The Risk of Incident Coronary Heart Disease Among Veterans With and Without HIV and Hepatitis C

Matthew S. Freiberg, MD, MSc; Chung-Chou H. Chang, PhD; Melissa Skanderson, MS; Kathleen McGinnis, MS; Lewis H. Kuller, MD, DrPH; Kevin L. Kraemer, MD, MSc; David Rimland, MD; Matthew B. Goetz, MD; Adeel A. Butt, MD; Maria C. Rodriguez Barradas, MD; Cynthia Gibert, MD; David Leaf, MD, MPH; Sheldon T. Brown, MD; Jeffrey Samet, MA, MPH; Lewis Kazis, SCD; Kendall Bryant, PhD; Amy C. Justice, MD, PhD; for the Veterans Aging Cohort Study

Background—Whether hepatitis C virus (HCV) confers additional coronary heart disease (CHD) risk among human immunodeficiency virus (HIV) infected individuals is unclear. Without appropriate adjustment for antiretroviral therapy, CD4 count, and HIV-1 RNA and substantially different mortality rates among those with and without HIV and HCV infection, the association between HIV, HCV, and CHD may be obscured.

Methods and Results—We analyzed data on 8579 participants (28% HIV+, 9% HIV/HCV+) from the Veterans Aging Cohort Study Virtual Cohort who participated in the 1999 Large Health Study of Veteran Enrollees. We analyzed data collected on HIV and HCV status, risk factors for and the incidence of CHD, and mortality from January 2000 to July 2007. We compared models to assess CHD risk when death was treated as a censoring event and as a competing risk. During the median 7.3 years of follow-up, there were 194 CHD events and 1186 deaths. Compared with HIV– Veterans, HIV+/HCV+ Veterans had a significantly higher risk of CHD regardless of whether death was adjusted for as a censoring event (adjusted hazard ratio, 2.03; 95% confidence interval, 1.28 to 3.21) or a competing risk (adjusted HR, 2.45; 95% confidence interval, 1.83 to 3.27 respectively). Compared with HIV+– Veterans, HIV+/HCV+ Veterans also had a significantly higher adjusted risk of CHD regardless of whether death was treated as a censored event (adjusted hazard ratio, 1.93; 95% confidence interval, 1.02 to 3.62) or a competing risk (adjusted hazard ratio, 1.46; 95% confidence interval, 1.03 to 2.07).

Conclusions—HIV+/HCV+ Veterans have an increased risk of CHD compared with HIV+/– and HIV–– Veterans. (Circ Cardiovasc Qual Outcomes. 2011;4:425-432.)

Key Words: viruses ▪ coronary disease ▪ mortality ▪ comorbidity

Human immunodeficiency virus (HIV) infection is associated with increased risk of coronary heart disease (CHD).1,2 Whether hepatitis C virus (HCV) infection confers additional risk over and above that of HIV infection remains unclear, and the reports are inconsistent.3–5 With the use of data from participants in the Veterans Aging Cohort Study (VACS) “Virtual Cohort” and the 1999 Large Health Survey of Veteran Enrollees,7 we first examined the association between HIV+/HCV+ Veterans and the risk of future CHD events compared with HIV–– Veterans who were demographically and behaviorally similar. Next, we compared HIV+– with HIV+/– Veterans to also account for baseline, duration of, and recent use of class of antiretroviral therapy and baseline and recent HIV-1 RNA and CD4 count levels. Finally, because HIV+– patients are at higher risk of death than HIV+/– and
HIV–HCV—patients,\textsuperscript{1,8} we constructed competing risk models to ensure that the association between HIV, HCV, and incident CHD was not obscured by an excess (competing) risk of death.

**WHAT IS KNOWN**

- Whether hepatitis C virus (HCV) infection confers additional coronary heart disease risk over and above that of human immunodeficiency virus (HIV) infection is not clear.
- The prior studies involving HIV and coronary heart disease do not compare HIV-infected people with HIV-uninfected people who are demographically and behaviorally similar.

**WHAT THE STUDY ADDS**

- HIV and HCV coinfection is associated with a higher risk of coronary heart disease as compared with HIV monoinfection and compared with no HIV and no HCV infection.
- The HIV-infected and HCV-uninfected people in this study were demographically and behaviorally similar.
- The association between HIV and HCV coinfection and coronary heart disease persisted even after adjusting for the high mortality rate among HIV and HCV coinfected people, using competing risk models.

**Methods**

The Virtual Cohort is a cohort of HIV-infected, age, sex, race/ethnicity, and clinical site–matched HIV-uninfected participants identified from United States Department of Veterans Affairs (VA) administrative data in the fiscal years 1998 to 2003, using a modified existing algorithm.\textsuperscript{6} This cohort consists of data from the immunology case registry; the VA HIV registry; the pharmacy benefits management data base, a VA centralized data base of outpatient prescriptions; the decision support system, a national data base of VA clinical and financial data including laboratory data; and the National Patient Care Database. The 1999 Large Health Study of Veteran Enrollees, a survey administered between June 1999 and January 2000, was designed to assess the health status of Veterans in the Veterans Health Administration. It contained the Veterans RAND 36 Item Health Survey (VR-36) instrument and other measures of sociodemographic and economic status.\textsuperscript{7,9} The institutional review boards at the University of Pittsburgh, Yale University, and the West Haven Veterans Administration Medical Center approved this study.

All participants in the Virtual Cohort/Large Health Study data set (n=13 250) were eligible for the present study. After excluding participants with baseline cardiovascular disease and cancer, participants who failed to answer baseline questions about cancer, and women (because of small numbers), our final sample included 8579 participants.

**Independent Variable**

We categorized participants into 1 of 4 groups: HIV+HCV+, HIV+HCV−, HIV−HCV+, and HIV−HCV− uninfected (referent). HIV infection was defined as a participant with ≥1 inpatient and/or ≥2 outpatient International Classification of Diseases (ICD)-9 codes for HIV infection and confirmed by the participant’s presence in the immunology case registry.\textsuperscript{6} HCV infection was defined as a positive HCV antibody test or ≥1 inpatient and/or ≥2 outpatient ICD-9 codes for this diagnosis.\textsuperscript{10}

**Dependent Variable(s)**

We used ICD-9 codes (410–411) to identify incident acute myocardial infarction and unstable angina events (CHD) events from January 2000 (entry into the Large Health Study) to July 2007. We chose these ICD-9 codes on the basis of the positive predictive value of the diagnosis of acute myocardial infarction in the Veterans Health Administration\textsuperscript{11} and the high agreement between these ICD-9 codes (both inpatient and outpatient ICD-9 codes) and formal reviewer adjudication in the Cardiovascular Health Study.\textsuperscript{12} Follow-up time was to a CHD or death event or the last known visit within the VA system. In contrast to a prior study that used only inpatient VA hospitalization data to assess the risk of cardiovascular disease among HIV-infected Veterans,\textsuperscript{13} the present study incorporates both inpatient and outpatient ICD-9 codes. Outpatient ICD-9 codes were used to capture participants who had non–VA-hospitalized CHD events but subsequently received their follow-up CHD care as part of the VA outpatient clinical care system. In the Veterans Aging Cohort Study, all CHD events are being formally adjudicated, using established protocols as part of a National Heart, Lung, and Blood Institute–funded collaborative research initiative. This process is not yet complete. We have observed after reviewing charts of nearly 4000 participants that approximately 90% of the acute myocardial infarctions occurring within and outside the VA hospital system were captured by using inpatient and outpatient ICD-9 codes 410 and 411. We confirmed deaths by using the VA vitals status file; the Social Security Administration death master file, the Beneficiary Identification and Records Locator Subsystem, and the VHA medical SAS inpatient data sets.

**Covariates**

Sociodemographic data included age, race/ethnicity, and level of education. Hypertension was defined with the use of ICD-9 codes. Diabetes was diagnosed by using a combination of glucose measurements, diabetic medication use, and or ICD-9 codes. We calculated body mass index (kg/m\textsuperscript{2}) by using self-reported height and weight. Smoking was categorized as history of current smoking, past smoking, or never smoking. Hypercholesterolemia was defined as use of a HMG-CoA reductase inhibitor medication; a total cholesterol value ≥200 mg/dL; or ICD-9 codes. History of cocaine dependence and abuse was defined by means of ICD-9 codes (304.20 to 304.23 and 305.6 to 305.63). History of alcohol dependence and abuse were defined by means of ICD-9 codes, based on prior work in the VACS.\textsuperscript{14}

Among the HIV-infected Veterans, we collected data on baseline and recent CD4 cell counts and HIV-1 RNA. Baseline CD4 count and HIV-1 RNA measurements were from 180 days before and up to 180 days after the time of enrollment in the Large Health Study, and recent measurements were the CD4 count and HIV-1 RNA collected closest to the date of the incident CHD event, mortality event, or the date of last follow-up observation. Duration of antiretroviral therapy (ART) was calculated by using the number of days a participant was taking ART. Duration of ART, calculated on the basis of prescription refill data in the pharmacy benefits management data base, was available from the time of enrollment into the Large Health Study through June 2005. We calculated the duration of ART by drug classes: protease inhibitors (PI), nonnucleoside reverse transcriptase inhibitors (NNRTI), and nucleoside reverse transcriptase inhibitors (NRTI). We also analyzed recent ART because recent studies suggest that ART taken within 6 months of a CHD event is significantly associated with an increased risk of CHD.\textsuperscript{15,16} Recent ART was defined as the use of ART by drug classes within 180 days of an incident CHD or mortality event or the date of last ART prescription recorded among those who did not have a CHD or mortality event. All ART medications that were available on the VA formulary during the time period of this study were considered in the analyses.
Statistical Methods

Descriptive statistics for all variables by HIV and HCV status were assessed with the use of t tests or its nonparametric counterpart for continuous variables and χ² test or Fisher exact test for categorical variables. When treating death as a censoring event, Cox proportional hazard models were used to estimate the hazard ratio (HR) and 95% confidence intervals (CI) for incident CHD associated with HIV and HCV status after adjusting for confounders. The proportional hazards assumption was assessed with the use of the Grambsch-Therneau method. We calculated age and race/ethnicity-adjusted incident CHD per 1000 person-years and mortality rates per 100 person-years. Multiple imputation was used to generate 5 data sets with complete covariate values to increase the robustness and efficiency of the estimated hazard ratio.

This sample represents HIV participants at the earliest period of combination ART. The mortality rates among those infected with HIV were substantially higher compared with Veterans not infected with HIV. Similarly, mortality rates among HIV+HCV+ were higher than those among HIV−HCV+. Cox proportional hazard models assume "noninformative censoring"; this means that patients censored (because of death or loss to follow-up) do not depend on the process of developing CHD. This assumption is violated for HIV+HCV+ Veterans who both substantially higher mortality rates and are at greater risk of CHD than HIV+HCV− and HIV−HCV− Veterans. Therefore, we conducted secondary analyses to ensure that the high mortality rates were not obscuring the association between the HIV and HCV status and incident CHD. To do this, we constructed regression models that incorporated death as a competing risk. Fine and Gray methodology requires that participants who have the competing event (ie, death) would never have died of CHD or developed the event of interest (ie, CHD) if they had not died of a non-CHD death and completed the follow-up period. This seems an implausible assumption for our analyses. Thus, to adapt this technique to account for differing underlying risks of CHD, we needed to identify among those participants who died, probability of either dying of CHD, or having CHD in the follow-up period. We calculated propensity scores by means of a multivariable logistic regression model to assess the likelihood of development of CHD, given an observed set of CHD risk factors (age, race, body mass index, hypertension, diabetes, current smoking, hypercholesterolemia, and cocaine use). The model’s calculated c-statistic (0.75, which represents good prediction of the likelihood of development of CHD), was used to assess the predictive capacity of the model. We then used the propensity score to identify, among those who died, who was at a high risk of dying of CHD or having CHD in the follow-up period. Each person was then reclassified into 1 of 3 categories: died of CHD; did not die of CHD but would have had CHD in the follow-up period; or did not die of CHD and did not have CHD in the follow-up period. Once participants were reclassified; we could then apply the Fine and Gray technique to our sample. It is important to note that during the median follow-up period of 7.3 years, 48 of the 254 HIV+HCV+ Veterans who died had propensity score estimates consistent with death from CHD or development of CHD during the follow-up period if they had not died of another cause.

For analyses restricted to HIV-infected participants, we added HIV-1 RNA, CD4 count, ART status, and traditional risk factors into the model. Our analyses considered baseline, duration of and recent ART, as well as baseline and recent CD4 count and HIV-1 RNA. Because ART data were only available through June 2005, these analyses were truncated to 2005.

Results

We excluded participants who reported at baseline CHD, congestive heart failure and stroke (n=3116), or cancer (except nonmelanomatous skin cancer, n=856) or who failed to answer questions regarding prevalent cancer (n=860). Women were excluded because of limited numbers (n=276). After these exclusions, our final sample size was 8579 participants (28% HIV-infected). Among the study participants, the prevalence of all established cardiovascular risk factors differed by HIV and HCV status (P≤0.001 for all Table 1). Compared with HIV+HCV+ Veterans, the number of days on NNRTI and NRTI use and the prevalence of recent use of NRTI use was higher among HIV+HCV− Veterans (P<0.05 for all, Table 1).

During the 7.5 years of follow-up (median, 7.3 years), there were 194 CHD events (2.3%) and 1186 deaths (13.8%). The age and race/ethnicity-adjusted mortality rate per 100 person-years was 4.59 for HIV-infected Veterans (HIV+HCV+ and HIV+HCV− combined; 95% CI, 4.47 to 4.71 person-years) and 1.38 for HIV uninfected (HIV−HCV+ and HIV−HCV− combined; 95% CI, 1.35 to 1.40). The age and race/ethnicity-adjusted CHD rate was 4.67 per 1000 person-years for HIV-infected (HIV+HCV+ and HIV+HCV− combined; 95% CI, 4.56 to 4.79 per 1000 person-years) and 3.23 per 1000 person-years for uninfected (HIV−HCV+ and HIV−HCV− combined; 95% CI, 3.18 to 3.28 per 1000 person-years). Compared with HIV-uninfected Veterans (HIV−HCV+ and HIV−HCV− combined), HIV-infected Veterans (HIV+HCV+ and HIV+HCV− combined) had an increased risk of incident CHD (Figure 1).

Compared with HIV−HCV− Veterans, HIV+HCV+ Veterans had significantly higher risks of incident CHD (Figure 2), whether death was censored or treated as a competing risk (Table 2). We examined the association between HIV+HCV+ and incident CHD by using models that adjust for death as a competing risk (Table 2) because CHD and mortality rates were highest among coinfected Veterans. Compared with HIV+HCV− Veterans, HIV+HCV+ Veterans had a higher risk of incident CHD, regardless of whether death was censored or treated as a competing risk (Table 3). This association persisted even after adjusting for traditional risk factors; baseline, duration of, and recent antiretroviral therapy (Table 3; models 1, 2, and 3, respectively); and baseline and recent HIV viral load and CD4 count (Table 3, model 3). Recent PI use (HR, 2.15; 95% CI, 0.99 to 4.65), recent NNRTI use (HR, 1.40; 95% CI, 0.70 to 2.77), and recent HIV-1 RNA >500 (HR, 1.29; 95% CI, 0.68 to 2.45) were not significantly associated with an increase in CHD. At baseline, classes of ART and duration of PI and NNRTI were also not significantly associated with CHD in multivariable models. Duration of NRTI per year was associated with a reduced risk of CHD (HR, 0.69; 95% CI, 0.53 to 0.90). The association between ART and mortality by class of ART was HR, 0.97; 95% CI, 0.88 to 1.07 for PI; HR, 0.97; 95% CI, 0.88 to 1.07 for NNRTI; and HR, 0.69; 95% CI, 0.63 to 0.76 for NRTI, respectively.

Discussion

Our findings suggest that HIV+HCV+ Veterans have an increased risk of CHD after adjustment for traditional CHD risk factors, use of ART; CD4 count, and HIV-1 RNA compared with HIV+HCV− and HIV−HCV− Veterans. This association persisted whether death was treated as a censored event or a competing risk.
Table 1. Baseline Characteristics of Veteran Participants

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>HIV—HCV— (n=5453)</th>
<th>HIV—HCV+ (n=701)</th>
<th>HIV+ HCV— (n=1687)</th>
<th>HIV+ HCV+ (n=738)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median, mean±SD</td>
<td>48, 48.2±9.9</td>
<td>47, 47.4±5.6</td>
<td>47, 47.8±10.7</td>
<td>48, 48.8±6.7</td>
<td>0.02</td>
</tr>
<tr>
<td>Race/ethnicity, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>39.0</td>
<td>29.8</td>
<td>47.5</td>
<td>30.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>African American</td>
<td>39.2</td>
<td>52.9</td>
<td>32.7</td>
<td>53.1</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>9.8</td>
<td>9.6</td>
<td>8.5</td>
<td>11.8</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>12.1</td>
<td>7.7</td>
<td>11.2</td>
<td>4.7</td>
<td></td>
</tr>
<tr>
<td>Education, %†</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;12th-grade education</td>
<td>9.8</td>
<td>15.4</td>
<td>8.9</td>
<td>14.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>High school graduate</td>
<td>35.1</td>
<td>39.3</td>
<td>29.6</td>
<td>38.7</td>
<td></td>
</tr>
<tr>
<td>Body mass index, median, mean±SD†</td>
<td>27.4, 28.2±5.3</td>
<td>26.4, 27.1±5.0</td>
<td>24.4, 25.1±4.2</td>
<td>24.4, 25.1±4.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>29.3</td>
<td>27.4</td>
<td>17.3</td>
<td>23.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>24.8</td>
<td>25.8</td>
<td>15.9</td>
<td>18.7</td>
<td>0.001</td>
</tr>
<tr>
<td>Smoking status, %†</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never smoking</td>
<td>26.5</td>
<td>9.6</td>
<td>23.3</td>
<td>10.9</td>
<td></td>
</tr>
<tr>
<td>Current smoking</td>
<td>42.5</td>
<td>66.2</td>
<td>49.9</td>
<td>65.6</td>
<td></td>
</tr>
<tr>
<td>Past smoking</td>
<td>31.0</td>
<td>24.2</td>
<td>26.7</td>
<td>23.5</td>
<td></td>
</tr>
<tr>
<td>Hypercholesterolemia, %</td>
<td>33.7</td>
<td>25.8</td>
<td>33.9</td>
<td>20.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>History of cocaine dependence or abuse, %</td>
<td>12.3</td>
<td>41.9</td>
<td>12.9</td>
<td>42.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>History of alcohol dependence or abuse, %</td>
<td>28.3</td>
<td>67.1</td>
<td>24.1</td>
<td>56.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Baseline log10 viral load, median, mean±SD; data available on n=1085 for HIV—HCV— and n=525 HIV+ HCV+</td>
<td>...</td>
<td>2.9, 3.2±1.3</td>
<td>2.7, 3.1±1.2</td>
<td>0.14</td>
<td></td>
</tr>
<tr>
<td>Baseline CD4 count, median, mean±SD; data available on n=1124 for HIV+ HCV— and n=535 HIV+ HCV+</td>
<td>...</td>
<td>371, 418.2±283.0</td>
<td>357, 402.1±267.2</td>
<td>0.37</td>
<td></td>
</tr>
<tr>
<td>Recent log10 viral load, median, mean±SD; data available on n=1424 for HIV+ HCV— and n=654 HIV+ HCV+</td>
<td>...</td>
<td>2.7, 3.1±1.3</td>
<td>2.6, 3.0±1.3</td>
<td>0.45</td>
<td></td>
</tr>
<tr>
<td>Recent CD4 count, median, mean±SD; data available on n=1392 for HIV+ HCV— and n=646 HIV+ HCV+</td>
<td>...</td>
<td>397, 435.3±292.9</td>
<td>391, 426.5±287.4</td>
<td>0.49</td>
<td></td>
</tr>
<tr>
<td>HAART at baseline, %</td>
<td>...</td>
<td>39.1</td>
<td>41.1</td>
<td>0.36</td>
<td></td>
</tr>
<tr>
<td>PI use</td>
<td>17.7</td>
<td>20.2</td>
<td>0.15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NNRTI use</td>
<td>9.0</td>
<td>8.7</td>
<td>0.79</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NRTI use</td>
<td>24.1</td>
<td>25.1</td>
<td>0.62</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any recent antiretroviral therapy, %‡</td>
<td>69.9</td>
<td>69.5</td>
<td>0.85</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PI use</td>
<td>44.2</td>
<td>44.7</td>
<td>0.82</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NNRTI use</td>
<td>33.4</td>
<td>27.2</td>
<td>0.003</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NRTI use</td>
<td>68.6</td>
<td>68.6</td>
<td>0.97</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of antiretroviral therapy (days) among those taking any class of antiretroviral therapy, median, mean±SD‡</td>
<td>726, 701.8±386.3</td>
<td>618, 652.1±387.8</td>
<td>0.07</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PI use</td>
<td>885, 920.9±771.4</td>
<td>743, 856.4±684.8</td>
<td>0.23</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NNRTI use</td>
<td>314, 570.9±658.5</td>
<td>150, 463.9±619.8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NRTI use</td>
<td>1683, 1386.5±634.2</td>
<td>1466, 1305.4±624.9</td>
<td>0.02</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

HAART indicates highly active antiretroviral therapy.
*ANOVA, χ² test, and Wilcoxon rank-sum test were used.
†Missing covariate data: education, 4.6%; smoking, <1%; body mass index, 1.6%.
‡Duration of and recent antiretroviral therapy is through 2005.
Currently there are no prospective data describing the risk of incident CHD among HIV+/HCV− individuals compared with HIV−/HCV− individuals who are similar demographically and behaviorally. The data describing the association between HCV and CHD among HIV-infected individuals are sparse, the results are inconsistent, and none of these studies used competing risk models. However, our results (Table 3; model 2, with death as a censored event) are very consistent with another study of 19,424 HIV infected Veterans, which reported a significant association between HCV infection and cardiovascular diseases (HR, 1.20; 95% CI, 1.04 to 1.38) after adjusting for hypertension, age, type 2 diabetes, and smoking.5

We used competing risk models in the present study because HIV+/HCV+ Veterans had higher adjusted incident mortality rates. We conducted these analyses to ensure that mortality was not obscuring the association between HIV, HCV, and incident CHD. Whether the referent group was HIV−/HCV− or HIV+/HCV− Veterans, HIV+/HCV+ Veterans had a significantly increased risk of CHD. This association persisted regardless of whether a Cox or competing risk model was used. Of note, whether the competing risk model increased (Table 2) or modestly decreased (Table 3) the estimation of CHD risk among HIV+/HCV+ Veterans was largely determined by the mortality rates of and the propensity estimates for CHD death or development of CHD in the follow-up period among those who died of a non-CHD death among the referent groups. In our analyses among HIV-infected Veterans, ART was associated with an increased risk of CHD and a reduced risk of death. Thus, ART almost certainly influenced the association between HIV, HCV, and the risk of CHD.

This analysis was not designed to determine whether HCV monoinfection is associated with increased risk of CHD. Among HIV-uninfected individuals, several studies report that HCV infection is associated with a higher prevalence of CHD risk factors,21,22 carotid atherosclerosis,23–25 and CHD.26,27 Other studies report no association.28–30 Our results did not demonstrate a significant association between HIV−/HCV+ infection and incident CHD. However, the
confidence intervals around these estimates were wide and did not preclude a clinically important difference in risk (up to 70% to 80% increased HR compared with HIV−HCV−). The width of these confidence intervals may be attributable to the small number of CHD events among the HIV−HCV− Veterans in this study.

The mechanism by which the HIV virus influences CHD risk remains unknown. One hypothesis suggests that chronic HIV infection causes microbial translocation of intestinal bacterial products leading to increased immune activation.31 Interestingly, markers of microbial translocation are also associated with the progression of HCV and cirrhosis, each of

Table 2. Association Between HIV, HCV, and CHD After Adjustment for Death as a Censoring Event and as a Competing Risk

<table>
<thead>
<tr>
<th>HIV and HCV Status</th>
<th>Death Events, n (%)</th>
<th>Adjusted Mortality Rate*</th>
<th>CHD Events, n (%)</th>
<th>Adjusted CHD Incidence Rate*</th>
<th>Model 1: HR for CHD With 95% CI (Death is Censored)</th>
<th>Model 2: HR for CHD With 95% CI (Death is a Competing Risk)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV+HCV+</td>
<td>254 (34.4%)</td>
<td>6.11 (5.91−6.31)</td>
<td>26 (3.5%)</td>
<td>6.24 (6.05−6.43)</td>
<td>2.03 (1.28−3.21)</td>
<td>2.45 (1.83−3.27)</td>
</tr>
<tr>
<td>HIV+HCV−</td>
<td>382 (22.7%)</td>
<td>3.92 (3.78−4.07)</td>
<td>39 (2.3%)</td>
<td>3.99 (3.85−4.13)</td>
<td>1.42 (0.97−2.06)</td>
<td>1.90 (1.52−2.37)</td>
</tr>
<tr>
<td>HIV−HCV+</td>
<td>97 (13.8%)</td>
<td>2.08 (2.02−2.15)</td>
<td>14 (2.0%)</td>
<td>3.01 (2.92−3.09)</td>
<td>0.97 (0.54−1.73)</td>
<td>1.15 (0.77−1.71)</td>
</tr>
<tr>
<td>HIV−HCV−</td>
<td>453 (8.3%)</td>
<td>1.29 (1.26−1.31)</td>
<td>115 (2.1%)</td>
<td>3.26 (3.20−3.31)</td>
<td>1.0</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Age, median, mean± SD

Race/ethnicity

White

African American

Hispanic

Other

Education

<12th-grade education

High school graduate

>High school graduate

Body mass index

<25 kg/m²

25 to ≤30 kg/m²

>30 kg/m²

Hypertension

Diabetes

Smoking status

Never smoking

Current smoking

Past smoking

Hypercholesterolemia

History of cocaine dependence or abuse

History of alcohol dependence or abuse

*Mortality and incidence rates are age- and race-adjusted per 100 and per 1000 person-years, respectively.

The mechanism by which the HIV virus influences CHD risk remains unknown. One hypothesis suggests that chronic HIV infection causes microbial translocation of intestinal bacterial products leading to increased immune activation.31 Interestingly, markers of microbial translocation are also associated with the progression of HCV and cirrhosis, each of

Table 3. Association Between HCV Status and CHD and Baseline, Duration of, and Recent ART Use Among HIV-Infected Participants After Adjustment for Death as a Censoring Event and as a Competing Risk*

<table>
<thead>
<tr>
<th>HIV and HCV Status</th>
<th>Death Events, n (%)</th>
<th>Adjusted Mortality Rate*</th>
<th>CHD Events, n (%)</th>
<th>Adjusted CHD Incidence Rate*</th>
<th>Model 1: HR for CHD With 95% CI (Death is Censored)</th>
<th>Model 2: HR for CHD With 95% CI (Death is a Competing Risk)</th>
<th>Model 3: Recent ART HR for CHD With 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV+HCV+, n=738</td>
<td>193 (26.2)</td>
<td>5.84 (5.65−6.03)</td>
<td>23 (3.1)</td>
<td>6.96 (6.72−7.21)</td>
<td>1.93 (1.02−3.62)</td>
<td>1.46 (1.03−2.07)</td>
<td>2.13 (1.12−4.05)</td>
</tr>
<tr>
<td>HIV+HCV−, n=1487</td>
<td>307 (18.2)</td>
<td>4.02 (3.88−4.16)</td>
<td>28 (1.7)</td>
<td>3.69 (3.54−3.83)</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
</tbody>
</table>

*Because duration of and recent ART data are through 2005, the follow-up of CHD and mortality events are only through 2005.

†Mortality and incidence rates are age- and race-adjusted per 100 and 1000 person-years, respectively.

‡All HRs were adjusted for age, race/ethnicity, education, body mass index, hypertension, diabetes, smoking, hypercholesterolemia, HIV viral load, CD4 count, history of alcohol dependence and abuse and cocaine dependence and abuse, and death as a censoring event or as a competing risk. Models adjusted for ART drug classes at baseline (model 1), duration of (model 2), and recent use (model 3).
which may also stimulate an increased immune response. Depending on the risk of CHD risk through microbial translocation and increased immune response is not known.

The present study has limitations. First, because our population consists entirely of men, our results may not be generalizable to women. The use of ICD-9 codes for CHD diagnoses may have resulted in some misclassification; however, prior work suggests these codes have high positive predictive values and demonstrate good agreement with formal chart review adjudication processes. Moreover, the ICD-9 codes used in this analysis represent both inpatient and outpatient records. This is important because CHD events occurring outside the VA system could not be captured if only VA inpatient hospitalization data were used to identify CHD events. Third, cause of death data were not available; however, our competing risk models were specifically designed to identify among those who died, who were at greatest risk of CHD death and to incorporate that risk in our analyses. Fourth, without HCV viral RNA values, we could not account for those individuals who might have spontaneously cleared their HCV infection or had false-positive tests. Fifth, we did not incorporate treatment for HCV infection; however, our prior studies in clinical settings show that treatment rates are low for HCV monoinfected people and even lower for HIV-HCV–coinfected patients.

In conclusion, HIV+HCV+ Veterans have an increased risk of incident CHD after adjustment for traditional CHD risk factors, and HIV factors including antiretroviral therapy, CD4 count, and HIV-1 RNA-1 RNA compared with HIV+HCV− and HIV−HCV− Veterans. Further investigations should focus on the mechanism of HCV infection and the risk of CHD among HIV-infected individuals.

Sources of Funding

This study was supported by the National Institute on Alcohol Abuse and Alcoholism (2U10 AA 13566 and K23 AA01594) and the National Heart, Lung, and Blood Institute (1RO1HL095136-03).

Disclosures

The views expressed in this article are those of the authors and do not necessarily reflect the position or policies of the Department of Veterans Affairs.

References

The Risk of Incident Coronary Heart Disease Among Veterans With and Without HIV and Hepatitis C
Matthew S. Freiberg, Chung-Chou H. Chang, Melissa Skanderson, Kathleen McGinnis, Lewis H. Kuller, Kevin L. Kraemer, David Rimland, Matthew B. Goetz, Adeel A. Butt, Maria C. Rodriguez Barradas, Cynthia Gibert, David Leaf, Sheldon T. Brown, Jeffrey Samet, Lewis Kazis, Kendall Bryant, Amy C. Justice and for the Veterans Aging Cohort Study

Circ Cardiovasc Qual Outcomes. 2011;4:425-432; originally published online June 28, 2011; doi: 10.1161/CIRCOUỘMES.110.957415
Circulation: Cardiovascular Quality and Outcomes is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2011 American Heart Association, Inc. All rights reserved.
Print ISSN: 1941-7705. Online ISSN: 1941-7713

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circoutcomes.ahajournals.org/content/4/4/425

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation: Cardiovascular Quality and Outcomes can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation: Cardiovascular Quality and Outcomes is online at:
http://circoutcomes.ahajournals.org//subscriptions/