "other forms of chronic ischemic heart disease," except 414.1; 36.0 (procedure code), "removal of coronary-artery obstruction and insertion of stent(s)"; 430, "subarachnoid hemorrhage"; 433, "occlusion and stenosis of precerebral arteries"; 434, "occlusion of cerebral arteries"; 436, "acute but ill-defined cerebrovascular disease"; 437.0, "cerebral atherosclerosis"; 437.1, "other generalized ischemic cerebrovas-

cular disease"; 431, "intracerebral hemorrhage"; and 435, "transient cerebral ischemia." Diagnoses of cerebrovascular disease were included only in the absence of codes for HIV-related infections or drug dependence. Measures of mortality attributable to various diseases were based on the same categories as the classification of admissions; we used conversion tables translating ICD-9 codes into ICD-10 codes for the coding of deaths in 1999.

STATISTICAL ANALYSIS

We determined the date of first receipt of care for HIV at a VA facility from the date of registration in the Immunology Case Registry or the date of the first HIV-related laboratory test or hospital admission. We used multiple imputation, as implemented in SAS Proc MI (SAS Institute), to impute the race for 7 percent of the study population, the risk factor for HIV for 13 percent, and the severity of illness or age for less than 0.5 percent. We analyzed the five resulting data sets using Proc MIANALYZE (SAS Institute), which incorporates the uncertainty caused by the imputation. We characterized the study population and all covariates in the original and imputed data sets using standard descriptive statistics and defined multiple distinct periods of receipt of VA care for each patient. We combined and selected variables to include in our models on the basis of previous knowledge and correlations among covariates. We tallied outcomes and use of medications according to year and calculated rates as events or years of drug dispensed per 100 patient-years of observation.

Before performing the modeling, we rearranged the data sets to accommodate staggered periods of receipt of care, then applied adaptations of the programs of Therneau and Grambsch²¹ and analyzed tied survival times with Efron's method.²² We generated Kaplan-Meier curves for all models. We investigated the fit of the data to the proportional-hazards assumption by evaluating the parallelism of plots of the logarithm of group-specific cumulative-hazard functions. We performed time-to-event modeling using the interval of January 1, 1993 (or the date of first VA-based care for HIV if it was later), through June 30, 2001, for all outcomes except for death attributable to cardiovascular or cerebrovascular disease, which was necessarily truncated at December 31, 1999. Data were censored at the end of the study, at the time of death, or six months after care was last received at a VA facility. We selected the six-month period because our analysis indicated

that veterans receiving care for HIV were unlikely to return to the VA for services after a gap of that length.

Regression models included a standard group of covariates that remained constant over time (year of first care for HIV at a VA facility, race or ethnic group, sex, age, risk factor for HIV, severity of illness, presence or absence of a history of AIDS-defining diagnosis, presence or absence of a diagnosis of drug abuse, and presence or absence of previous treatment for serious vascular disease, diabetes, hypertension, hyperlipidemia, or smoking), as well as covariates related to use of antiretroviral drugs that varied over time. These included variables for the cumulative months of exposure to each of the three classes of antiretroviral drugs. We also included variables equal to the squares and the cubes of these terms in order to accommodate possible changes in hazards over time. The results obtained with cubic terms added little to the analysis and were omitted. We included variables denoting any exposure to each class of drugs and set the values at 1 after the first month of treatment in order to correct partially for selection by absorbing the effects of choosing to start therapy.

To evaluate the effects of secular trends, we conducted separate stratified analyses for the periods January 1996 through December 1998 and January 1999 through June 2001. We tested for the statistical significance of changes over time by calculating z scores for the difference between the logarithms of the hazard ratios associated with exposure to therapy during the first and second periods. We report the results of modeling as estimates of the hazard ratios for 24 months of exposure as compared with 0 months of exposure, calculated by the following formula:

$$\log(\text{hazard ratio}) = (24 \times \beta_{\text{linear exposure term}}) + (576 \times \beta_{\text{quadratic exposure term}}).$$

RESULTS

STUDY POPULATION

We identified 36,766 patients who used VA services for HIV disease during the 8.5-year reference period, including 21,659 who were alive at the end of the study period. The mean duration of follow-up was 40 months, and total follow-up was 1,463,227 patient-months. As compared with typical patients with HIV in the United States, members of the cohort receiving services at VA facilities were more likely to be black (52.4 percent) and far more likely

to be men (98.1 percent) (Table 1).²³ The VA cohort was also slightly older (17.6 percent were less than 35 years old) and had less severe illness (36.7 percent were asymptomatic and had more than 500 CD4 cells per cubic millimeter at diagnosis). How-

ever, only 11.0 percent were older than 55 years of age, and 28.7 percent had an AIDS-defining illness at presentation to the VA facility. A total of 23.9 percent had been previously treated at a VA facility for diabetes, hypertension, hyperlipidemia, or smok-

Table 1. Selected Characteristics of Patients with HIV.*

Characteristic	Patients Using VA Services between January 1993 and June 2001 (N=36,766)	All Adults in the United States Receiving Care in 1996	All Men in the United States Receiving Care in 1996
	<i>percent</i>		
Sex			
Male	98.1	77.4	100
Female	1.9	22.6	0
Age at date of first care for HIV			
<35 yr	17.6	55.7	54.1
35–55 yr	71.3	42.2	43.7
>55 yr	11.0	2.1	2.2
Race or ethnic group			
White	44.2	62.7	67.7
Black	52.4	34.2	27.3
American Indian	0.3	0.8	0.8
Asian	0.3	0.9	1.0
Other	2.8	1.4	3.2
Risk factor for HIV			
Injection-drug use	30.5	24.1	23.0
Homosexual contact with men	27.0	48.6	62.5
Heterosexual contact	13.4	18.4	8.9
Other	2.4	3.3	2.4
Unknown	26.8	5.5	3.3
Severity of disease at presentation			
>500 CD4 cells/mm ³ , asymptomatic	36.7	9.5	8.1
200–500 CD4 cells/mm ³ , asymptomatic	22.5	5.6	6.0
AIDS-related complex, symptomatic	8.8	31.9	29.9
<200 CD4 cells/mm ³ , asymptomatic or symptomatic or AIDS-related opportunistic condition	32.0	53.1	56.0
Presence of AIDS-defining illness before date of first care for HIV at VA facility			
No	71.3	NA	NA
Yes	28.7	NA	NA
Treatment at VA facility for diabetes, hypertension, hyperlipidemia, or smoking before date of first care for HIV at VA facility			
No	76.1	NA	NA
Yes	23.9	NA	NA
Treatment at VA facility for any vascular disease before date of first care for HIV at VA facility			
No	93.4	NA	NA
Yes	6.6	NA	NA

* No confidence intervals are given for the percentages of the study population because percentages refer to a census rather than a sample of patients known to be treated at Department of Veterans Affairs (VA) facilities during the study period. However, if the cohort were a sample, the confidence intervals would be small. Other than data on age, the data for adults and men receiving care in the United States in 1996 are from Bozzette et al.²³; data on age are unpublished data from the same data set. NA denotes not applicable. Because of rounding, percentages may not total 100.

ing, and 6.6 percent had been treated at a VA facility for vascular disease.

ANTIRETROVIRAL-DRUG EXPOSURE

A total of 70.2 percent (25,821) of patients took antiretroviral drugs for a mean of 15 months each, for a total of 641,820 patient-months (Table 2 and Fig. 1). Essentially all these patients took a nucleoside analogue for a median of 17 months (interquartile range, 5 to 37) and a total of 609,533 patient-months. A total of 41.6 percent (15,296) of patients took protease inhibitors for a median of 16 months (interquartile range, 6 to 33) and a total of 323,489 patient-months; 25.6 percent (9420) took nonnucleoside reverse-transcriptase inhibitors for a median of 9 months (interquartile range, 4 to 17) and a total of 112,168 patient-months. In about 99 percent of cases, the latter two classes of drugs were used in combination with a nucleoside analogue; about 1000 patients received combination therapy including a protease inhibitor for at least 48 months, and about 1000 patients received combination therapy including a nonnucleoside reverse-transcriptase inhibitor for at least 24 months.

CARDIOVASCULAR AND CEREBROVASCULAR DISEASE, DEATH, AND ANTIRETROVIRAL THERAPY

Overall, there were 1207 admissions for cardiovascular disease, 1764 admissions for cardiovascular or cerebrovascular disease, and 2006 admissions for or deaths from cardiovascular or cerebrovascular disease (Table 2). The rates of these events in the study population remained constant or declined during the eight years of observation, averaging about 1, 1.5, and 2 per 100 patient-years of follow-up, respectively (Fig. 1). After the introduction of highly active antiretroviral therapy, the rate of admission for cardiovascular or cerebrovascular disease decreased from 1.7 per 100 patient-years in 1995 to 0.9 per 100 patient-years in 2001, and the overall rate of death dropped steadily, from a peak of 21.3 per 100 patient-years in 1995 to 5.0 per 100 patient-years in 2001. Rates of the combined end point of admission for cardiovascular or cerebrovascular disease or death from any cause fell in a parallel fashion. The rates of first events were necessarily lower, but the trends were similar (data not shown).

Patient-level analysis showed that the rate of admission for cardiovascular or cerebrovascular dis-

Table 2. Patients Receiving Care for HIV, Antiretroviral Therapy Used, and End Points.*

Year	No. of Patients	Antiretroviral Drugs				End Point				
		Nucleoside Analogues	Protease Inhibitors	Nonnucleoside Reverse-Transcriptase Inhibitors	Any	Admission for Any Cardiovascular Disease	Admission for Any Cardiovascular or Cerebrovascular Disease	Admission for or Death from Cardiovascular or Cerebrovascular Disease	Death from Any Cause	Admission for Any Cardiovascular or Cerebrovascular Disease or Death from Any Cause
<i>patient-mo of use</i>						<i>number of patients</i>				
1993	16,763	35,081	0	0	35,081	134	207	246	2,273	2,457
1994	18,055	32,681	4	0	32,682	137	225	389	2,860	3,071
1995	17,717	37,944	45	2	37,973	141	234	298	2,922	3,138
1996	16,976	62,206	15,575	75	64,269	150	225	283	2,221	2,432
1997	16,779	90,153	55,436	4,922	94,138	136	184	247	1,305	1,481
1998	17,357	93,665	72,720	15,321	100,691	157	212	269	1,104	1,308
1999	18,183	100,506	74,530	30,623	107,685	149	198	274	1,064	1,250
2000	18,610	101,892	69,699	38,542	109,818	150	203	NA	915	1,111
2001†	17,891	55,405	35,480	22,683	59,483	53	76	NA	410	483
All	36,766	609,533	323,489	112,168	641,820	1207	1764	2006	15,074	16,731

* NA denotes not available.

† Data are for January through June only.

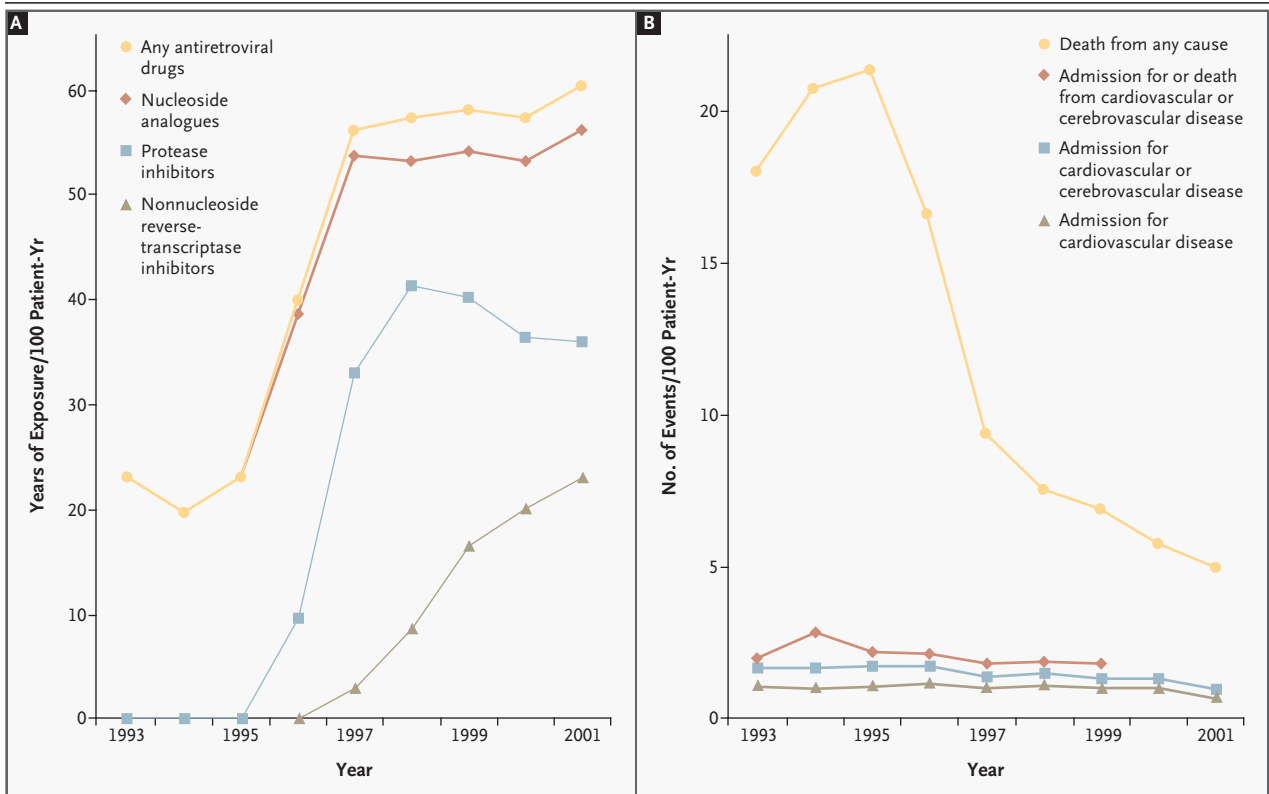


Figure 1. Changing Rates of Use of Antiretroviral Drugs (Panel A) and Vascular Events and Death (Panel B).

ease (Fig. 2) and the rate of death due to cardiovascular or cerebrovascular disease (data not shown) did not increase with increasing exposure to antiretroviral therapy. The remainder of the patient-level analyses used regression to control for the effect of secular trends and covariates. Time-to-first-event models showed that the hazard of admission for cardiovascular or cerebrovascular disease was significantly higher among older patients and those with more advanced HIV disease, an AIDS-defining illness, a history of treatment for a cardiovascular risk factor or preexisting vascular disease, and earlier date of first care for HIV at a VA facility. The relation between covariates and the hazards of other end points were similar.

Models of the effect of exposure to each of the three classes of antiretroviral drugs were estimated with control for the covariates listed above, for use of antiretroviral drugs, and partially for selection. Use of any of the three classes of antiretroviral drugs was associated with a reduced hazard of death from any cause and a reduced hazard of the composite end

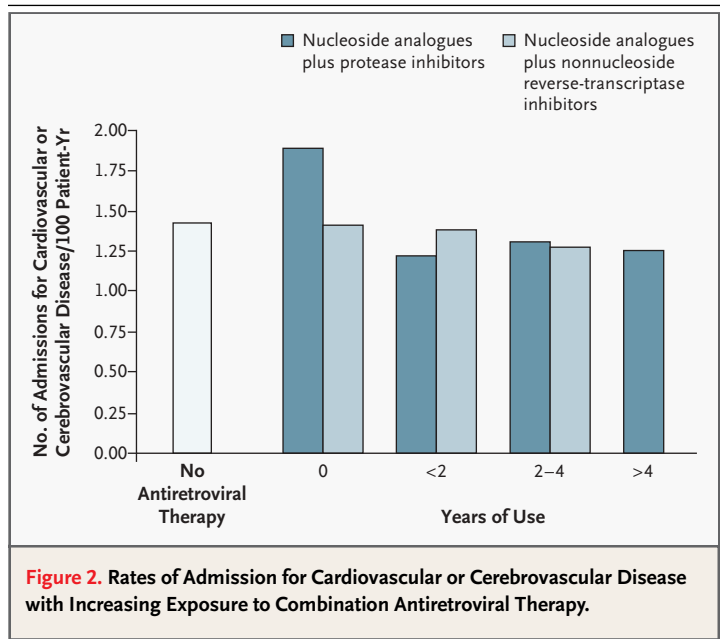


Figure 2. Rates of Admission for Cardiovascular or Cerebrovascular Disease with Increasing Exposure to Combination Antiretroviral Therapy.

Table 3. Estimated Hazard Ratios for 24 Months of Exposure to Antiretroviral Drugs as Compared with 0 Months of Exposure.*

Antiretroviral Drug or Combination	Admission for Cardiovascular Disease		Admission for Cardiovascular or Cerebrovascular Disease		Admission for or Death from Cardiovascular or Cerebrovascular Disease		Death from Any Cause		Admission for Cardiovascular or Cerebrovascular Disease or Death from Any Cause	
	HR (95% CI)	P Value	HR (95% CI)	P Value	HR (95% CI)	P Value	HR (95% CI)	P Value	HR (95% CI)	P Value
Nucleoside reverse-transcriptase inhibitors	0.88 (0.63–1.22)	0.72	0.86 (0.66–1.11)	0.49	0.88 (0.68–1.14)	0.34	0.67 (0.62–0.72)	<0.001	0.69 (0.64–0.74)	<0.001
Protease inhibitors	1.23 (0.78–1.93)	0.57	0.79 (0.54–1.14)	0.40	0.92 (0.61–1.40)	0.88	0.54 (0.47–0.61)	<0.001	0.56 (0.49–0.64)	<0.001
Nonnucleoside reverse-transcriptase inhibitors	1.09 (0.56–2.09)	0.97	0.96 (0.55–1.68)	0.85	1.10 (0.38–3.19)	0.97	0.62 (0.50–0.77)	<0.001	0.62 (0.50–0.76)	<0.001
Nucleoside analogues plus protease inhibitors	1.08 (0.69–1.67)	0.85	0.67 (0.47–0.97)	0.28	0.81 (0.54–1.23)	0.46	0.36 (0.32–0.41)	<0.001	0.38 (0.34–0.44)	<0.001
Nucleoside analogues plus nonnucleoside reverse-transcriptase inhibitors	0.95 (0.47–1.93)	0.95	0.82 (0.45–1.50)	0.79	0.96 (0.32–2.88)	0.70	0.41 (0.33–0.52)	<0.001	0.42 (0.34–0.53)	<0.001

* Exposure to other classes of drugs was controlled for; other covariates that were controlled for are listed in the Methods section. P values indicate the level of significance of the effects of exposure, as defined by a combination of the linear terms for exposure and the squared terms for exposure. The observation period was January 1993 through June 2001 for all end points except admission for or death from cardiovascular or cerebrovascular disease, for which data were not available after December 1999. HR denotes hazard ratio, and CI confidence interval.

point of admission for cerebrovascular or cardiovascular disease or death from any cause. Use was not associated with reductions in the hazards of other outcomes related to vascular disease. Table 3 shows these relations in terms of the hazard ratios for 24 months as compared with 0 months of exposure to antiretroviral drugs. This period was chosen for its clinical relevance and because patients in the sample had substantial experience with all antiretroviral drugs for at least 24 months.

To better reflect clinical practice, we estimated the relations between outcomes and therapy with the combination of a nucleoside analogue and either a protease inhibitor or a nonnucleoside reverse-transcriptase inhibitor. Results were similar to those found with monotherapy, except that reductions in the hazard of death were larger (Table 3).

Given the variability of the estimates, the effects of drugs during the period from January 1996 through December 1998 and during the period from January 1999 through June 2001 were similar. In the analyses of these subperiods, the hazard ratios for 7 of the 25 exposure–outcome pairs shown in Table 3 shifted from greater than 1.0 to less than 1.0 or from less than 1.0 to greater than 1.0, but the 95 percent confidence intervals for all these estimates included 1.0, and none of these differences were statistically significant at $P < 0.05$. There were significant differences between the two subperiods in the hazard ratio for death from any cause associated with exposure to protease inhibitors (hazard ratio, 0.61 for 1996 through 1998 and 0.79 for 1999 through June 2001), in the hazard ratio for death from any cause associated with exposure to combinations of protease inhibitors and nucleoside analogues (0.50 and 0.70, respectively), and in the hazard ratio for admission for cardiovascular or cerebrovascular disease or death from any cause (0.54 and 0.71, respectively), but these differences do not alter the clinically relevant conclusions.

For comparison, we adjusted the rates of admission for cardiovascular and cerebrovascular disease in the U.S. population to match the age and sex distribution of the study cohort. The average of the adjusted U.S. rates in 1995, 1997, and 1999 was 11.8 admissions per 1000 persons per year for cardiovascular disease and 14.1 admissions per 1000 persons per year for cardiovascular or cerebrovascular disease, as compared with 8.1 and 11.7 admissions per 1000 persons per year, respectively, in the study cohort.

DISCUSSION

Large increases in the use of antiretroviral drugs by a large population of VA patients with HIV during the second half of the 1990s were accompanied by small decreases rather than the feared increases in the rates and hazards of cardiovascular and cerebrovascular events. Moreover, the rate and hazard of the key composite outcome of a first admission for cardiovascular or cerebrovascular disease or death from any cause also decreased. This finding indicates that, even if cardiovascular and cerebrovascular complications were considered to be as bad as death, HIV-infected patients have been enormously better off since the advent of highly active antiretroviral therapy.

These results are not consistent with case series showing an excess of myocardial infarctions associated with short-term use of a particular drug or class of drugs. The reasons for these inconsistencies are not clear; potential explanations include the possibility that these case series do not correct for selection or are not robust because they include small numbers of patients. It is also possible that our results apply only to men, reflect a counterbalancing benefit of starting antiretroviral therapy on possible HIV-related vascular disease, or have greater potential for bias because of the retrospective design.²⁴

We are confident that the end-point data we used are accurate reflections of the medical and vital records, but the choice of end points was limited by the available data. We are less confident of our ability to control for risk factors. The absence of laboratory and medical records required a reliance on surrogates for staging and determination of clinical status. The analysis of trends in the overall rates of vascular events among patients receiving care for HIV from the VA is reassuring in this regard, unless changes in risk factors were offsetting an increased risk associated with exposure to antiretroviral drugs. This possibility seems unlikely, because of the timing and size of the effects that would be required. However, the use of antilipemic agents (e.g., statins, niacin, and gemfibrozil) by VA patients with HIV has increased: there were 61 users of such agents in 1990, 140 in 1995, and 2417 in 2001.

As an observational study, this work is also subject to effects of selection: certain outcomes may be associated with being the type of patient who begins, adheres to, and continues to receive treatment.

If so, both the outcome and the cumulative level of exposure are dependent in part on health-related behavior and tolerance of treatment. The resulting bias may affect the results in either direction, depending on whether outcomes are associated with a higher or lower likelihood of receipt of treatment. We do not think there is a serious risk of such bias, because we found no association between the prescription of antiretroviral drugs and the hazard of vascular disease, and we partially adjusted for the possibility of such a bias with the use of covariates. Finally, it may be that the restriction of our evaluation to classes of drugs rather than individual drugs obscured some effects.

Most of the observations in this study were made during a shorter period than is usually required for the development of serious vascular disease. For this reason, these observations do not imply that the metabolic abnormalities associated with treated HIV are of no concern. Lipodystrophy is harmful in itself because of its large effect on self-esteem and quality of life, and it is associated with hypercholesterolemia and other abnormalities.²⁵ Hyperglycemia can cause considerable short-term and long-term complications. Hyperlipidemia is a leading risk factor for atherosclerotic disease. It is reasonable to expect that metabolic abnormalities will be harmful to HIV-infected patients over the longer term. Indeed, in this study population, patients with a history of treatment for diabetes or hyperlipidemia had a much higher rate of vascular events than those without such a history (data not shown).

In conclusion, fear of accelerated vascular disease should not deter patients and providers from using the highest-quality care for HIV, as defined by the use of combination antiretroviral therapy that is compatible with current guidelines. HIV-infected patients are appropriate candidates for all usual methods of risk reduction and health maintenance.

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