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Rate of Comorbidities Not Related to HIV Infection or AIDS among HIV-Infected Patients, by CD4 Cell Count and HAART Use Status

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Abstract

The rate of comorbidities not related to human immunodeficiency virus (HIV) infection or acquired immunodeficiency syndrome (AIDS) among HIV-infected patients may be higher than expected. We assessed the incidence of comorbidities not related to HIV infection or AIDS by CD4 cell count and highly active antiretroviral therapy (HAART) use status in an HIV clinical practice. A total of 2824 patients contributed 9172 person-years of longitudinal data during the period 1997–2006. HAART receipt was associated with a significantly decreased incidence of comorbidities not related to HIV infection or AIDS among patients who required hospital admission because their CD4 cell counts were <350 cells/mm^3.

Recent research has suggested that the rate of comorbidities not related to HIV infection or AIDS among HIV-infected patients may be higher than expected. This concern was raised particularly by results from the Strategies for Management of Antiretroviral Therapy Study, a clinical trial of continuous versus interrupted combination antiretroviral therapy [1]. In addition, other researchers have suggested increased rates of hepatic, cardiovascular, metabolic and/or endocrine, renal, neurologic, and pulmonary events and non–AIDS-defining malignancy among HIV-infected patients [2–7].

If the risk of many of these comorbidities is increased because of HIV infection or advancing immunosuppression, early HAART use may prevent the occurrence of these comorbidities. This analysis assessed the incidence of comorbidities not related to HIV infection or AIDS by CD4 cell count and HAART use status in a large HIV clinical practice.

Methods

This analysis is based on data collected as part of the Johns Hopkins HIV Clinical Cohort study. This is a clinic-based observational study of a cohort of patients receiving longitudinal HIV primary care at the Johns Hopkins HIV ambulatory clinic in Baltimore, Maryland [8]. Comprehensive data collection is based on information abstracted from medical records, electronic laboratory sources, and pharmacy claims. Diagnoses are determined for all Johns Hopkins Hospital admissions and also for admissions that occur at outside hospitals with use of obtained discharge summaries. Collection of data begins at clinic enrollment and continues longitudinally for the duration of clinical care. As part of the cohort study, we track continuity of HIV care on the basis of visits to the HIV clinic during each 6-month period after clinic enrollment.

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The analysis in our study is based on data collected for patients who first presented for HIV care during the period 1997–2005. The follow-up period extended through December 2006. For each hospitalization for acute illness, the primary diagnosis and the first-listed secondary diagnosis were identified. Comorbid medical conditions were stratified on the basis of *International Classification of Diseases, Ninth Revision, Clinical Modification* codes for these diagnoses and were grouped by organ system with use of the Clinical Classifications software developed by the Agency for Healthcare Research and Quality [9]. Categories used in this analysis included cardiovascular, renal, hepatic and/or gastrointestinal, pulmonary, malignancy (non–AIDS-defining and nonskin malignancies, except melanoma), and neurologic diagnoses. Obstetric conditions, trauma, psychiatric conditions and substance abuse, infectious diseases, other medical diagnoses, and AIDS-defining illnesses were all excluded. All diagnoses were confirmed by review of medical records by trained research assistants to be the clinical diagnoses recorded by the provider of record. Only those periods during which the patient was documented to be receiving follow-up care were used.

We also determined associated CD4 cell counts and HAART use status at the time of diagnosis. HAART was defined as a protease inhibitor or nonnucleoside reverse-transcriptase inhibitor administered in combination with nucleoside reverse-transcriptase inhibitors. Other data abstracted included demographic characteristics of the patients (i.e., age, sex, self-reported race, and HIV transmission risk group) and prior HAART use status. The CD4 cell count used was the one obtained before diagnosis that was closest to the date of diagnosis—no earlier than 180 days before diagnosis and no later than 14 days before diagnosis—to minimize a transient effect on these values that may have resulted from an acute illness. The median time from measurement of a CD4 cell count to diagnosis was 58 days.

Incidence rates were computed as the number of diagnoses (numerator) divided by the person-time contributed; rates were reported as the number of diagnoses per 100 person-years. Negative binomial regression analysis (SAS Genmod; SAS) was used to compute incidence rate ratios and associated 95% CIs within each of 3 CD4 cell count strata ($\leq$200 cells/mm^3, 201–350 cells/mm^3, and >350 cells/mm^3), which were then further stratified by status of HAART receipt. General estimating equations adjustment (exchangeable correlation) for clustering of individual patients was used in the computation of the incidence rate ratio.

Results

A total of 2824 patients contributed 9172 person-years of longitudinal data through December 2006. The median age of the patients at clinic enrollment was 38 years (range, 18–81 years); 66% of the patients were male. Seventy five percent of the patients were African-American, and 23% were non-Hispanic white persons. Forty-one percent were injection drug users, 27% were men who had sex with men, and 31% were heterosexual (HIV transmission risk groups).

During longitudinal follow-up, 817 comorbid events not related to HIV infection or AIDS occurred in 679 patients. These included cardiovascular (206 events), hepatic and/or gastrointestinal (185), renal (168), non-AIDS malignancy (110), pulmonary (90), and neurologic (58) events.

The incidence rate of comorbidity diagnosis and the incidence rate ratio associated with receiving versus not receiving HAART, stratified by CD4 cell count, are shown in table 1. The incidence rate of comorbidities not related to HIV infection or AIDS decreased as the CD4 cell count increased. Of note, not receiving HAART, compared with receiving HAART, was associated with a significantly higher risk of comorbidity among patients with a CD4 cell count $\leq$350 cells/mm^3; not receiving HAART was associated with a higher risk of comorbidity among those who had a CD4 cell count >350 cells/mm^3, but the association was not statistically

significant. Other factors associated with an increased risk of comorbidities not related to HIV infection or AIDS in multivariate analysis were age >50 years, injection drug use (transmission risk group), and African-American race (P <.05 for all).

In a separate analysis (data not shown), the higher incidence rate of comorbidity diagnosis among patients not receiving HAART, compared with those receiving HAART, was found both among patients who had previously received HAART and among those who had never received HAART. The duration of previous HAART use was not associated with a high rate of comorbidity diagnosis.

Conclusions

Recent evidence from observational studies and a clinical trial suggests that rates of comorbidities not related to HIV infection or AIDS among demographically similar HIV-uninfected individuals are higher than expected [1–7]. This suggests that HAART may be effective in reducing the rate of comorbidities not related to HIV infection or AIDS in addition to reducing the rate of AIDS-defining illnesses. The Strategies for Management of Antiretroviral Therapy Study may have provided the best evidence of the efficacy of HAART in preventing non–AIDS-related comorbidities [1], although it is not known how well the results from this trial can be generalized to clinical contexts in which structured interruption of therapy does not occur. Our results demonstrate that comorbidities not related to HIV infection or AIDS that result in hospitalization are relatively common in our clinical practice. The incidence rate of these comorbidities was highest when the CD4 cell count was low, and the incidence rate ratio was significantly higher among patients not using HAART who had a CD4 cell count <350 cells/mm^3 than it was among the other patients; this indicated a protective effect associated with HAART use. The overall rate of non–AIDS-related comorbidities was lower among patients with a CD4 cell count >350 cells/mm^3 than it was among patients with a CD4 cell count ≤350 cells/mm^3. There was also a higher relative risk associated with not using HAART, compared with using HAART, but the association was not statistically significant.

Other factors associated with a high incidence of comorbidities not related to HIV infection or AIDS were injection drug use, African-American race, and older age. Other researchers have revealed that injection drug use is associated with high AIDS-defining morbidity and mortality [1], and older age is well-known to be associated with most of these non–AIDS-related comorbidities. In the United States, compared with non-Hispanic white race, African-American race has been found to be associated with a higher risk of renal, cardiovascular, pulmonary, and other disease [10,11].

Although *International Classification of Diseases, Ninth Revision, Clinical Modification* coding was used to categorize diagnoses, we did not rely on coding alone; we also required the diagnoses to be consistent with the clinical diagnoses in the medical records. However, because our data were retrospective, we were limited to relying on the diagnoses of the care providers. Therefore, there is the possibility of some degree of misclassification. Unfortunately, our sample size was not sufficient to support analyses of individual diagnostic categories (e.g., cardiovascular conditions only). Another caveat is that the use of HAART could be a surrogate for better engagement in HIV care, making hospital admission less likely. For that reason, we restricted our analysis to a longitudinal follow-up period during which the patients were documented to have received care in our HIV clinic; thus, the bias may have been mitigated.

In summary, this analysis provides evidence from clinical practice that HAART use is associated with a decreased risk of comorbidities not related to HIV infection or AIDS among patients with a CD4 cell count <350 cells/mm^3. HAART may have a protective effect on the

occurrence of comorbidities not related to HIV infection or AIDS and may reduce the risk of AIDS-defining illness.

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References

1. El-Sadr W, Neaton J. Episodic CD4-guided use of antiretroviral therapy is inferior to continuous therapy: results of the SMART study. N Engl J Med 2006;355:2283–96. [PubMed: 17135583]
2. Palella F, Baker RK, Moorman AC, et al. HIV Outpatient Study Investigators. Mortality in the highly active antiretroviral therapy era: changing causes of death and disease in the HIV outpatient study. J Acquir Immune Defic Syndr 2006;43:27–34. [PubMed: 16878047]
3. Friis-Møller N, Reiss P, Sabin CA, et al. DAD Study Group. Class of antiretroviral drugs and the risk of myocardial infarction. N Engl J Med 2007;356:1723–35. [PubMed: 17460226]
4. Gebo KA, Fleishman JA, Moore RD. Hospitalizations for metabolic conditions, opportunistic infections, and injection drug use among HIV patients: trends between 1996 and 2000 in 12 states. J Acquir Immune Defic Syndr 2005;40:609–16. [PubMed: 16284539]
5. Braithwaite RS, Justice AC, Chang CC, et al. Estimating the proportion of patients infected with HIV who will die of comorbid diseases. Am J Med 2005;118:890–8. [PubMed: 16084183]
6. Salmon-Ceron D, Lewden C, Morlat P, et al. Liver disease as a major cause of death among HIV infected patients: role of hepatitis C and B viruses and alcohol. J Hepatol 2005;42:799–805. [PubMed: 15973779]
7. Bonnet F, Lewden C, May T, et al. Malignancy-related causes of death in human immunodeficiency virus–infected patients in the era of highly active antiretroviral therapy. Cancer 2004;101:317–24. [PubMed: 15241829]
8. Moore RD. Understanding the clinical and economic outcomes of HIV therapy: the Johns Hopkins HIV Clinical Practice Cohort. J Acquir Immune Defic Syndr Hum Retrovirol 1998;17(Suppl 1):S38–41. [PubMed: 9586651]
9. Healthcare Cost and Utilization Project. Clinical Classifications Software (CCS) for ICD-9-CM. 2008. Available at: http://www.hcup-us.ahrq.gov/toolssoftware/ccs/ccs.jsp
10. Adler NE, Rehkopf DH. U.S. disparities in health: description, cause, and mechanisms. Annu Rev Public Health 2008;29:235–52. [PubMed: 18031225]
11. Saha S, Freeman M, Toure J, Tippens KM, Weeks C, Ibrahim S. Racial and ethnic disparities in the VA health care system: a systematic review. J Gen Intern Med 2008;23:685–91. [PubMed: 18196352]

Table 1

Incidence rate and incidence rate ratio of noninfectious comorbidity, stratified by CD4 cell count and HAART use

CD4 cell count, HAART use	No. of events/no of person-years	Incidence rate if noninfectious comorbidity, no. of events per 100 person-years	Incidence rate ratio (95% CI)[a]	*P*
≤200 cells/mm^3			0.53 (0.42–0.67)	.001
Yes	125/1029	1.2		
No	400/1495	2.7		
201–350 cells/mm^3			0.58 (0.41–0.81)	.002
Yes	64/1022	0.6		
No	151/1172	1.3		
>350 cells/mm^3			0.78 (0.52–1.15)	.16
Yes	103/2023	0.5		
No	185/2386	0.8		
All			0.63 (0.53–0.75)[b]	.001
Yes	292/4074	0.7		
No	736/5053	1.5		

[a] Adjusted for age, sex, race, and HIV transmission risk group (injection drug user vs. non–injection drug user).

[b] Also adjusted for CD4 cell count.