Hepatitis C and Progression of HIV Disease

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Due to shared routes of transmission, an estimated 15% to 30% of human immunodeficiency virus (HIV)-infected persons are coinfected with hepatitis C virus (HCV) in the United States and Europe.1,2 Human immunodeficiency virus infection appears to increase the persistence of the hepatitis C virus, the level of HCV RNA, and, in most studies, progression of HCV-related liver disease.3-9 However, there are conflicting reports regarding the effect of HCV on the natural history of HIV disease. Prior to the availability of highly active antiretroviral therapy (HAART), increased rates of progression of HIV disease were detected in some studies5,10,11 but not others.12-17 Recently, Greub et al18 reported that, in a study involving HIV-infected patients in Switzerland, among patients receiving HAART, HCV-coinfected patients had decreased survival rates, increased risk of progression to acquired immunodeficiency syndrome (AIDS), and impaired CD4 cell recovery.

The objective of this study was to assess the effect of HCV coinfection on clinical and immunologic progression of HIV-1 disease and immunologic response to HAART in a large, urban US patient cohort observed before and during the advent of HAART.

METHODS

Subjects

The outcomes of HIV disease progression, survival, and CD4 cell recovery are presented in this article. For editorial comment see p 241.

Context

Conflicting reports exist regarding the effect of hepatitis C virus (HCV) on the progression of human immunodeficiency virus (HIV) disease.

Objective

To assess the effect of HCV infection on clinical and immunologic progression of HIV disease and immunologic response to highly active antiretroviral therapy (HAART).

Design

Prospective cohort study.

Setting

University-based, urban HIV clinic in the United States.

Patients

There were 1955 patients enrolled between January 1995 and January 2001 who were eligible for analysis because of having at least 1 visit return to the clinic and being free of acquired immunodeficiency syndrome (AIDS) at enrollment. Median (interquartile range) length of follow-up was 2.19 (1.00-3.50) years for HCV-infected and 2.00 (1.00-3.00) years for HCV-uninfected patients.

Main Outcome Measures

Progression to an AIDS-defining illness, survival, and progression to a CD4 cell count below 200/µL; CD4 cell count change following initiation of effective HAART (resulting in a viral load of <400 copies/mL recorded at ≥75% of measurements).

Results

No difference was detected in the risk of acquiring an AIDS-defining illness (HCV-infected patients, 231 events [26.4%] and HCV-uninfected patients, 264 events [24.4%]; relative hazard [RH], 1.03; 95% confidence interval [CI], 0.86-1.23) or in the risk of death (HCV-infected patients, 153 deaths [17.5%] and HCV-uninfected patients, 168 deaths [15.5%]; RH, 1.05; 95% CI, 0.85-1.30). Although an increased risk of death was detected in the subgroup of 429 HCV-infected patients with a baseline CD4 cell count of 50/µL through 200/µL (RH, 1.51; 95% CI, 1.01-2.27), after adjustment for exposure to HAART and its effectiveness in a multivariate Cox regression analysis, death was not independently associated with HCV infection in this subgroup (RH, 1.01; 95% CI, 0.65-1.56). Similarly, in those receiving effective HAART (n=208), there was no difference in the increase in CD4 cell count or CD4 percentage during HAART in HCV-infected compared with HCV-uninfected patients.

Conclusions

Among patients in this urban US cohort, we did not detect evidence that HCV infection substantially alters the risk of dying, developing AIDS, or responding immunologically to HAART, especially after accounting for differences in its administration and effectiveness.
were analyzed in a cohort of patients receiving medical care from January 1995 to January 2001 in the Johns Hopkins Hospital HIV Clinic. In this urban, university-based setting, all patients undergo a comprehensive evaluation as previously described. The Johns Hopkins HIV observational cohort study was approved by the Johns Hopkins University Joint Committee on Clinical Investigation in 1990 with waiver of written informed consent. Since 1993, written informed consent has been obtained from all cohort participants, including those represented in the analyses herein using consent forms approved by the committee. The participation rate of patients in the Johns Hopkins HIV cohort exceeded 99%. The use of the Johns Hopkins HIV Clinical Database in an identity-unlinked manner for this analysis had been approved by the committee.

Data regarding patient demographics, social practices such as sexual risk behavior and injection drug use, clinical variables, and laboratory testing were abstracted from the patient charts (data on demographic and social practices had been obtained via written or computerized questionnaires) and the Johns Hopkins Hospital laboratory database at enrollment and every 6 months by trained personnel using standard data collection forms. Abstracted data included information regarding clinical outcomes, such as new illnesses, hospitalization, and records of prescribed medications. The AIDS-defining illnesses were recorded according to the US Centers for Disease Control and Prevention 1993 revised classification system. Information on death is obtained from clinic and hospital records as well as the Maryland Bureau of Vital Records and the national Social Security Death Index; deaths due to any cause were recorded.

Recorded medication prescription information included drug name, dose, and number dispensed in the patient chart. This is updated at each clinical encounter and includes information on telephoned and mailed prescriptions. Validity checks are done cumulatively on a 5% sample of abstracted variable fields, including medication prescription and clinical outcome fields, and data captured via direct computer interface (eg, laboratory data); to date, errors have been found in 0.2% of variable fields. Patients were classified as receiving HAART if a protease inhibitor or a nonnucleoside reverse transcriptase inhibitor was prescribed.

Patients had clinic visits and laboratory evaluations performed at regular intervals according to written practice guidelines. The clinical clinic visit schedule for patients prescribed antiretroviral therapy was 4 weeks after initiation of therapy and subsequently every 12 weeks. At each visit, standard laboratory assessments, performed by licensed clinical laboratories, included a complete blood cell count; serum chemistry panels; alanine aminotransferase, aspartate aminotransferase, and total bilirubin levels; CD4 cell count; and plasma HIV RNA level (reverse transcriptase-polymerase chain reaction used for viral load determination). According to the practice guidelines of the clinic and the United States Public Health Service (http://www.hivatis.org/trtgldns.html), HCV testing is routinely performed on all cohort participants by a licensed clinical laboratory using a second- or third-generation enzyme immunoassay (EIA) (EIA 2.0, Abbott Laboratories, Abbott Park, Ill; EIA 3.0, Ortho Diagnostics, Raritan, NJ). Persons who had a repeatedly reactive HCV antibody EIA were considered to have HCV infection. In the absence of definitive guidelines for the standard of care in the management of HIV infection in HIV-infected patients, coinfected patients in this cohort were infrequently treated (<2%) for HCV infection. Treatment consisted of interferon alfa (standard or pegylated) with or without ribavirin. Because HCV treatment was infrequent and ineffective among patients in this cohort, the analysis was not adjusted for treatment of HCV infection.

Statistical Methods
Baseline characteristics were compared according to HCV serostatus using the χ² test for categorical variables and the Mann-Whitney test for continuous variables. Time-to-event analysis was performed using Kaplan-Meier survival curves, the log-rank test (another method used to compare survival curves [P values obtained using the log-rank test were similar to those derived from the univariate Cox model; thus, only those from the Cox analysis are reported herein), and Cox proportional hazards regression. Assumptions of the Cox proportional hazard analysis were tested and met. Three sets of outcomes were analyzed: the development of an AIDS-defining illness, death from any cause, and CD4 cell count below 200/µL. Individuals were censored at their last follow-up visit. Variables considered in all Cox multivariate analyses included HCV serostatus, age, sex, race, baseline CD4 cell count, and baseline HIV viral load. The CD4 cell count and viral load were also analyzed as time-dependent covariates for which the change from baseline at the time of each event was incorporated into the model.

In order to account for the use of antiretroviral therapy, measures of the total exposure time to HAART and of the effectiveness of HAART were included. Total exposure time was calculated as the maximum number of years receiving either a protease inhibitor or a nonnucleoside reverse transcriptase inhibitor. Assessment of HAART effectiveness was based on the percentage of total visits in which HIV RNA was detectable. Well-controlled HIV replication was defined as a viral load below 400 HIV RNA copies/mL recorded at 75% or more of measurements. The subset of patients with well-controlled HIV infection represents the most appropriate group to assess the effect of HCV infection on the progression of HIV disease, since these individuals are more homogeneous with respect to the administration of and adherence to HAART, allowing focus on the variable of interest, HCV infection. Patients without well-controlled HIV infection represent a more heterogeneous group regarding antiretroviral administration and adherence, which
Hepatitis C and Progression of HIV Disease

may confound the relationship of HCV infection and HIV progression.

We also examined the effect of HCV infection on CD4 cell response to HAART among persons who received effective HAART. For this analysis, effective HAART was defined as a viral load below 400 HIV RNA copies/mL recorded at 75% or more of measurements for patients receiving HAART for at least 90 days (n = 1042) and having at least 2 HIV RNA determinations (n = 872). Using the Mann-Whitney test, we compared the median change in CD4 cell count at 1 year, 2 years, and 3 years in subjects who had at least 1 year of follow-up derived from the subset of 208 HAART recipients with well-controlled HIV replication following the initiation of HAART. Stepwise multivariate logistic regression was used to analyze factors associated with well-controlled HIV replication (the event [HIV suppression] was considered a dichotomous non–time-dependent event for this analysis). Because the outcome of interest was common (>10%), we used the method of Zhang and Yu24 to assess whether correction of calculated adjusted odds ratios (ORs) was necessary to avoid the overestimation or underestimation of the risk ratio (RR) in this cohort study. For each variable, we found that the calculated adjusted ORs closely approximated the corrected RR (M.S.S., unpublished data, April 2002). It should be noted that ORs should not be interpreted as RRs in the setting of common outcomes.24 Statistical analyses were performed using STATA v6.0 (Stata Corp, College Station, Tex) and SAS v6.12 (SAS Institute Inc, Cary, NC).

RESULTS

Of 2237 cohort participants enrolled between January 1995 and January 2001, 1955 patients who had at least 1 return visit to the clinic and who had not developed an AIDS-defining illness prior to enrollment were eligible for analysis. The clinical and demographic characteristics at cohort entry (baseline) are shown in Table 1. A total of 873 (44.6%) patients were HCV-infected, and compared with those without HCV infection, were older and more likely to be African American, and to use or have used injection drugs. No significant differences were detected between groups with respect to sex, hepatitis B surface antigen reactivity, and HIV RNA level. The HCV-infected patients had a lower absolute CD4 cell count but a higher CD4 cell percentage at entry compared with HCV-uninfected persons. While the majority of both HCV-infected and HCV-uninfected individuals were not receiving antiretroviral drug therapy at study entry, HCV-infected persons were less likely to have been prescribed antiretroviral drugs than those not infected with HCV (24% and 28%, respectively; P < 0.001). In multivariate logistic regression analysis of baseline variables asso-

### Table 1. Patient Clinical and Demographic Characteristics at Enrollment in the Johns Hopkins HIV Clinical Cohort

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>HCV-Uninfected (n = 1082)</th>
<th>HCV-Infected (n = 873)</th>
<th>P Value†</th>
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</thead>
<tbody>
<tr>
<td>Age, median (IQR), y</td>
<td>36 (31-42)</td>
<td>39 (35-43)</td>
<td>.001</td>
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<tr>
<td>By category, No. (%), y</td>
<td></td>
<td></td>
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<tr>
<td>&lt;30</td>
<td>227 (21)</td>
<td>66 (8)</td>
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<tr>
<td>30-39</td>
<td>499 (46)</td>
<td>396 (45)</td>
<td>.001</td>
</tr>
<tr>
<td>40-49</td>
<td>249 (23)</td>
<td>342 (39)</td>
<td></td>
</tr>
<tr>
<td>≥50</td>
<td>107 (10)</td>
<td>69 (8)</td>
<td></td>
</tr>
<tr>
<td>Sex, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>316 (29)</td>
<td>274 (32)</td>
<td>.30</td>
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<tr>
<td>Men</td>
<td>766 (71)</td>
<td>599 (69)</td>
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<tr>
<td>Race, No. (%)</td>
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<tr>
<td>White</td>
<td>330 (31)</td>
<td>112 (13)</td>
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<tr>
<td>African American</td>
<td>738 (68)</td>
<td>752 (86)</td>
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<td>Other</td>
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<td>9 (1)</td>
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<td>HIV risk factor, No. (%):†</td>
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<tr>
<td>Homosexual/ bisexual</td>
<td>460 (43)</td>
<td>100 (11)</td>
<td>.001</td>
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<td>Heterosexual contact with an infected partner</td>
<td>252 (23)</td>
<td>187 (21)</td>
<td>.33</td>
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<td>Heterosexual contact with a high-risk partner</td>
<td>287 (27)</td>
<td>302 (35)</td>
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<td>Intravenous drug use</td>
<td>141 (13)</td>
<td>742 (85)</td>
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<td>Chronic hepatitis B virus infection§</td>
<td>66 (6)</td>
<td>47 (5)</td>
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<td>CD4 cell count at baseline, median (IQR), cells/µL</td>
<td>266 (99-468)</td>
<td>237 (58-437)</td>
<td>.02</td>
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<td>By category, No. (%), cells/µL</td>
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<td>&lt;50</td>
<td>237 (23)</td>
<td>157 (18)</td>
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<td>50-200</td>
<td>234 (22)</td>
<td>196 (23)</td>
<td>.06</td>
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<td>&gt;200</td>
<td>571 (55)</td>
<td>501 (59)</td>
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<td>CD4 cell percentage at baseline, median (IQR)</td>
<td>16 (7-26)</td>
<td>19 (9-28)</td>
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<td>HIV RNA at baseline, median (IQR), copies/mL</td>
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<tr>
<td>&lt;400</td>
<td>135 (14)</td>
<td>93 (11)</td>
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<td>400-10,000</td>
<td>240 (24)</td>
<td>185 (23)</td>
<td>.25</td>
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<tr>
<td>&gt;10,000</td>
<td>625 (63)</td>
<td>538 (66)</td>
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<td>Antiretroviral therapy</td>
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<tr>
<td>at baseline, No. (%)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>No therapy</td>
<td>776 (72)</td>
<td>664 (76)</td>
<td></td>
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<tr>
<td>NRTIs</td>
<td>132 (12)</td>
<td>132 (15)</td>
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<tr>
<td>NRTIs + PIs or NNRTIs</td>
<td>174 (16)</td>
<td>77 (9)</td>
<td>.001</td>
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HEPATITIS C AND PROGRESSION OF HIV DISEASE

associated with HCV exposure at entry into the cohort, age 30 years (OR, 2.05; 95% confidence interval [CI], 1.42-2.95), African American race (OR, 1.93; 95% CI, 1.39-2.67), and a history of injection drug use (OR, 3.36; 95% CI, 2.53-4.37) were independently associated with HCV status. The median (interquartile range) length of follow-up was 2.19 (1.00-3.50) years for HCV-infected and 2.00 (1.00-3.00) years for HCV-uninfected patients. We did not exclude patients based on a minimum duration of follow-up. Of 1955 patients included in the analysis, 29 (1.5%) had fewer than 90 days of follow-up, of whom 12 (41%) and 17 (59%) were HCV-infected and HCV-uninfected, respectively. When these 29 individuals were removed from analyses of progression to AIDS, death, or CD4 cell count below 200/µL, in the 1926 patients with more than 90 days of follow-up we found no significant changes from the reported findings (M.S.S, unpublished data, January 2002).

Progression to AIDS-Defining Illness

No difference was detected in the risk of acquiring an AIDS-defining illness among HCV-infected patients (231 events [26.4%]) and HCV-uninfected patients (264 events [26.4%]) (relative hazard [RH] by Cox proportional hazards regression, 1.03; 95% CI, 0.86-1.23). Figure 1 shows the Kaplan-Meier curves for probability of developing an AIDS-defining illness (conditional probability based on number of events per number of patients surviving to a given time point, giving cumulative incidence). Similarly, no difference was detected in the risk of progression to an AIDS-defining illness among HCV-infected patients compared with HCV-uninfected patients in the subgroup of 1199 patients who ultimately received HAART (RH, 1.09; 95% CI, 0.88-1.34) and in the subgroup of 230 patients with well-controlled HIV replication (RH, 0.57; 95% CI, 0.29-1.13). After stratification by baseline CD4 cell count category, no significant difference was detected in the risk of acquiring an AIDS-defining illness among HCV-infected and HCV-uninfected patients with CD4 cell counts below 50/µL (RH, 0.95; 95% CI, 0.73-1.24), from 50/µL through 200/µL (RH, 1.35; 95% CI, 0.93-1.88), or above 200/µL (RH, 1.25; 95% CI, 0.87-1.79).

Survival

No difference was detected in the risk of death among HCV-infected (153 deaths [17.5%]) compared with HCV-uninfected (168 deaths [15.5%]) patients (RH, 1.05; 95% CI, 0.85-1.30) (Figure 2A). Similarly, no difference was detected in the risk of death among HCV-infected compared with HCV-uninfected patients in the subgroup of 1199 patients who ultimately received HAART (RH, 1.22; 95% CI, 0.22-1.61) and in the subgroup of 250 patients with well-controlled HIV replication (RH, 1.49; 95% CI, 0.33-6.68). After stratification by baseline CD4 cell count category, no significant difference was detected in the risk of death among HCV-infected and HCV-uninfected patients with CD4 cell counts below 50/µL (RH, 1.13; 95% CI, 0.82-1.56) or above 200/µL (RH, 0.89; 95% CI, 0.56-1.42).

Among the 429 patients with baseline CD4 cell counts from 50/µL through 200/µL, the risk of death was higher among HCV-infected patients compared with HCV-uninfected patients (RH, 1.51; 95% CI, 1.01-2.27) (Figure 2B) and among the subset in this CD4 strata who received HAART (RH, 1.85; 95% CI, 1.11-3.07). However, among

FIGURE 1. Probability of Developing an AIDS-Defining Illness in HIV-Infected Patients, by HCV Antibody Status

![Figure 1](image1.png)

Curves represent Kaplan-Meier time-to-event analyses. AIDS indicates acquired immunodeficiency syndrome; HIV, human immunodeficiency virus; HCV, hepatitis C virus. There was no difference detected in the risk of progression to an AIDS-defining illness among HCV-infected and HCV-uninfected patients (relative hazard, 1.03; 95% confidence interval, 0.86-1.23).

FIGURE 2. Probability of Death in HIV-Infected Patients, by HCV Antibody Status

![Figure 2](image2.png)

Curves represent Kaplan-Meier time-to-event analyses. HIV indicates human immunodeficiency virus; HCV, hepatitis C virus. A, Survival of all 1955 patients. There was no difference detected in the risk of death in HCV-infected and HCV-uninfected patients (relative hazard [RH], 1.05; 95% confidence interval [CI], 0.85-1.30). B, Survival of the subset of 429 patients with baseline CD4 cell count from 50/µL through 200/µL at entry. In this subset, HCV-infected patients had an increased risk of death compared with HCV-uninfected patients (RH, 1.51; 95% CI, 1.01-2.27). However, the significant difference in survival detected among those with baseline CD4 cell count of 50/µL through 200/µL (panel B) was not sustained in a multivariate model adjusted for the use of highly active antiretroviral therapy and for HIV suppression (adjusted RH, 1.01; 95% CI, 0.65-1.56).
this group of patients with baseline CD4 cell counts from 50/µL through 200/µL, multivariate Cox regression analysis revealed that death was independently associated with total exposure time (years) to HAART (RH, 0.47; 95% CI, 0.36-0.63), percentage of clinic visits with detectable HIV RNA level (RH, 7.96; 95% CI, 2.00-31.66), older age (RH, 1.05; 95% CI, 1.03-1.08), and baseline CD4 cell count (RH, 0.71 per 50 cells/µL; 95% CI, 0.56-0.91), but not HCV infection (RH, 1.01; 95% CI, 0.65-1.56).

**Progression to CD4 Cell Count Below 200/µL**

Among all persons with a baseline CD4 cell count above 200/µL (n = 1073), HCV-infected patients had a greater but statistically nonsignificant probability of progression to CD4 cell count below 200/µL (RH, 1.28; 95% CI, 0.98-1.68) (Figure 3). However, in multivariate Cox regression analysis, progression to CD4 cell count below 200/µL was independently associated with percentage of clinic visits with detectable HIV RNA level (RH, 2.80; 95% CI, 1.67-4.70), baseline CD4 cell count (RH, 0.74 per 50 cells/µL; 95% CI, 0.70-0.79), and log baseline HIV RNA level (RH, 1.09; 95% CI, 1.03-1.16), but not HCV infection (RH, 1.13; 95% CI, 0.83-1.50). The median (interquartile range) CD4 cell count at time of HAART initiation for those with a baseline CD4 cell count above 200/µL was 336 (243-476) cells/µL and 373 (272-489) cells/µL for HCV-infected and HCV-uninfected patients, respectively (P = .09, Mann-Whitney test).

**Effect of Antiretroviral Therapy by HCV Antibody Status**

During the follow-up period, 1199 patients were prescribed HAART, including 54% of HCV-infected patients and 67% of HCV-uninfected patients (P < .001). The duration of exposure to HAART was significantly shorter for HCV-infected patients compared with HCV-uninfected patients except among the subgroup of patients with baseline CD4 cell count below 50/µL (Table 2).

In univariate analysis, no difference was detected in the percentage of HCV-infected patients who had well-controlled HIV replication during HAART compared with HCV-uninfected patients receiving HAART in the entire cohort (29% for both groups; P = .89, χ² test) or among the subsets of patients with different baseline CD4 cell counts (above 200/µL: 38.4% for HCV-infected and 37.2% for HCV-uninfected patients, P = .37; 50/µL through 200/µL: 23.3% for HCV-infected and 25.6% for HCV-uninfected patients, P = .66; below 50/µL: 21.3% for HCV-infected and 16.9% for HCV-uninfected patients, P = .80). In a multivariate logistic regression model, well-controlled HIV replication was independently associated with older age (OR, 1.03 per year; 95% CI, 1.01-1.05), white race (OR, 1.57; 95% CI, 1.14-2.17), and baseline CD4 cell count (OR for 50-200 cells/µL, 0.22; 95% CI, 0.14-0.35; OR for >10000 copies/mL, 0.14; 95% CI, 0.09-0.21), but not HCV infection (OR, 1.17; 95% CI, 0.86-1.60).

Among 208 subjects receiving effective HAART, defined as undetectable HIV RNA level at 75% or more of visits, no difference was detected between HCV-infected and HCV-uninfected patients in the increase in absolute CD4 cell count and CD4 cell percentage at 1, 2, and 3 years following the start of HAART (Table 3). In addition, at 1, 2, and 3 years after the start of HAART, no difference was detected in the probability of experiencing a CD4 cell count increase of at least 50/µL or 100/µL among HCV-infected and HCV-uninfected patients receiving effective HAART (Table 4).

**COMMENT**

In this large, urban US HIV cohort, relatively high incidence of AIDS and death was observed, principally in persons not receiving HAART. However, when HCV-infected patients were compared with those without HCV infection, no differences were observed in the incidence of AIDS-defining illness, death, CD4 cell count decline to below 200/µL, or CD4 cell count increase following effective HAART, especially after accounting for differences in the use of HAART by multivariate adjustment and by subgroup analysis of those with well-controlled HIV replication.

In our cohort, HCV-coinfected patients differed from patients without HCV infection in many respects, including...
ing the administration of HAART. The reasons for the disparity in the administration of HAART are incompletely understood. The HCV-infected patients may be more likely to develop antiretroviral-associated hepatotoxicity, which may influence medical decisions regarding the use of HAART. In addition, HCV-infected patients who are actively using injection drugs may be less likely to be prescribed HAART than are HCV-uninfected patients, who are substantially less likely to use or have used injection drugs. Nonetheless, among patients prescribed HAART, we found no evidence that HCV infection substantially alters the virologic or immunologic response to potent antiretroviral therapy. These findings underscore the importance of the consideration of effective antiretroviral therapy for HIV-infected persons at immediate risk of developing AIDS, including those infected with HCV.

These findings are similar to the results of prior studies that found no evidence that HCV coinfection altered HIV disease progression. Our data contribute substantially to this literature because we prospectively evaluated a large number of patients, included more than 4300 person-years of follow-up after the advent of HAART, and considered a spectrum of HIV-related outcomes among antiretroviral-treated and untreated patients.

Our findings differ from the results of the Swiss HIV Cohort investigation which found, among 3111 patients receiving HAART, a greater risk of progression to AIDS or death among persons coinfected with HCV (adjusted hazard ratio for combined end point of AIDS or death, 1.70; 95% CI, 1.26-2.30) and, among those who suppressed their HIV virus load, smaller increases in CD4 cell counts. We observed 187 deaths in 1199 patients (15.6%) receiving HAART in our cohort but only 6 deaths in 208 patients (2.9%) with well-controlled HIV replication. Our mortality rate was higher than that of the Swiss HIV Cohort study in which there were 181 deaths in 3111 patients (5.8%) receiving HAART and 20 deaths in 1596 patients (1.3%) having undetectable HIV RNA levels during the follow-up period. However, our mortality rate was similar to that of other North American studies. In the Multicenter AIDS Cohort Study, there were 41 deaths in 2888 men (14.2%) between July 1995 and July 1997, a time in which HAART was available to participants. In British Columbia, Hogg et al reported 23 deaths in 227 patients (10.1%) followed up in the HAART era. Finally, in participants in the HIV Outpatient Study, there was a death rate of 7.8% to 14.4% in yearly quartiles following HAART availability. While interesting, direct comparisons of these findings are limited by differences in patient populations and duration of follow-up among these patient cohorts. Furthermore, the ability to directly compare our findings with those of Greub and coworkers may be somewhat limited by differences in the clinical and sociodemographic characteristics of the respective cohort participants. For example, in our cohort, compared with HCV-uninfected patients, HCV-infected patients were older and more likely to be African American, whereas in the Swiss HIV Cohort, compared with HCV-uninfected patients, HCV-infected patients were younger, more likely to be female, and were principally white. In addition, Greub and coworkers analyzed only the cohort members who were receiving HAART, while in the investigation herein, all cohort members were considered (and HCV-infected patients were less likely to receive HAART).
HEPATITIS C AND PROGRESSION OF HIV DISEASE

Nonetheless, our study included data on 1199 patients who were receiving HAART, of whom 208 patients had durable suppression of HIV replication, comprising a subgroup of patients similar to those studied in the Swiss HIV Cohort. Among this subgroup of 1199 HAART recipients, we did not find evidence that HCV infection substantially alters the risk of progression to AIDS (RH, 1.09; 95% CI, 0.88-1.34) or death (RH, 1.22; 95% CI, 0.22-1.61) or the combined end point of AIDS or death (RH, 1.11; 95% CI, 0.92-1.34). Similarly, among those with effective HIV suppression, we did not find evidence that HCV infection substantially diminishes CD4 cell recovery during HAART. In addition, we considered the change in CD4 cell percentage following effective HAART, which may be less subject to within-subject variability over time compared with measurements of the absolute CD4 cell count, and thus may provide a more reliable assessment of the effect of HCV coinfection on immune recovery.36 Interestingly, since the CD4 cell count increase following HAART has been associated with significant reductions in AIDS-related illnesses, the lack of an independent association between HCV infection and HIV disease progression in our cohort may be explained by our finding that, in contrast to the findings of the Swiss HIV Cohort study, HCV infection did not alter CD4 cell recovery.18 Further research is needed to better understand the complex interaction between HCV and HIV infections and the immune system.

The results of this study could be affected by several potential limitations. First, since we did not differentiate between the causes of death, we were unable to evaluate the effect of HCV infection on the risk of death due to AIDS or liver disease. We do not provide data on cause of death because its ascertainability is not reliable and uniform. Smith et al.17 compared clinical and autopsy-based cause-of-death data for 494 autopsies performed at Johns Hopkins Hospital and found that only 59% of certificates were properly completed and, of those, there was substantial disagreement between the clinical and autopsy-derived cause-of-death determinations in 49%. We reviewed records for the 321 observed deaths in this study and identified cause of death in only 60% of patients; we found that the role of contributory factors such as concurrent liver disease were not consistently reported, which could lead to inaccurate estimates of the burden of advanced liver disease in this population (M.S.S., unpublished data, January 2002). However, since deaths due to non-AIDS causes, such as opiate overdose, violence, and liver disease, occur more frequently among HCV-infected persons compared with HCV-uninfected persons, this approach should exaggerate rather than obscure an effect of HCV coinfection on mortality.8,38,39 Since we did not find an increased risk of death among HCV-infected patients after adjusting for HAART and its effectiveness, the absence of cause-of-death information should not affect our findings. In addition, we found no difference in HIV progression between HCV-infected and HCV-uninfected patients, measured by time to first opportunistic infection and to CD4 cell decline to below 200/µL.

Second, since some persons with HCV antibodies have cleared their infection, the effect of HCV infection could have been underestimated by classifying all HCV antibody–positive patients as infected.40 However, we have previously found that more than 90% of HCV-infected persons with a reactive HCV antibody test have detectable plasma HCV RNA, suggesting that our case definition is reasonable.8 Third, since some HIV-infected patients may have HCV infection in the absence of a reactive antibody test, some patients could have been misclassified as HCV-uninfected. However, in a similar Baltimore cohort of 559 HIV-infected subjects, the sensitivity and specificity of the ELA 3.0 were both greater than 99%.21 In high-risk populations the ELA versions 2.0 and 3.0 have similar sensitivity and specificity.61 Fourth, the relatively short period of follow-up may limit our ability to assess the effect of HCV coinfection on HIV disease progression. However, we analyzed the subset of 191 persons with follow-up of greater than 4 years duration, and did not detect a significant difference in the risk of progression to AIDS, death, or to CD4 cell count below 200/µL in HCV-infected compared with HCV-uninfected persons (M.S.S., unpublished data, January 2002). Furthermore, it would seem that we observed a sufficient number of persons at risk of HIV disease progression, as there was a large number who experienced a new opportunistic infection (n=231) or death (n=321). An analysis of a cohort of 1955 patients who were relatively balanced with respect to proportions having HCV infection should have sufficient precision to detect relatively small differences in HIV progression. Fifth, our findings may not be generalizable to HIV-infected patients receiving care outside of urban settings in which HCV infection and injection drug use may be less prevalent. Finally, we did not evaluate the effect of other potential cofactors such as GB virus C and TT virus infections.42-46 In particular, since GB virus C infection has been associated with reduced progression of HIV disease, the presence of GB virus C infection could mask an adverse effect of HCV if it occurred more often in HCV-infected persons.42,45,46 Thus, these and other unmeasured factors may confound the relationship of HCV and HIV progression.

In conclusion, after adjustment for the administration of HAART and its effectiveness, we did not detect an increased risk of development of AIDS-defining illness, death, or CD4 cell count decline to below 200/µL among HCV-infected compared with HCV-uninfected patients. In addition, among patients prescribed HAART, we found no evidence that HCV infection alters the virological or immunologic response to potent antiretroviral therapy. While further research is needed to understand the effect of HCV infection on HIV disease and immune reconstitution in response to HAART, these findings emphasize the importance of the consideration of effective antiretroviral...
rality for HCV-infected and HCV-uninfected persons at immediate risk for the development of AIDS.

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