

Impact of Chronic Viral Hepatitis on Health-Related Quality of Life in HIV: Results from a Nationally Representative Sample

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- BACKGROUND:** Little is known about the health burden of chronic viral hepatitis in HIV-infected patients. We compared health-related quality of life (HRQOL) of patients with HIV and hepatitis C virus (HCV) or HIV and hepatitis B virus (HBV) coinfection to those with HIV mono-infection.
- METHODS:** Using a nationally representative sample of 1,874 adults with HIV who completed a baseline and two follow-up interviews, we identified those with HIV mono-infection (n = 1,493), HIV-HCV coinfection (n = 279), and HIV-HBV coinfection (n = 122). We measured baseline and change over time scores for physical and mental health (PHS, MHS), overall quality of life (QOL), overall health, and disability days. To identify the independent effect of coinfection, we adjusted for demographic and clinical predictors of HRQOL using multivariable regression.
- RESULTS:** Despite significant differences in socio-demographic characteristics between groups, there were no differences in the baseline scores for PHS, MHS, overall QOL, overall health, or disability days between groups. The HRQOL did not decline significantly over time for the HIV patients with or without HCV or HBV coinfection. All groups reported similar longitudinal changes in the HRQOL scores for all measures.
- CONCLUSIONS:** We found no significant differences in disease burden as assessed by a generic HRQOL instrument between patients with HIV mono-infection and HIV-HCV or HIV-HBV coinfection. These data are relevant in counseling coinfecting patients regarding the impact of coinfection on HRQOL, and are important in designing clinical trials and conducting cost-effectiveness analyses including this vulnerable cohort.

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BACKGROUND

Chronic viral hepatitis in HIV-infected patients has emerged as a significant public health problem (1). Chronic hepatitis C (HCV)-related chronic liver disease is the leading cause of morbidity, mortality, and hospital admission in HIV-infected patients (2-7). The heightened awareness of coinfection is reflected by several recent recommendations from national public health agencies including the U.S. Public Health Service (8), the Infectious Disease Society (8), and the National Institutes of Health (9) recommending early detection and treatment of this vulnerable population. Although data on the prevalence and health consequences of HIV-HCV coinfection are emerging (10), few attempts have been made to

evaluate coinfecting patients' health-related quality of life (HRQOL) (11). Although less common, chronic hepatitis B virus (HBV) also coexists with HIV at a higher prevalence than in the general population (12-14). Data on the impact of HBV coinfection on the HRQOL of HIV-infected patients do not exist. These quality-of-life data are important as part of efforts to design and prioritize disease treatment and management strategies (15, 16).

It is not necessarily obvious that HCV and HBV coinfection would affect the quality of life of HIV-infected patients. HIV, HCV, and HBV mono-infections have all been found to be associated with diminished HRQOL (17-22). Coinfection with HIV and HCV (23, 24) or with HIV and HBV (13) is synergistic in terms of liver disease progression. In

addition, chronic viral hepatitis adversely affects the course and management of HIV infection (25, 26). These relationships provide the basis for a hypothesized negative synergism between HIV and chronic viral hepatitis on HRQOL. In fact, a recent study comparing the cost-effectiveness of competing management strategies for coinfecting patients assumed a multiplicative (*i.e.*, synergistic) relationship between HIV and HCV infection (27). Despite these data, there are several reasons to believe that HIV and chronic viral hepatitis may not be synergistic in terms of HRQOL decrement. First, traditional biological outcomes like liver disease severity do not correlate well with patient-oriented outcomes like HRQOL (28). Therefore, it is uncertain that both outcomes will be influenced in the same way. Second, data from other disease states such as gastroesophageal reflux disease, asthma, and peptic ulcer disease show that the presence of medical comorbidities does not consistently result in a synergistic or even an additive decrement in HRQOL (29). Third, the impact of a new comorbidity depends upon the graveness of the baseline disease. For example, in a systematic review Gijsen *et al.* found that presence of comorbidity did not affect HRQOL in patients with cancer and stroke, but led to HRQOL decrements in patients with diabetes mellitus and asthma (30). Because HIV is often perceived to be a serious and life-threatening condition, and because HIV monoinfection itself is associated with significant deterioration in HRQOL, coexistence of chronic viral hepatitis may not lead to further decrement in HRQOL of HIV patients.

In light of these data, we sought to measure the association between HRQOL and HCV or HBV coinfection among HIV-infected patients who participated in the HIV Cost and Services Utilization Study (HCSUS)—a prospective study that followed a national probability sample of HIV-infected adults receiving care in the contiguous United States from 1996 to 1998 (31, 32). We hypothesized that there would not be a negative synergism between HIV and chronic viral hepatitis on HRQOL, and that the HRQOL decrements would be similar in both monoinfected and coinfecting groups. If this were true, then it would have important clinical and health economic consequences and would run contrary to the unilateral acceptance in recent cost-effectiveness models that coinfection is negatively synergistic on HRQOL—an unproven assumption.

METHODS

Study Sample and Subjects

The HIV Cost and Services Utilization Study (HCSUS) collected extensive data from a series of in-person patient interviews and medical records in a multistage, national probability sample of HIV-infected adults receiving care in the contiguous United States from 1996 to 1998 (31, 32). The reference population consists of patients at least 18 yr of age with known HIV infection who made at least one visit for regular or ongoing care to other than a military, prison, or

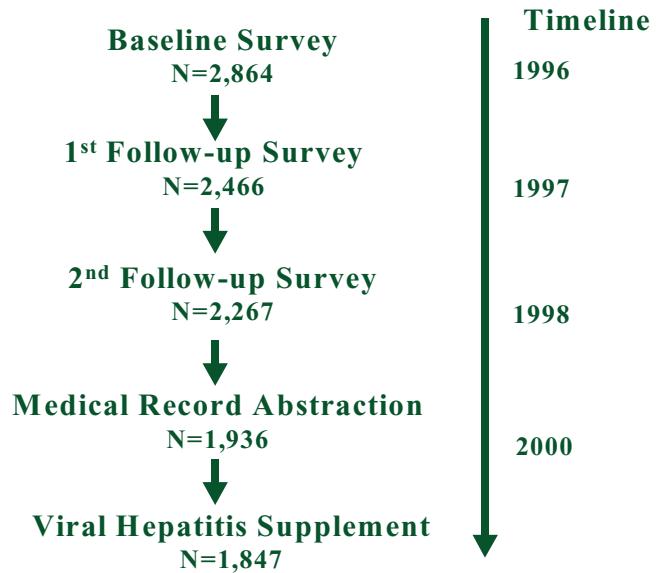


Figure 1. Patient follow-up in the HIV Cost and Services Utilization Study. A total of 1,874 patients were included in the present analysis.

emergency facility between January 5, 1996 and February 29, 1996. Because of the sampling strategy employed, the HCSUS sample is representative of all HIV-infected adults receiving care in the United States in 1996. Further details of the study and sampling design are described extensively elsewhere (31, 33, 34). Figure 1 displays the patient follow-up over the HCSUS study period. Overall, 4,042 subjects were eligible for enrollment, and 2,864 completed a baseline interview between January 1996 and April 1997 (stage 1). The first follow up interview (stage 2) included 2,466 patients interviewed between December 1996 and July 1997. The second follow up interviews (stage 3) included 2,267 patients interviewed between August 1997 and January 1998. Medical record data were based on 2,267 patients who completed the stage 3 interviews (64% of the surviving baseline sample). Of these, 1,936 (85%) of the stage 3 respondents had medical records from their primary care provider available during the study time frame (32). Information regarding coinfection with viral hepatitis B and C was abstracted from the medical record progress notes and laboratory reports using a standardized viral hepatitis supplement. Sixty-two patients (3.2%) had missing viral hepatitis supplement information and were therefore excluded.

In this analysis we examine data from 1,874 HIV-infected adults who completed a baseline and two follow-up interviews, had their medical record data abstracted, and had a completed viral hepatitis supplement. The present study was reviewed and approved by the RAND and UCLA institutional review boards.

Case Ascertainment

We assumed that patients were HIV–HCV coinfecting if they met any of the following three criteria: (1) positive HCV virological test (qualitative or quantitative RNA), (2)

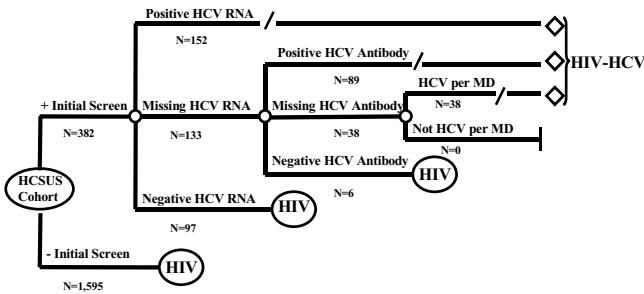


Figure 2. Displays the hierarchical algorithm for case ascertainment for HIV–HCV-coinfection group. Initial screening used three tests: (1) positive HCV RNA test, (2) positive HCV antibody, and (3) diagnosis of HCV per physician note. 382 patients selected as being positive per at least 1/3 tests. We identified patients as HIV–HCV coinfection ($n = 279$) if they had: (1) positive HCV RNA ($n = 152$), (2) if missing HCV RNA, a positive HCV antibody ($n = 89$), and (3) if missing HCV RNA & HCV antibody, HCV per physician note ($n = 38$).

positive HCV antibody test, or (3) diagnosis of HCV in the physician note. We employed a prespecified hierarchical strategy to identify cases as portrayed in Figure 2. We identified 279 HIV–HCV-coinfection patients using this strategy. We assumed that patients were HIV–HBV coinfection if they either had a positive hepatitis B surface antigen ($n = 65$), or if they had a diagnosis of chronic HBV infection in the physician note ($n = 57$). We identified 122 HIV–HBV-coinfection patients using these criteria. Patients without either HCV or HBV coinfection comprised the HIV-monoinfection group ($n = 1,493$). Twenty patients had both HCV and HBV coinfections.

Data Collection

PATIENT DATA. Based on *a priori* hypotheses guided by empirical data from the literature, we specified relevant demographic characteristics, socioeconomic characteristics, HIV-related characteristics, comorbidities, and risk characteristics that might affect the relationship between coinfection and HRQOL. We obtained these data from the patient baseline interview (31). We collected medical comorbidity data from the abstracted medical record and included any diagnosis of hypertension, congestive heart failure, coronary artery disease, cerebrovascular disease, diabetes, hemophilia, sickle cell disease, chronic obstructive pulmonary disease, and chronic renal failure. We diagnosed patients with major depression based on DSM-IV criteria from the Composite International Diagnostic Interview survey short form—a mental health-screening instrument (35, 36).

THE HRQOL DATA. All respondents completed the HCSUS HRQOL survey during each interview stage (17, 37). The questionnaire is a derivative of several leading survey instruments in HIV including the Medical Outcomes Study HIV health survey (38) and the AIDS Clinical Trials Group HRQOL survey (39, 40). Support for the reliability and construct validity of the HCSUS HRQOL survey has been provided in previous studies (17, 18). The survey included

multi-item measures of physical functioning (nine items), role functioning (two items), pain (two items), general health perceptions (three items), emotional well-being (seven items), social functioning (two items), and energy (two items). Table 1 lists the measures and items in the HCSUS HRQOL measures and compares these items to those included the Short Form-36 Health Survey and the AIDS Clinical Trials Group HRQOL instrument. The HCSUS HRQOL measures emphasize the dimensions identified as relevant and important for HIV-infected patients. For example, physical functioning items represent a range of functioning from basic (*e.g.*, feeding) to advanced (*e.g.*, vigorous activity). We included two global items assessing overall health and overall quality of life (QOL), and a single item measure of days in bed due to illness within the past 30 days (disability days).

Analyses

We imputed missing data using the hot deck multiple imputation procedure to fill in less than 1% of HRQOL items for which data were missing, less than 5% of CD4+ lymphocyte counts, less than 3% of insurance and income values, and less than 0.5% of other essential missing variables (41). We derived the physical and mental (PHS, MHS) health summary scores as described elsewhere (17, 37). We then standardized the summary scores with a linear transformation to have a mean of 50 and standard deviation of 10. We linearly transformed the overall health and overall QOL measures to range between 0 and 100, with higher scores indicating a better HRQOL (37). Disability days ranged from 0 to 30 days within the past month. Our outcome measures included PHS, MHS, overall health, overall QOL, and disability days. We also calculated the change in the PHS, MHS, overall health, overall QOL, and disability days between the baseline and 2-yr follow-up for each group. We used longitudinal effect size (ES) to express the change in HRQOL over time as $(HRQOL_{Last\ Follow-up} - HRQOL_{Baseline}) / SD_{Baseline}$. Because the minimally clinically important difference in the HCSUS HRQOL instrument has not been previously established, we relied upon HRQOL differences across several relevant clinical anchors to set our thresholds for clinical significance. For example, it has been previously shown that the mean HRQOL score on the HCSUS physical functioning scale is 59 ± 6 for asymptomatic *versus* 52 ± 9 for symptomatic HIV patients, with corresponds to an ES of 1.0. An example of a more subtle HRQOL difference is the comparison between AIDS patients with a CD4 of 50–199 *versus* 0–49. The effect size for this comparison is 0.4 SD (50 ± 10 vs 46 ± 10). The smallest published HRQOL difference using the HCSUS instrument is the comparison between patients with CD4 counts >500 *versus* 200–499. The effect size for this comparison is 0.2 SD (54 ± 8 vs 52 ± 9). Based upon these anchor-based data, we prespecified the effect sizes of ≤ 0.20 as small, 0.50 moderate, and >0.80 large changes in HRQOL over time. These assumptions are also consistent with previously established rules regarding the interpretation of effect sizes (42).

Table 1. The HCSUS HRQOL Measures and Items. Comparison with ACTG and SF-36 Survey

| Domains | HCSUS Survey | ACTG Survey | SF-36 Survey |
|----------------------------|--|-------------|--------------|
| Physical functioning | 9 items | 4 items | 10 items |
| | Vigorous activity | + | + |
| | Climbing stairs | | + |
| | Walking more than mile | | + |
| | Walking one block | | + |
| | Bathing or dressing | | + |
| | Preparing meals or doing laundry | | |
| | Shopping | | |
| | Getting around inside home | | |
| | Feeding yourself | | |
| Role functioning | 2 items | 2 items | 7 items |
| | Working at a job, doing work around house, going to school Some kinds/amounts work or house/school work | + | |
| Pain | 2 items | 2 items | 2 items |
| | Pain interfere with work Amount of pain | + | + |
| General health perceptions | 3 items | 3 items | 5 items |
| | Excellent-poor health | + | |
| | Get sick easier than others | + | |
| Emotional well-being | 7 items | 2 items | 5 items |
| | Calm and peaceful | + | + |
| | Downhearted and blue | + | + |
| | Happy person | + | + |
| | Very nervous person | | + |
| | Down in dumps | | + |
| | Anxious and worried | | |
| | Depressed | | |
| Social functioning | 2 items | 2 items | 2 items |
| | Social life interfered with Amount of time interfered with | + | + |
| Energy and fatigue | 2 items | 2 items | 4 items |
| | Feeling tired Enough energy to do things | + | + |
| Disability days | 1 item | 0 item | 0 item |
| | Days in bed due to ill health | | |
| Overall health | 1 item | 1 item | 0 item |
| | Overall how rate current health | + | |
| Overall quality of life | 1 item | 0 item | 0 item |
| | Overall how rate current quality | | |

HCSUS, HIV Cost and Services Utilization Study.

ACTG, AIDS Clinical Trials Group.

SF-36, Short Form-36 from Medical Outcomes Study.

The plus sign in the last two columns indicate that the particular item is included in the ACTG Quality of Life Survey or SF-36 Survey.

We conducted two between-group comparisons (HIV-monoinfected vs HIV-HCV-coinfected, and HIV-monoinfected vs HIV-HBV-coinfected patients) using the *t*-tests for the mean HRQOL scores, and the χ^2 tests for categorical data. For the baseline PHS and MHS comparisons, the study had a 80% power to detect a difference of 2.5 points between the HIV-monoinfected and HIV-HCV-coinfected groups (ES = 0.25) and 2.9 points between the HIV-monoinfected and HIV-HBV-coinfected groups (ES = 0.29) with an $\alpha = 0.05$. The study had a power of 80% to detect a difference of 1.7 and 4.8 points (ES = 0.20 and 0.40) in PHS and MHS over time for the HIV-HCV- and HIV-HBV-coinfected groups, and a power of 95% to detect a difference of 1.4 points (ES = 0.20) in PHS and MHS for the HIV-monoinfected group. Because it was possible

to observe a type II error in the analyses including HIV-HBV-coinfected patients, we focused our interpretation not only on statistical significance, but also on clinical significance.

We created multivariable linear regression models and adjusted for prespecified covariates to identify the independent effects of HIV-HCV and HIV-HBV coinfection on the PHS, MHS, overall health, overall QOL, and disability days. We did not adjust for depression in the models assessing the relationship of coinfection and mental HRQOL since this would create a circular argument with mental health variables on both sides of the regression equation. Table 2 provides the full list of covariates and their method of categorization.

We incorporated sampling weights in all regression analyses to appropriately account for the sampling design of the survey (31-34). We considered analyses to be statistically

Table 2. Socio-Demographic and Clinical Correlates of HRQOL in HIV-Infected and HIV-HCV- and HIV-HBV-Coinfected Groups

| Variables (%) | HIV Only (n = 168,178) | HCV-HIV ¹ (n = 34,466) | <i>p</i> Value ² | HBV-HIV ¹ (n = 13,558) | <i>p</i> Value ³ |
|--|---------------------------|--------------------------------------|-----------------------------|--------------------------------------|-----------------------------|
| Demographics | | | | | |
| Age in years | | | 0.0005 | | 0.0001 |
| 18-29 | 7.8 | 7.6 | | 9.8 | |
| 30-34 | 21.6 | 12.6 | | 24.1 | |
| 35-39 | 23.1 | 27.8 | | 30.1 | |
| 40-44 | 17.7 | 23.4 | | 13.4 | |
| 45-49 | 11.8 | 14.2 | | 14.2 | |
| 50+ | 10.9 | 14.3 | | 8.6 | |
| Male | 75.4 | 79.8 | 0.0003 | 88.6 | 0.0001 |
| Race | | | | | |
| | | | 0.0009 | | 0.0001 |
| White | 49.9 | 41.9 | | 71.1 | |
| Black | 31.1 | 38.5 | | 18.5 | |
| Latino | 15.2 | 15.6 | | 10.3 | |
| Other | 3.6 | 3.8 | | 0.0 | |
| Socio-economic status | | | | | |
| Education | | | | | |
| | | | 0.0022 | | 0.01 |
| LTHS | 22.9 | 32.1 | | 23.7 | |
| HS | 29.4 | 24.0 | | 23.7 | |
| Some college | 28.6 | 27.1 | | 28.8 | |
| BA, BS | 19.0 | 16.7 | | 23.7 | |
| Living with Spouse | 36.2 | 34.4 | 0.76 | 38.1 | 0.5 |
| Income | | | | | |
| | | | 0.02 | | 0.003 |
| \$0 | 4.0 | 4.8 | | 5.1 | |
| \$1-10,000 | 39.4 | 48.7 | | 31.9 | |
| \$10,001-40,000 | 38.6 | 33.9 | | 43.3 | |
| \$40,001 and above | 17.9 | 12.6 | | 19.6 | |
| Employment Status | | | | | |
| Not working | 60.6 | 70.2 | 0.08 | 57.7 | 0.1 |
| Insurance Type | | | | | |
| | | | 0.01 | | 0.06 |
| Private | 21.04 | 18.1 | | 21.6 | |
| Medicare | 14.1 | 18.8 | | 19.6 | |
| Medicaid only | 28.0 | 36.4 | | 21.6 | |
| HMO | 15.9 | 10.5 | | 17.5 | |
| No Insurance | 20.8 | 16.1 | | 19.6 | |
| Risk Category | | | | | |
| | | | <0.0001 | | <0.0001 |
| IVDA | 18.6 | 48.6 | | 23.7 | |
| MSM | 50.6 | 36.4 | | 65.9 | |
| Heterosexual contact | 20.9 | 10.7 | | 5.15 | |
| Other exposures | 9.8 | 4.1 | | 5.15 | |
| HIV-related variables | | | | | |
| Clinical Stage of HIV⁴ | | | | | |
| | | | 0.11 | | 0.05 |
| Asymptomatic (CDC stage A) | 10.2 | 8.6 | | 8.2 | |
| Symptomatic (CDC stage B) | 53.8 | 56.5 | | 43.3 | |
| Clinical AIDS (CDC stage C) | 36.1 | 34.8 | | 48.4 | |
| Lowest CD4 count⁴ | | | | | |
| | | | 0.05 | | 0.03 |
| >500 | 10.1 | 10.9 | | 4.1 | |
| 200-499 | 39.7 | 39.5 | | 35.1 | |
| <200 | 50.1 | 50.2 | | 60.8 | |
| HIV Symptoms | | | | | |
| | | | 0.40 | | 0.31 |
| 0 | 9.7 | 6.6 | | 10.3 | |
| 1-4 | 44.1 | 46.0 | | 43.3 | |
| 5+ | 46.2 | 47.4 | | 46.4 | |
| Any antiretroviral ever | | | | | |
| | | | 0.29 | | 0.2 |
| No | 12.5 | 15.3 | | 11.3 | |
| Yes | 87.4 | 84.7 | | 88.6 | |
| Any antiretroviral use in last 6 months | | | | | |
| | | | 0.32 | | 0.24 |
| No | 17.1 | 18.0 | | 15.5 | |
| Yes | 82.8 | 81.9 | | 84.5 | |

(Continued.)

Table 2. Continued.

| Variables (%) | HIV Only (n = 168,178) | HCV-HIV ¹ (n = 34,466) | p Value ² | HBV-HIV ¹ (n = 13,558) | p Value ³ |
|---------------------------|------------------------|-----------------------------------|----------------------|-----------------------------------|----------------------|
| Coexisting comorbidity | | | | | |
| Medical comorbidity | | | 0.6 | | 0.6 |
| 0 | 49.9 | 43.5 | | 43.5 | |
| 1 | 36.3 | 34.2 | | 34.2 | |
| 2 | 10.1 | 18.7 | | 18.7 | |
| 3 | 2.1 | 2.9 | | 2.9 | |
| 4 | 0.5 | 0.6 | | 0.6 | |
| 5 | 0.12 | 0.0 | | 0.0 | |
| 6 | 0.08 | 0.0 | | 0.0 | |
| Depression | 29 | 25 | 0.05 | 41 | 0.003 |
| Alcohol/Drug Use | | | | | |
| Alcohol within past month | 55 | 58 | 0.2 | 58 | 0.5 |
| Drug use within past year | 49.5 | 54.4 | 0.02 | 61.8 | 0.01 |

HCV = chronic hepatitis C; LTHS = less than high school; HS = high school; BA/BS = college; IVDA = intravenous drug use; MSM = men who have sex with men; AIDS = acquired immunodeficiency syndrome.
¹Individuals with simultaneous HCV and HBV infection excluded from coinfecting groups.
²p value for HIV monoinfected and HIV/HCV coinfecting group comparisons.
³p value for HIV monoinfected and HIV/HBV coinfecting group comparisons.
⁴Self-report of clinical stage and lowest ever CD4 count. Clinical AIDS (CDC stage C) defined as a reported history of an AIDS-defining illness.

significant when 2-tailed p values were less than 0.05. We used Bonferroni correction for the HRQOL comparisons. We performed all analyses using Stata Statistical Software Release 8.0 (Stata Corporation, College Station, TX).

RESULTS

Sample Characteristics

Extrapolating from our nationally probabilistic sample, we estimated that there were 213,642 adults in the contiguous United States receiving care for HIV in 1996. Of these, 34,466 (16%, 95% CI 15–18%) were known to have chronic HCV coinfection. Another 13,558 (6%; 95% CI 6–7%) had known chronic HBV coinfection.

HIV-HCV-Coinfected Versus HIV-Monoinfected Groups

SOCIO-DEMOGRAPHIC CHARACTERISTICS. Compared with HIV-monoinfected patients, those with HIV-HCV coinfection were older, more likely to be men, more likely to be African American, less educated, more likely to be unemployed, and more likely to be living below the federal poverty level (Table 2). Although the proportion of uninsured was similar in the two groups, more HIV-HCV-coinfected patients were receiving public insurance (Medicaid and Medicare) than those with HIV alone (55% vs 42%, p = 0.01). Forty-seven percent of the coinfecting group versus 18% of HIV group acquired HIV via intravenous drug use (IVDU) (p < 0.0001). More than half of HIV-HCV-coinfected individuals reported use of drugs (54%) within the past year. Similarly 58% reported use of alcohol within the past month.
CLINICAL CHARACTERISTICS. There were no significant differences in the stage and symptoms of HIV, lowest CD4 count, and past or recent use of antiretroviral drugs (Table 2). Similarly, there were no differences in the prevalence

(Table 2) and type of medical comorbidities and major depression between the two groups.

HRQOL. There was no difference in the baseline PHS, MHS, overall health, and overall QOL between the HIV-monoinfected and HIV-HCV-coinfected groups (Figure 3A). Furthermore, there was no difference in the number of disability days between the two groups (3.1 ± 6.1 vs 3.1 ± 6.2 days; p > 0.05). As depicted in Table 3, the results did not change after adjusting for prespecified covariates. There was a decrement in the PHS and MHS over time in both groups (Figure 3B). However, the change was not clinically or statistically significant. In contrast to the PHS and MHS, the global rating items (overall health and overall QOL) improved over time (Figure 3B) and the mean number of disability days decreased over time for both groups (data not shown). Despite statistically significant improvement in overall health (both groups) and overall QOL (HIV-monoinfected group) between the baseline and the last follow-up interviews, the magnitude of these HRQOL changes over time was not clinically significant (all ES < 0.20). The change in disability days was not statistically or clinically significant in both groups (data not shown). Both groups reported similar changes in the mean scores over time for all measures (all p > 0.05).

HIV-HBV-Coinfected Versus HIV-Monoinfected Groups

SOCIO-DEMOGRAPHIC CHARACTERISTICS. Compared with HIV-monoinfected patients, those with HIV-HBV coinfection were younger, more likely to be men, and more likely to be white (Table 2). There were no significant differences in the type of health insurance coverage between the two groups. Most of the HIV-HBV-coinfected persons acquired HIV via same sex contact (66% vs 51%, p < 0.0001). Sixty-two percent of the HIV-HBV-coinfected individuals reported use of drugs within past year and 58% reported use of alcohol within past month (Table 2).

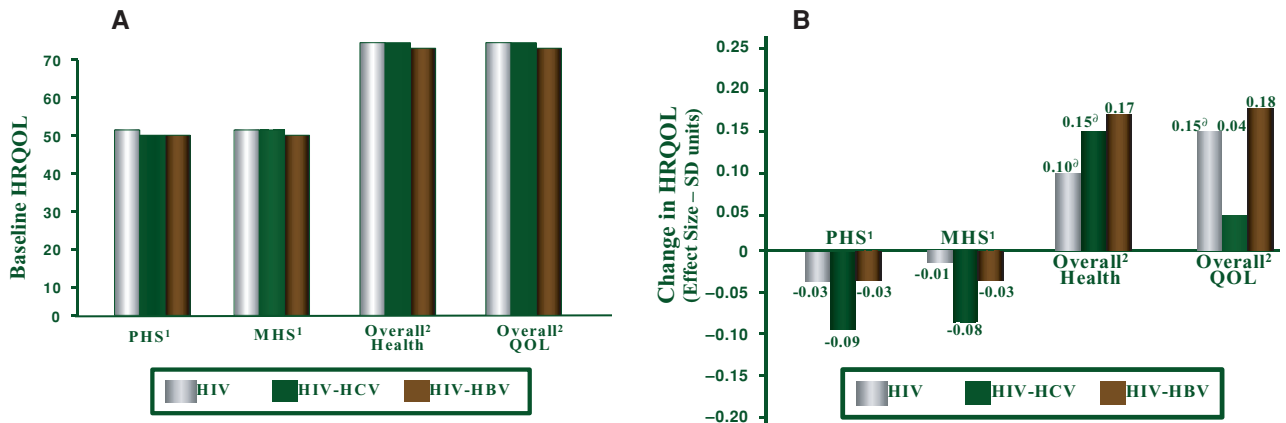


Figure 3. Baseline (A) and change in health-related quality of life (B) comparisons between HIV-monoinfected versus -coinfected patients. (A) displays the baseline health-related quality of life (HRQOL) comparisons between HIV-monoinfected (light gray bars), HIV-HCV-coinfected (dark gray bars), and HIV-HBV-coinfected (black bars) patients. There were no differences in the mean (SD) physical component summary score, PHS (50.5 [9.6] vs 49.5 [9.7] vs 49.8 [10.2]), mental component summary score, MHS (50.3 [9.7] vs 49.8 [9.9] vs 49.3 [10.7]), overall health (72.5 [21.0] vs 70.3 [22.0] vs 69.3 [21.4]), overall quality of life (72.0 [23.0] vs 70.6 [23.7] vs 68.5 [25.0]) between the three groups. All *p* values > 0.05. B: The unadjusted change in the HRQOL over time expressed as effect size (ES = Δ score/baseline SD) between the HIV-monoinfected (light gray bars), HIV-HCV-coinfected (dark gray bars), and HIV-HBV-coinfected patients (black bars). The PHS and MHS for all study groups decreased over time. However, the change was not clinically or statistically significant for the HIV-monoinfected (effect size [ES] for PHS = -0.03 and MHS = -0.09), the HIV-HCV-coinfected (ES for PHS = -0.09 and MHS = -0.08), or the HIV-HBV-coinfected group (ES for PHS = -0.03 and MHS = -0.03) (All *p* > 0.05). The HIV-monoinfected group reported statistically significant improvement in overall health (ES = 0.10, *p* = 0.0002) and overall QOL (ES = 0.15, *p* < 0.0001) over time. The HIV-HCV-coinfected group reported statistically significant improvement in overall health (ES = 0.15, *p* = 0.002) but not in overall QOL (ES = 0.04, *p* = 0.2). All ES were less than 0.20. The HIV-HBV-coinfected group reported statistically and clinically insignificant improvements in overall health (ES = 0.17, *p* > 0.05) and quality of life (ES = 0.18, *p* > 0.05) over time. ¹*t*-scores, ²linearly transformed score, and ¶*p* < 0.002.

CLINICAL CHARACTERISTICS. Compared with HIV-monoinfected patients, those with HIV-HBV coinfection were more likely to report a history of an AIDS-defining illness (48% vs 36%, *p* = 0.05), CD4 counts that were below 200 (61% vs 50%, *p* = 0.03), and had major depression (41% vs 29%, *p* = 0.0003). The use of antiretroviral drugs was similar in both groups. There were no differences in the prevalence of medical comorbidities between groups (Table 2). **HRQOL.** As shown in Figure 3A and Table 3, there was no difference in the unadjusted or adjusted baseline PHS, MHS, overall rating of health, overall QOL between the HIV-monoinfected and HIV-HBV-coinfected groups. There was also no difference in the number of disability days between the two groups (3.1 ± 6.1 vs 3.2 ± 5.5 days; *p* > 0.05). Similar to the HIV-monoinfected group, the HIV-HBV-coinfected group reported decrements in the PHS and MHS and improvements in the overall health and overall QOL scores over time (Figure 3B). However, none of these HRQOL changes, including changes in disability days (data not shown), were statistically or clinically significant. Both groups reported similar changes in the mean scores over time for all measures (all *p* > 0.05).

DISCUSSION

This analysis of data from a national probability sample of HIV-infected adults receiving care in the contiguous United

States reveals that HIV patients coinfecting with chronic viral hepatitis (HCV or HBV) have a self-reported burden of disease that is similar to those with HIV monoinfection. Furthermore, our analysis suggests that coinfecting and monoinfected patients experience similar changes in HRQOL over time. Therefore, contrary to widely held beliefs, these data support our *a priori* hypothesis that patients with HIV do not experience a synergistic decrement in their HRQOL in the setting of HCV or HBV coinfection. In fact, we failed to find even an additive effect of coinfection on HRQOL. We observed several differences in the socio-demographic and clinical characteristics between the HIV-monoinfected and -coinfected groups. For example, the HIV-HCV-coinfected group was more likely to be socio-economically under-privileged, the HIV-HBV-coinfected group was more likely to be depressed, and both coinfecting groups were slightly more likely to report recent IVUDU compared to the monoinfected patients. Despite these differences, the HRQOL decrement engendered by HIV remains constant in the setting of HCV or HBV coinfection. This finding is at odds with the well-described negative synergism between HIV and HCV coinfection on hard clinical outcomes such as liver disease progression, hospital admission, resource utilization, and mortality (2–7), and reinforces the notion that patient-oriented outcomes like HRQOL behave differently than traditional clinical outcomes.

These data are relevant not only to the thousands of HIV patients coinfecting with chronic viral hepatitis, but also to the physicians who provide care and counseling to this

Table 3. Results of Multivariable Regression Analyses. Adjusted Differences Between HIV-Monoinfected and -Coinfected Groups

| HRQOL | Adjusted Score Difference | p Value |
|--------------------------|---------------------------|---------|
| PHS | | |
| HIV (<i>reference</i>) | — | — |
| HCV coinfection | 0.45 | 0.37 |
| HBV coinfection | 0.14 | 0.84 |
| MHS | | |
| HIV (<i>reference</i>) | — | — |
| HCV coinfection | 0.76 | 0.19 |
| HBV coinfection | -0.44 | 0.57 |
| Days in bed | | |
| HIV (<i>reference</i>) | — | — |
| HCV coinfection | 0.15 | 0.69 |
| HBV coinfection | -0.38 | 0.46 |
| Overall health | | |
| HIV (<i>reference</i>) | — | — |
| HCV coinfection | 0.55 | 0.67 |
| HBV coinfection | -0.80 | 0.65 |
| Overall QOL | | |
| HIV (<i>reference</i>) | — | — |
| HCV coinfection | 1.74 | 0.25 |
| HBV coinfection | -2.77 | 0.18 |

HCV = chronic hepatitis C; HBV = chronic hepatitis B; PHS = physical health summary score; MHS = mental health summary score; HRQOL = health-related quality of life.

Multivariate linear regression models used to adjust for demographic, socioeconomic, risk group, coexisting comorbidity, and HIV-related variables. No comparisons were significant after Bonferonni correction. Depression was excluded from the analysis using MHS as the outcome variable.

burgeoning population. While making decisions regarding treatment for their patients, physicians use a network of data regarding traditional clinical outcomes, economic outcomes, and patient-centered outcomes like HRQOL. For example, recent clinical trial data indicate that treatment of HCV in eligible coinfecting patients is effective and improves the short-term traditional clinical outcomes (*i.e.*, virologic response). However, a subset of coinfecting patients may not be eligible for treatment or may defer treatment altogether. HRQOL outcomes become particularly relevant for this subset of patients. In light of this, our results suggest that clinical trials in coinfecting patients should incorporate both traditional outcomes (*e.g.*, virological response) and HRQOL, as there is a chance that successfully treating HCV may not produce HRQOL improvements in these patients, despite the positive effect on HRQOL in non-HIV patients with HCV. Our results are also important from a health economic standpoint. Commonly employed assumption of a negative synergism between HIV and chronic viral hepatitis overstates the case for active treatment in cost-effectiveness analyses. Our data may be useful in performing future cost-effectiveness analyses of competing management strategies for HIV-infected individuals with HCV or HBV coinfection.

Although we did not include a healthy control group in the present analysis, we have previously compared the HRQOL of the HCSUS sample with the age and gender matched U.S. general population norms (17). In this previous study, we found that the physical functioning was similar for patients with asymptomatic HIV *versus* the U.S. general population, but was worse for those with symptomatic HIV or AIDS.

Emotional well-being was comparable among patients with various stages of HIV, but was significantly worse than the U.S. general population. Taken together, these results suggest that the HRQOL in HIV is lower than U.S. general population norms, independent of coinfection, and that the presence of HCV or HBV coinfection does not lead to a further decrement in HRQOL.

Several explanations may account for our findings. First, the impact of chronic viral hepatitis on the well-being of an otherwise healthy individual is likely to be greater than on an individual with a coexisting chronic illness, possibly due to different internal standards, values and/or conceptualization of HRQOL (43). In other words, the impact of a new comorbidity depends upon the severity of baseline disease (44). For example, the presence of HCV in a person with coexisting mild hypertension may have a larger impact on HRQOL than in a person with HIV. Second, the lack of impairment in HRQOL in HIV patients with HCV or HBV coinfection may reflect a floor effect where any further decrement is not possible. Third, HIV-related symptoms are one of the strongest predictors of HRQOL in HIV-monoinfected patients (18). The presence of HCV or HBV coinfection did not affect the presence or number of HIV-related symptoms in our cohort and this may explain the stability of HRQOL between groups. Fourth, impaired HRQOL in HCV may be related to the knowledge of having the disease itself, and not a direct consequence of the disease process *per se* (45, 46). It is possible that the HRQOL decrements in two diseases may not be synergistic when these decrements are based exclusively on knowledge of disease status as opposed to when HRQOL impairments are a result of the direct consequences of disease processes. Finally, there may be important differences in HRQOL that were simply not detected in this study, possibly because our generic HRQOL instrument was insufficiently sensitive to these differences (47).

Not only do our data support our hypothesis, but also they are convergent with recent data from similar coinfecting cohorts. For example, in a cross-sectional analysis Fleming *et al.* found that HRQOL in a tertiary care cohort with HIV-HCV was similar to groups with HCV or HIV alone (11). Our study corroborates these data by showing similar results in a large, nationally representative sample of patients. We also extend these data by evaluating changes in HRQOL over time in HIV-monoinfected and -coinfecting patients. Whereas Fleming *et al.* compared cross-sectional baseline HRQOL data between groups, we compared both cross-sectional and longitudinal data. Using these methods, we not only found similar cross-sectional HRQOL at baseline, but also found no important between group differences in the HRQOL over time.

Our analysis has several strengths. First, the HCSUS sample is representative of all HIV-infected adults receiving care in the United States in 1996. Unlike the previously published studies of HRQOL among patients with HIV or HCV, our study using this national probability sample does not suffer from the potential selection bias associated with

recruitment limited to treatment trials or tertiary care clinics. Our results are therefore generalizable to all HIV-infected patients with known coinfection, and are not limited to highly selected populations. Second, we used several constructs to comprehensively assess HRQOL. Similar findings on all measures increase the reliability of our results. Third, a large sample size, the presence of an HIV-monoinfection control group, and a longitudinal study design increase the internal validity of our findings. Fourth, we adjusted our results for covariates that influence HRQOL in order to identify the independent effect of coinfection. Last, ours is the first description of the prevalence, clinical, socio-demographic, and HRQOL characteristics of HIV patients with HBV coinfection.

Our analysis also has several limitations. First, in the absence of viral (RNA) tests in 35% of the initially selected cohort, our case ascertainment relied upon the presence of a positive serology (89 of 279 [32%] the final HCV-coinfected group) or physician note indicating the presence of HCV (38 of 279 [13%] of the final HCV-coinfected group). The presence of a positive serology is a reliable indicator of chronic HCV coinfection in HIV (10). The reliability of physician note indicating HCV coinfection cannot be determined. However, our hierarchical strategy for diagnosing HCV was likely to be specific but not overly sensitive, thereby resulting in an underestimation of the true prevalence of HCV. In contrast, our strategy for identifying HBV was sensitive, but may have lacked specificity. Importantly, our strategies captured those with known coinfection and this is particularly relevant as the data suggesting that the HRQOL decrement in HCV may be related to the knowledge of having the disease (45, 46). Second, because we lacked reliable variables, we could not determine the severity of underlying liver disease in the study population. However, this is unlikely to confound the results of our analysis as the degree of hepatocyte necrosis, inflammation, and fibrosis do not correlate with impairment in HRQOL in HCV monoinfection (20, 21). We also could not ascertain the progression of chronic liver disease in the coinfecting individuals. Therefore, this lack of data regarding advanced liver disease represents a potential omission bias. However, given the absence of HRQOL differences between groups, this omission bias is unlikely to compromise the validity of our results. Third, although most of the HCSUS sample (82%) was receiving antiretroviral therapy including protease inhibitors and nonnucleoside reverse transcriptase inhibitors, new agents have become available since the collection of HCSUS data. As highly active antiretroviral therapy is associated with improvements in HRQOL in HIV patients, it is likely that the impact of coinfection of HRQOL may be more significant now. Although these potential secular time trends might affect the generalizability of our data, we nonetheless believe our results are valid given the large sample size, extensive follow-up, robustness of the results across multiple HRQOL constructs, and corroboration with more recent (although smaller) studies addressing similar questions.

In conclusion, our analysis of data from a national probability sample of HIV-infected adults receiving care in the contiguous United States indicates that patients coinfecting with chronic viral hepatitis (HCV or HBV) have a self-reported burden of disease similar to those with HIV monoinfection. These data are relevant not only to the thousands of HIV patients coinfecting with chronic viral hepatitis, but also to the physicians who provide care and counseling to this burgeoning population. Our results are also important from a health economic standpoint and may be useful in performing future cost-effectiveness analyses of competing management strategies, and also in designing clinical trials for HIV-infected individuals with HCV or HBV coinfection.

SIGNIFICANCE OF RESEARCH

Chronic viral hepatitis in HIV-infected patients has emerged as a significant public health problem. Little is known about the health burden of chronic viral hepatitis in HIV-infected patients. We compared health-related quality of life (HRQOL) of patients with HIV and hepatitis C virus (HCV) or HIV and hepatitis B virus (HBV) coinfection to those with HIV monoinfection. We found no differences in the baseline and change over time scores for multiple HRQOL domains between the HIV-monoinfected and the HIV-HCV- and HIV-HBV-coinfecting groups. These data are relevant in counseling coinfecting patients regarding the impact of coinfection on HRQOL, and are important in designing clinical trials and conducting cost-effectiveness analyses including this vulnerable cohort.

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