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Prevalence and Predictors of Chronic Liver Disease in an Urban HIV Population

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PREVALENCE AND PREDICTORS OF CHRONIC LIVER DISEASE IN AN URBAN HIV POPULATION

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Chronic liver disease (CLD) is a leading cause of morbidity and mortality in HIV-infected individuals. The purposes of this study were to determine the prevalence and etiologies of CLD in an urban HIV-infected population and to identify CLD risk factors. We conducted a retrospective chart review of 799 HIV-infected patients seen at four New Haven health centers from 2002 to 2003. We applied the New Haven County Liver Study definition to identify patients with CLD. 65% were male, 44% were African American, and 23% were of Hispanic ethnicity. The mean age was 45 years. 30% had a history of alcohol abuse. 35% reported injection drug use as their HIV risk factor. Heterosexual contact and men having sex with men (MSM) were reported in 31% and 16% of cases. 50% of patients had a diagnosis of AIDS. 60% percent of patients had CLD. Over 50% of cases of CLD were attributed to chronic hepatitis C (HCV), either alone or with coexisting alcoholic liver disease. Alcoholic liver disease alone, hepatitis B virus (HBV), HAART-induced liver disease, and non-alcoholic liver disease (NAFLD) accounted for smaller percentages. 84% of patients were on HAART, but only 3.6% of patients with positive HCV or HBV serologies were on treatment for CLD. 75% of patients received pneumococcal and influenza vaccines, but only half of eligible patients received hepatitis A and B vaccines. In multivariate analysis, alcohol abuse and positive HCV status were associated with CLD. CLD is prevalent in our population. Preventive care and treatment for CLD are being overlooked in many. Vaccines, treatment for viral hepatitis, and strategies for reducing drug and alcohol abuse are priorities.

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INTRODUCTION

I. Epidemiology of HIV and AIDS

An estimated 1,039,000 to 1,185,000 persons in the United States are currently living with HIV/AIDS, including 250,000 to 320,000 who are unaware of their serostatus [1]. Each year, approximately 40,000 new HIV infections occur, 70% of which occur amongst men, although a growing number of women are affected yearly [2]. Men who have sex with men (MSM) currently represent the largest proportion of cases by transmission category on both national and state-wide levels (49% in 2003), but heterosexuals and intravenous drug users are also significantly affected (34% and 19%, respectively in 2003) [2].

In the absence of treatment, HIV progresses to full-blown AIDS in the majority of individuals. It is estimated that 10 to 12 percent of HIV-infected patients progress to AIDS within the first 5 years following infection, and over 50% develop AIDS within 10 years [3,4] Approximately five percent of individuals have stable CD4+ T cell counts and no symptoms even after 12 or more years [5]. The progression from HIV to untreated AIDS is recognized as being universally fatal. Only a very small percent of people with untreated AIDS survive five years after they are diagnosed.

Reports by the CDC have documented steep declines in AIDS mortality within the United States over the last decade (from 50,000 deaths per year in 1995 to 16,000 in 2004 [2,6]. This trend is mostly attributed to the advent of potent antiretroviral therapy, which gained widespread acceptance and use in the mid 1990s. In recent years, however,

the rate of decline has slowed, due to emerging problems such as unequal access to HIV care, incomplete adherence to therapeutic regimens, and viral resistance to therapy.

The distribution of HIV and AIDS cases by demographic characteristics has also changed substantially over time. The disease disproportionately affects ethnic minorities, such as African Americans and Hispanics, women, and adolescents, and recent studies have shown that infection and mortality rates are in fact increasing within several subsets of these populations. The largest proportional increase in new cases has occurred amongst heterosexual women, from approximately 9% in 1992 to 27% in 2003. In addition, the proportion of cases in African Americans has increased from 25% to 50% of the total and that of Hispanics has increased 14% to 20% over two decades. Minority Americans currently represent the majority of new cases (71%), as well as the largest proportion of people living with AIDS (64%). This puts certain populations, such as minority MSM and minority women at particularly high risk [2, 6-10].

II. Epidemiology of Chronic Liver Disease (CLD)

Chronic liver disease (CLD) is one of the ten leading causes of mortality in the United States, and accounts for over 25,000 deaths each year [11,12]. Although overall mortality from CLD has shown a gradual decline over the last three decades, death rates within certain subgroups have increased over time. For example, CLD deaths attributable to hepatitis C increased 220% between 1993 and 1998, while mortality from other causes of CLD decreased or remained unchanged over the same time period [12]. Cirrhosis and CLD also disproportionately affect men, certain ethnic minorities, and the middle-aged population. In fact, CLD ranks as the fifth leading cause of death in men between the

ages of 45 and 64 years, and accounts for more than twice as many deaths amongst Native Americans, Hispanics, and African Americans than other ethnic groups [11]. Alcohol and viral hepatitis are considered the two most important etiologies for CLD; however, NAFLD (non-alcoholic fatty liver disease) is increasingly being recognized as a common cause. Risk factors for chronic liver disease include low socioeconomic status, drug use, exposure to environmental and industrial toxins, and genetic predisposition.

Alcohol use is one of the most significant causes of chronic liver disease in the United States. Alcoholic liver disease can be classified into three distinct, often overlapping histologic categories: steatosis, acute alcoholic hepatitis, and cirrhosis. While steatosis is often asymptomatic and thought to be reversible with abstinence, hepatitis is much more severe, with up to 80% of patients progressing to cirrhosis or hepatocellular carcinoma upon continued ingestion of alcohol [13]. There is a direct correlation between alcohol consumption and liver-related mortality [14]. Of the 14 million Americans who meet criteria for alcoholism, 2 million are suspected of having significant liver disease. It is estimated that men who drink more than 80 g/d of ethanol for several years will be at substantial risk of developing clinical liver disease [15]. Women who ingest a similar amount are up to four times more likely than men to develop alcoholic liver disease, and they exhibit a tendency to progress to cirrhosis even with abstinence [16,17].

Hepatitis C virus is the single most common cause of chronic liver disease, and poses a significant public health problem in the United States and worldwide. Infection with HCV causes chronic hepatitis in 80% of patients, and up to 25% of monoinfected individuals develop cirrhosis and end-stage liver disease within the next thirty to forty

years [18]. Chronic liver disease from HCV infection is currently the most common indication for liver transplantation, accounting for up to 35% of orthotopic transplant recipients [19]. Although treatment response varies by genotype, treatment for HCV genotype 1 (the genotype that infects the vast majority of individuals) has thus far been rather disappointing, with the best response rates to interferon and ribavirin reported at 40% [20, 21]. Alcohol use and HCV infection frequently coexist in patients, and many studies have shown that their effects are synergistic in promoting liver damage, hastening both cirrhosis and hepatocellular carcinoma [22,23].

Although the development of the hepatitis B vaccine in the mid-1980's is considered one of the major achievements of modern medicine, HBV infection remains an important cause of morbidity and mortality worldwide. One analysis found that the rate of HBV-related hospitalizations, cancers, and deaths in the United States had more than doubled over the last decade [24]. The manifestations of chronic HBV infection range from an asymptomatic carrier state to chronic hepatitis, cirrhosis, and hepatocellular carcinoma. Long term studies have shown that the majority of individuals who are HbsAg positive remain asymptomatic [25]; however, there is still approximately a 15% lifetime risk of developing cirrhosis or hepatocellular carcinoma [26]. Like HCV, treatment for HBV has been suboptimal, which may be complicated by the fact that infected patients often have comorbid disease such as chronic HCV infection and alcoholic hepatitis.

The prevalence and risk factors for NAFLD are not well-described, although it is a condition currently under active investigation. NAFLD is frequently associated with obesity, insulin resistance, type 2 diabetes mellitus, and hyperlipidemia. In unselected

populations, the prevalence is reported to range between 3 and 23 percent [27, 28]; however, in patients with diabetes, the prevalence may be as high as 63% [29]. Symptomatic NAFLD is extremely uncommon, but there remains a small risk of cirrhosis, hepatocellular carcinoma, and mortality from end stage liver disease, reported in retrospective studies as occurring in fewer than 3% of patients with NAFLD [30].

III. Relationship between CLD and HIV

Since the introduction of HAART, the life expectancy of patients with HIV has dramatically increased [31, 32]. The use of HAART has led to declines in opportunistic infections and acute bacterial infections, both of which were implicated in the majority of AIDS-related deaths during the pre-HAART era. As a result of increased longevity, mortality and morbidity due to other co-existing conditions, such as liver cirrhosis, renal failure, cardiac disease, and cancer, are assuming greater importance.

End-stage liver disease in particular has become a leading cause of death amongst HIV-infected patients, accounting for up to 50% of deaths amongst hospitalized HIV positive patients [33]. Most etiologies of liver disease in these patients are similar to those in the general population, such as chronic HCV, chronic HBV, and alcoholic hepatitis. However, the high risk of hepatotoxicity from antiretroviral drugs and the effects of immunosuppression on the natural courses of these diseases present additional challenges in HIV-infected patients.

Due to the shared route of transmission, coinfection with HCV and HIV has become an especially common diagnosis, reported to affect up to 30% of all HIV-infected patients [34]. Coinfection is particularly prevalent in IV drug users, whose rates of

coinfection may range from 75% to 90% [35-37]. Several studies have established that HIV infection modifies the natural history of HCV infection, accelerating the progression from chronic hepatitis to cirrhosis and end-stage liver disease and placing HIV-positive patients at increased risk for morbidity and mortality secondary to these conditions. [33, 38-41]. The effect of HCV infection on the natural history of HIV, however, is a much more controversial issue and results have been conflicting thus far. While some studies suggest that certain HCV genotypes or higher HCV viral loads are associated with more rapid progression to AIDS or death [42-44], others detect no correlation between HCV infection and progression of HIV [45-47].

Like HCV, hepatitis B virus is transmitted through blood and body fluids, and therefore may be found in HIV-infected populations. In the absence of treatment for HBV, there is an increased frequency of cirrhosis in coinfected patients compared with HIV or HBV-monoinfected patients [48, 49]. Liver-related mortality in HIV/HBV coinfection is reported to be 14-fold higher than that for either virus alone, and patients who have HIV are three to six times more likely to develop chronic hepatitis B following occult infections compared with patients who do not have HIV [50]. There are several medications, such as lamivudine and tenofovir, which are approved to treat both HIV and HBV.

Although clinical manifestations of liver toxicity are somewhat rare from antiretroviral therapy alone, mild to moderate elevations in liver transaminases (AST and ALT) are relatively common in patients on HAART. Chronic viral hepatitis, alcohol ingestion, and use of other drugs are co-factors that increase the incidence of elevated hepatic markers in HIV patients. Several studies have, furthermore, suggested that HCV

increases the risk of hepatotoxicity from antiretroviral regimens [51, 52], which complicates the fact that suppression of HIV viral load in coinfected patients may decrease the rate of HCV progression [53]. This is particularly true nevirapine, full-dose ritonavir, and tipranavir, which are associated with increased risk of hepatotoxicity in coinfected patients. Although the overwhelming evidence supporting the benefit of antiretroviral therapy indicates that HAART should not be withheld in coinfected patients, liver injury may be one of the major limiting factors in the effectiveness of therapy.

Alcohol abuse frequently coexists with HIV, and may play a significant role in determining patient outcome. Alcoholism is associated with greater mortality and morbidity, increased symptom burden, poorer compliance with antiretroviral therapy, more rapid progression of disease, increased severity of comorbid disease (particularly chronic HCV infection), and greater risk of viral resistance [54-57]. Because alcohol abuse, HCV, and HBV may often act synergistically in accelerating liver damage, HIV-infected patients with multiple risk factors for chronic liver disease are at particular risk for liver-related morbidity and mortality.

Risk factors for steatohepatitis in the non-HIV population are also valid in individuals with HIV. However, HIV-infected patients who are treated with NRTIs and d4T in particular may be especially prone to severe macrosteatosis. Protease inhibitors (PIs) and nucleoside reverse transcriptase inhibitors (NRTIs) appear to act synergistically in development of HIV-related lipodystrophy, and the length of therapy with these medications positively correlates with the amount of lipodystrophy [58]. Consequently, HIV-positive patients on HAART tend to have a higher incidence of insulin resistance

and visceral abdominal obesity. Furthermore, insulin resistance and the incidence of lipoatrophy are increased significantly in patients with HIV/HCV coinfection compared with those with HIV alone, which may also predispose to NAFLD and lead to hepatic fibrosis [59].

SPECIFIC AIMS

The burden of chronic liver disease is considerable in HIV-infected patients; however, very few studies have described this phenomenon in an entire urban HIV population. Therefore, the purposes of this study were:

1. To calculate the prevalence and etiologies of chronic liver disease in urban HIV clinics.
2. To identify risk factors associated with an increased risk of chronic liver disease in this population.

METHODS

Subjects. This study is a retrospective chart review of HIV-infected patients followed at four different urban health centers in New Haven (Nathan Smith Clinic, Hill Health Center, St. Raphael's Hospital/Haelen Center, and Fair Haven Clinic and Health Center). Patients were included if they were HIV seropositive, and had attended clinic between 2002 and 2003; abstracted data, however, was not limited to this twelve month period but also included information prior to 2002 and following 2003. Any data that was dated past January 1, 2006 was not abstracted. A 50% random sample was used at Nathan Smith Clinic and the St. Raphael's Hospital/Haelen Center, while 100% samples were included from the other sites. The chart review was started prior to my involvement in the study; therefore, most of the abstraction at Hill Health Center and Fair Haven Clinic was carried out by other individuals, while abstraction at Nathan Smith Clinic and Haelen Center was completed by me.

Data Collection. Data were abstracted from the patient charts by trained individuals using a standard data collection form; charts were in the form of either computerized or paper records depending on site. Abstracted data included demographic characteristics, such as age, gender, race/ethnicity, height, weight, and town of residence; social practices such as HIV exposure and alcohol abuse; clinical and laboratory data regarding liver function, HIV progression, hepatitis and HIV serology, vaccinations (hepatitis A and B, pneumococcal, and influenza), and treatment history. Alcohol abuse was defined as alcohol intake of > 3 drinks per day for 10 years, hospitalization or rehabilitation,

withdrawal, history of DUI, or physician impression of alcoholism. Liver-related clinical data consisted of biopsy results, clinical events (hepatic encephalopathy, variceal bleed, ascites, spontaneous bacterial peritonitis (SBP), hepatorenal syndrome, or cholangitis), and diagnostic imaging results (US, CT, MRI, liver/spleen scan, or endoscopy). In addition, liver transaminases (AST, ALT, alkaline phosphatase, and GGT), iron studies, and triglycerides were recorded (first, last, and all abnormal tests ≥ 6 months apart). HIV-related data included immunologic markers recorded at intervals of ≥ 6 months (CD4, viral load, WBC, % lymphocyte) and diagnosis of AIDS, based on AIDS-defining illnesses (ADIs) or CD4 count. ADIs were defined according to the CDC 1993 revised classification system [60]. Treatment for chronic liver disease (CLD), as well as antiretroviral medication history, was recorded. Abstracted information for CLD included treatment regimen (standard interferon alfa, pegylated interferon alfa, ribavirin, lamivudine, adefovir, or Cellcept), length of treatment, reason for discontinuation, and treatment response (ETR and SVR). Data regarding antiretroviral medication included drug name, dose, and duration of use.

Assessment of CLD. Patient charts were screened for evidence of CLD using the New Haven County Liver Study (NHCLS) case definition. This study defines chronic liver disease as: two sets of abnormal LFTs (elevated ALT, elevated AST, or concurrently elevated alkaline phosphatase and GGT) ≥ 6 months apart, a liver-related clinical event (hepatic encephalopathy, variceal bleed, ascites, or SBP), a diagnostic imaging result indicating chronic hepatitis, cirrhosis, or hepatocellular or cholangiocarcinoma, or a biopsy result consistent with chronic hepatitis, cirrhosis, or hepatocellular or

cholangiocarcinoma. The classification of cirrhosis was made if biopsy showed features consistent with cirrhosis, or if diagnostic imaging studies showed positive signs such as nodular/shrunken liver, portal hypertension, colloid shift, ascites, varices/collaterals, and/or cirrhosis. In those patients who satisfied the case definition for CLD, a diagnostic impression of etiology was made based on clinic notes and laboratory data. Etiologies included alcoholic liver disease (based on classification of alcohol abuse), chronic hepatitis B, chronic hepatitis C, HIV antiretroviral induced liver disease, or NASH/fatty liver. Chronic hepatitis B was defined as positive HBV sAg or positive HBV eAg on serology. Chronic hepatitis C was defined as positive ELISA, RIBA, or PCR. "Possible" HCV infection was defined as positive ELISA or RIBA results, without quantitative or qualitative PCR results or genotype results. "Definite" HCV infection was identified as positive PCR or HCV genotype results. Patients could be classified as having more than one etiology.

Assessment of Clinical Care. Markers of clinical care included treatment for CLD and HIV, gastroenterology referrals, and vaccination history. Because CLD treatment was defined as antiviral therapy, only patients with evidence of HCV infection or HBV infection were included in this analysis. Patients included in HAV or HBV vaccination analysis were those who did not have serological evidence of chronic disease or previous immunity. Only one dose of each vaccine was required to qualify a patient as having a positive vaccination history.

Statistical Analysis. Descriptive statistics were expressed as means and percentages for continuous and categorical variables, respectively. CLD was the outcome measured in all analyses; univariate chi-squared tests were used to determine predictors. Baseline variables examined were age (dichotomous variable expressed as >/=mean age or <mean age); gender; race (white, African-American, or other); ethnicity (Hispanic/Latino or not Hispanic/Latino); HIV risk factor (IDU, MSM, IDU/MSM, heterosexual contact, or other); alcohol abuse; CD4 count (dichotomous variable expressed as <200 or >/=200); viral load (dichotomous variable expressed as <10,000or >/=10,000); infection with HCV; use of antiretroviral therapy; and AIDS diagnosis.

Liver function test abnormalities were examined in several different ways. For patients who were on HAART and had AST or ALT values recorded before and after initiation of treatment, "pre-HAART" and "post-HAART" values were recorded. The pre-HAART values were those that were closest to initiation of HAART; these were defined as that patient's baseline LFTs. The post-HAART values were the highest values recorded following initiation of HAART. The means of these pre-HAART and post-HAART values, as well as the mean percent change (delta), was described. The mean values and deltas were also expressed as function of whether patients had CLD or chronic HCV infection.

HIV-related tests (CD4 count and viral load) were only used in statistical analyses if they were recorded prior to initiation of HAART or in the absence of antiretroviral therapy.

RESULTS

Data from a total of 799 patients were reviewed (262 patients from Nathan Smith Clinic; 244 patients from Hill Health Center; 237 from St. Raphael's Hospital/Haelen Center; and 56 from Fair Haven Clinic and Health Center). Demographic characteristics of the study population are shown in table 1, both as a whole and separately by clinic. The majority of patients were male (65%) and African-American (44%), and these

TABLE 1: DEMOGRAPHIC CHARACTERISTICS

		ALL PTS* (N=799)	NSC (N=262)	HHC (N=244)	HC/HSR (N=237)	FHCHC (N=56)
Gender (%)	Male	64.7	61.1	70.9	62.5	62.5
	Female	34.0	37.0	27.5	37.1	35.7
	Transgender	0.6	1.1	0	0.4	1.8
	Unknown	0.7	0.8	1.6	0	0
Age (mean; years, range)		44.7 (8-81)	45.9 (26-75)	43.5 (8-67)	45.8 (28-81)	40.0 (9-62)
Race (%)	White	20.1	19.9	10.3	32.1	14.3
	Black	44.1	29.8	58.2	50.2	23.2
	Asian	0.5	0	0.8	0.8	0
	Other	2.4	5.3	0.4	1.3	1.8
	Unknown	32.9	45.0	30.3	15.6	60.7
Ethnicity (%)	Hispanic/Latino	22.7	14.9	28.3	16.5	60.7
	Not Hispanic/Latino	51.9	17.2	68.9	76.3	37.5
	Unknown	25.4	67.8	2.8	7.2	1.8
Town (%)	New Haven	61.6	37.0	82.0	62.0	85.7
	New Haven County	19.9	20.2	10.6	31.2	10.7
	Non-New Haven County	6.9	15.7	0.4	4.7	3.6
	Unknown	11.6	27.1	7.0	2.1	0
Alcohol Abuse (%)	Yes	30.4	24.8	34.4	32.9	28.6
	No	59.0	64.1	59.0	50.6	69.6
	Unknown	10.6	11.1	6.6	16.5	1.8

*NSC = Nathan Smith Clinic (Yale New Haven Hospital)
HHC = Hill Health Center
HC/HSR = Haelen Center (Hospital of St. Raphael)
FHCHC = Fair Haven Clinic and Health Center

findings were consistent across all four clinics. At Hill Health Clinic and Haelen Center, over 50% of patients were African-American. The mean age was 45 years. Overall, approximately 23% of patients were found to be of Hispanic or Latino heritage, although there were many patients for whom ethnicity was not reported. Ethnicity varied widely by clinic, with Fair Haven Clinic having the largest proportion of Hispanic/Latino patients (61%). Although the majority of patients from all health centers were from New Haven (62%), Nathan Smith Clinic had the largest percentage of patients from outside New Haven County. This finding is consistent with the fact that Nathan Smith Clinic is a university affiliate and therefore likely to receive a substantial number of referrals. Approximately 30% of patients were found to have a history of alcohol abuse.

Table 2 summarizes HIV-related characteristics. The majority of patients in this study population acquired HIV through intravenous drug use (35%); at Hill Health Center, IDU made up over 50% of cases by transmission category. Heterosexual contact and MSM were also major sources of HIV exposure, accounting for 31% and 16% of cases, respectively. The mean pre-HAART CD4 count in this population was 296, and the mean pre-HAART viral load was 116,233. Over half of all patients were diagnosed with AIDS, and of these, most qualified by having a CD4 count of 200 or below or by having both an AIDS-defining illness as well as a CD4 count under 200.

Liver-related characteristics are recorded in table 3. About 60% of patients met the CLD case definition; of these, the majority qualified by having two sets of abnormal LFTs six months apart. Of note, 84% of all patients were found to have abnormal LFTs at some point in their clinical care; however, only 57% of these met the CLD case

TABLE 2: HIV CHARACTERISTICS

		ALL PTS (N=799)	NSC (N=262)	HHC (N=244)	HC/HSR (N=237)	FHCHC (N=56)
HIV Exposure (%)	IDU	34.5	32.8	50.4	23.6	19.6
	MSM	16.2	17.6	7.8	22.4	19.6
	MSM/IDU	1.0	0.4	2.1	0.4	1.8
	Heterosexual	31.3	27.1	22.9	43.0	37.5
	Other	0.8	1.5	0	0	3.6
	Unknown	16.2	20.6	16.8	10.6	17.9
CD4 count (mean, range)*		296 (1-1520)	292 1-1520)	307 (2-1155)	274 (2-1163)	368 (1-1391)
Viral load (mean, range)†		116233 (1-4100K)	104796 (50-750K)	78262 (50-1380K)	187026 (50-4100K)	87817 (400-817K)
AIDS (%)	Yes	52.2	49.2	51.6	59.5	37.5
	CD4 count	50.8	53.5	54.8	45.4	47.6
	ADI°	6.5	8.5	3.2	7.8	4.8
	Both	36.7	30.2	30.9	46.8	42.8
	Unknown	6.0	7.8	11.1	0	4.8
	No	43.4	44.3	46.7	35.0	60.7
	Unknown	4.4	6.5	1.7	5.5	1.8

*CD4 count included only if patient had values recorded prior to ART;
N=666 (all), N=246 (NSC), N=195 (HHC), N=181 (HC/HSR), N=44 (FHCHC)
†Viral load included only if patient had values recorded prior to ART;
N=603 (all), N=224 (NSC), N=183 (HHC), N=152 (HC/HSR), N=44 (FHCHC)
°AIDS-defining illness

TABLE 3: LIVER-RELATED CHARACTERISTICS

		ALL PTS (N=799)	NSC (N=262)	HHC (N=244)	HC/HSR (N=237)	FHCHC (N=56)
CLD case definition (%)	Yes	59.7	57.6	65.2	57.8	53.6
	Biopsy*	8.4	15.9	2.5	8.1	3.3
	Imaging*	13.9	20.5	8.8	14.8	3.3
	Clinical Event*	3.9	5.3	3.8	3.4	0
	LFTs*	94.1	94.7	96.2	90.6	96.7
	No	38.8	42.4	34.8	37.1	46.4
	Unknown	1.5	0	0	5.1	0
HCV Status (%)	Positive	39.8	42.4	44.7	34.2	30.4
	Definite	56.3	64.0	56.9	53.1	17.6
	Possible	43.7	36.0	43.1	46.9	82.4
	Negative	52.8	48.9	43.8	63.7	64.3
	Unknown	7.4	8.8	11.5	2.1	5.4
HBV Status (%)	Positive	4.8	5.3	3.7	6.3	0
	Negative	83.6	85.1	78.3	84.4	96.4
	Unknown	11.6	9.5	18.0	9.3	3.6
LFTs† (mean values, range)	Baseline pre-ART ALT	46 (4-636)				
	Baseline pre-ART AST	52 (5-688)				
	Baseline post-ART ALT	65 (2-638)				
	Baseline post-ART AST	73 (7-998)				

*Patients may qualify for CLD case definition by more than one criteria.
†Significance testing revealed that $p<0.0001$ between mean pre-HAART and mean post-HAART LFTs.

definition through the more stringent LFT criterion. Forty percent of patients were HCV positive by serology, and of these patients, 56% were categorized as having "definite" infection (PCR or genotype results) while the rest had only ELISA or RIBA results and were therefore classified as having "possible" infection. Over 81% of patients with a history of intravenous drug use tested positive for HCV, whereas only 11% of men who have sex with men and 17% of patients with heterosexual HIV risk factors had positive HCV serologies (data not shown). Only about 5% of patients had chronic HBV by serology. Mean baseline pre-HAART ALT and AST were significantly lower than mean baseline post-HAART ALT and AST ($p<0.0001$).

Table 4 describes the etiologies for CLD in the subset of patients who met the NHCLS case definition. Greater than 50% of patients had chronic liver disease as a result of hepatitis C, either alone or with coexisting alcoholic liver disease. Alcoholic liver disease alone made up a substantial proportion of the total number of patients with

TABLE 4: CLD ETIOLOGY

	ALL PTS (N=488)	NSC (N=151)	HHC (N=159)	HC/HSR (N=147)	FHCHC (N=31)
HCV	40.8	37.8	55.4	27.9	41.9
HCV/Alcohol	10.3	11.9	5.0	15.7	3.2
Alcohol	8.6	4.0	7.6	14.3	9.7
HBV/HCV	3.5	6.6	1.9	0	3.2
HBV	2.3	1.3	2.5	2.7	3.2
NASH	2.1	1.3	0.6	4.8	0
HAART-induced liver disease	1.6	0	3.1	0.7	6.5
Alcohol/HBV	1.0	2.0	0	1.3	0
HCV/HAART	1.0	0	2.5	0	3.2
HCV/NASH	0.8	2.6	0	0	0
Alcohol/HCV/HBV	0.4	0	0	1.3	0
Alcohol/HAART	0.4	0	0	0.7	3.2
HBV/HAART	0.4	0	1.3	0	0
Other	3.0	4.0	4.4	0	6.5
Unknown	23.8	28.5	15.7	26.6	19.4

CLD (8.6%), but the percentage varied widely by clinic (4% to 14.3%). Although HBV alone only accounted for 2.3% of the total population, a number of patients were coinfected with HBV and HCV. Other etiologies for chronic liver disease (including HAART-induced liver disease and NAFLD) accounted for smaller percentages; however, almost 18% of patients were found to have more than one etiology for their liver disease.

Table 5 summarizes the clinical care provided to this study population. Approximately 84% of patients were treated with HAART; however, only a very small percentage of patients who were HCV or HBV positive underwent treatment for CLD

TABLE 5: CLINICAL CARE

		ALL PTS (N=799)	NSC (N=262)	HHC (N=244)	HC/HSR (N=237)	FHCHC (N=56)
HAART (%)	Yes	83.5	79.0	79.5	91.1	89.3
	No	16.5	20.0	20.5	8.9	10.7
CLD treatment (%)*	Yes	3.6	8.4	0.9	1.1	0
	No	96.4	91.6	99.1	98.9	100
Gastroenterologist (%)	Yes	3.7	2.7	6.6	5.9	12.5
	No	93.9	96.6	92.2	94.1	87.5
	Unknown	2.34	0.7	1.2	0	0
Vaccines (%)						
Pneumococcal	Yes	74.6	53.0	80.3	87.8	94.6
	No	19.4	44.3	9.4	5.5	5.4
	Unknown	6.0	2.7	10.3	6.7	0
Influenza	Yes	77.7	71.4	72.1	87.3	91.1
	No	16.2	26.0	17.6	5.5	8.9
	Unknown	6.1	2.6	10.3	7.2	0
Hepatitis A†		N=346	N=126	N=82	N=120	N=18
	Yes	50.9	41.3	31.7	74.2	50.0
	No	36.7	57.1	54.9	0.8	50.0
	Unknown	12.4	1.6	13.4	25.0	0
Hepatitis B†		N=317	N=94	N=95	N=95	N=33
	Yes	49.2	44.7	60.0	32.6	78.8
	No	26.2	51.1	29.5	2.1	15.1
	Unknown	24.6	4.2	10.5	65.3	6.1

*Patients only included if they were HCV positive (both "possible" and "definite") or HBV positive; N=338 (all), N=119 (NSC), N=112 (HHC), N=90 (HC/HSR), N=17 (FHCHC)

†Patients were only included if they did not have evidence of current infection or prior immunity.

(3.6%). Treatment for CLD varied significantly by clinic, with the largest percentage (8.4%) being treated at Nathan Smith Clinic. Gastroenterology referrals were provided to between 2.7% and 12.5% of patients, depending on clinic. With respect to vaccination history, 75% and 78% of patients had documented receipt of pneumococcal and influenza vaccines, respectively. However, only about half of patients who did not have evidence of chronic HAV or HBV infection or previous immunity received vaccinations against these pathogens. The history of vaccination varied widely depending on specific clinic; at Haelen Center, almost three-fourths of patients received the hepatitis A vaccine, and at Fair Haven Clinic, approximately 79% of patients were vaccinated against hepatitis B.

In table 6, antiretroviral therapy and liver function tests are compared in patients who either do or do not meet the CLD case definition, as well as in patients who do or do not have serological evidence for chronic HCV infection. The proportion of patients on ART was similar in the group of patients that meet the case definition for CLD as in those who do not. The mean post-HAART LFTs were significantly higher than the mean pre-HAART LFTs in patients who had CLD ($p<0.0001$), as well as in patients who were HCV positive ($p<0.0001$).

TABLE 6: LIVER-RELATED CHARACTERISTICS FOR SUBSETS

		CLD	**No CLD**	**HCV**	**No HCV**
		(N=477)	(N=310)		
ART	Yes	86.4	80.0		
	No	13.6	20.0		
LFTs†	Baseline pre-ART ALT	55.4	29.9	59.1	38.6
	Baseline pre-ART AST	61.6	34.4	68.3	41.8
	Baseline post-ART ALT	81.6	35.0	87.9	51.0
	Baseline post-ART AST	91.0	40.6	103	54.3

†Significance testing revealed that $p<0.0001$ between mean pre-HAART and mean post-HAART LFTs for patients with CLD, as well as patients with HCV.

The results of univariate chi-squared analysis are shown in table 7. Mean age greater than or equal to 45 years; male gender; history of alcohol abuse; HIV risk factor of MSM, intravenous drug use, or heterosexual contact with an HIV-positive individual; positive HCV status (and, more specifically, positive PCR or genotype results); treatment with HAART; and diagnosis of AIDS were all significantly associated with an increased risk of chronic liver disease by the NHCLS case definition. Multivariate analysis was performed using four different models and is shown in Table 8. The first model included all patients and found alcohol abuse and HCV status to be the only significant independent risk factors for CLD. The second model looked at predictors of CLD in patients with HCV alone and found that treatment with HAART was the only significant risk factor. The last two models included patients with "definite" HCV and patients with neither HCV or HBV, respectively; none of the risk factors were significant.

TABLE 7: PREDICTORS OF CLD (UNIVARIATE)

Age	Age >45 yrs	$p = 0.01$
Gender	Male	$p = 0.006$
Alcohol Abuse	Positive	$p < 0.001$
HIV Risk Factor	MSM IDU Heterosexual Contact	$p < 0.001$ $p < 0.001$ $p < 0.001$
HCV status	Positive	$p < 0.001$
HCV category	Definite	$p < 0.001$
ART	Yes	$p = 0.018$
AIDS	Yes	$p = 0.032$
Race		$p = 0.595$
Ethnicity		$p = 0.420$
CD4 count		$p = 0.728$
Viral Load		$p = 0.611$

TABLE 8: PREDICTORS OF CLD (MULTIVARIATE)

MODEL	INCLUSION CRITERIA	PREDICTORS	P-VALUES
Model 1	All patients	Alcohol abuse HCV status	$p = 0.02$ $p < 0.0001$
Model 2	HCV-positive patients	ART	$p = 0.03$
Model 3	"Definite" HCV infection	none	
Model 4	Patients with no HCV or HBV infection	none	

DISCUSSION

In this large, urban cohort of HIV-infected patients in New Haven County, we observed a high prevalence of chronic liver disease. Sixty percent of individuals in our study population qualified as having CLD according to the New Haven County Liver Study case definition. The most common causes of CLD were chronic hepatitis C and alcoholic liver disease, which together accounted for almost 60% of percent of cases. These findings are in agreement with prior studies, which have reported similar conclusions regarding the prevalence and etiologies for chronic liver disease in HIV-infected populations [34-37].

HIV/HCV coinfection was extremely common in our cohort. Approximately 40% of the total population was found to have positive HCV serologies, and over half of all cases of CLD were attributed to chronic hepatitis C (with or without coexisting alcoholic liver disease). HCV infection was particularly common in patients who reported a history of intravenous drug use, accounting for over 80% of this group. This finding was similar to that in several previous studies, which reported coinfection rates of between 75% and 90% in intravenous drug users [35-37]. Patients with positive HCV serologies were found to have higher liver function tests than patients who were not infected with HCV, both prior to the initiation of HAART as well as after starting treatment.

In our study population, HAART-induced liver toxicity did not account for a substantial proportion of cases of chronic liver disease. HAART alone was attributed to only 1.6% of cases, but several patients had were found to have both HAART-induced

liver disease as well as chronic viral hepatitis or alcoholic liver disease. When mean pre-HAART LFTs were compared with mean post-HAART LFTs, significant elevations of approximately 50% were observed ($p<0.0001$). Other causes of CLD (chronic hepatitis B and NAFLD) accounted for under 5% of all cases in our study population.

We identified several predictors of CLD in our study using univariate analysis, including older age, male gender, history of alcohol abuse, HIV exposure (through MSM, IDU, or heterosexual contact), positive HCV serology, treatment with HAART, and diagnosis of AIDS. As has been reported in many previous studies, age appears to be an important factor driving the development of chronic liver disease. Since the advent of HAART, HIV-infected patients are enjoying greater longevity but are also more likely to develop long-term complications from chronic disease. In our cohort, male gender was also significantly associated with risk of CLD. This could be due to the fact that alcohol abuse was more common in men; we found that 41% of males had a history of alcohol abuse, compared with only 22% of females. Additionally, men have a worse long-term prognosis with HCV infection. Regarding HIV exposure, intravenous drug use was likely associated with CLD due to shared routes of transmission between HIV and HCV. AIDS diagnosis was found to be a predictor of CLD, which suggests that the extremely immunocompromised state in these patients renders them more susceptible to comorbid disease. As expected, our study also confirmed that alcohol abuse and positive HCV serology were strong predictors of chronic liver disease. Although HAART was found to be a predictor of CLD, it is possible that age acted as a confounding factor, as the mean age of patients on HAART was slightly higher that that of patients not on HAART (45 years versus 43 years).

In multivariate analysis, we found that alcohol abuse and HCV status remained significant independent risk factors for CLD in all patients. When we looked at patients with HCV infection only, we found that HAART remained as the only significant predictor of CLD. It can be speculated that these patients might have had elevated ALT only, which their physicians were willing to tolerate given the benefit of antiretroviral therapy in their HIV care.

We found that preventive care and treatment for CLD were being overlooked in a substantial proportion of patients in our study. With regards to immunization, pneumococcal and influenza vaccines were provided in approximately three-fourths of patients. However, these numbers varied quite widely by clinic (53% to 95% for the pneumococcal vaccine, and 71% to 91% for the influenza vaccine.) Vaccinations for hepatitis A and B were provided to only half of all eligible patients, and ranged from 32% to 74% for the HAV vaccine and 33% to 79% for the HBV vaccine depending on clinic. Furthermore, these numbers included even those patients who had received only one dose of these vaccines, which may not actually be sufficient to confer immunity.

The immunocompromised state that develops in HIV infection puts patients at increased risk for morbidity and mortality from infections that can usually be prevented by vaccination, such as pneumococcal pneumonia, influenza, hepatitis A, and hepatitis B. As was shown in our study, many patients already have underlying liver disease caused by HCV or alcoholic hepatitis and are at increased risk of decompensation if they are exposed to HBV or HAV. There is also evidence that HIV-infected individuals are less likely to clear HBV DNA and are at increased risk of chronic infection [61]. Although concerns have been raised about the safety of vaccination in HIV-positive patients,

specifically the risk of activating the immune system and the potential for accelerating HIV replication and disease progression, the benefits of vaccine administration appear to outweigh the risks.

We also found that only a very small percentage of this population underwent treatment for their CLD. Of the patients that had positive HCV or HBV serologies, only 3.6% were treated with interferon, ribavirin, lamivudine, adefovir, or Cellcept. Once again, this proportion varied broadly by clinic (0% to 8.4%), with the highest percentage of patients treated at Nathan Smith Clinic. A similarly small proportion of patients were followed by a gastroenterologist (3.7%) for specialty care.

Our study has several limitations. First, we admit biases derived from the retrospective design of the study and the lack of uniform interpretation of data. We did not interview patients, and data such as liver function tests, serologies, alcohol intake, and imaging studies were not collected in a routine fashion. A considerable amount of data were missing in several categories, such as race and ethnicity, since these categories depended on individual physicians' history and note-taking. Other categories, such as HIV exposure, were self-reported by patients, and involved disclosure of certain lifestyle choices, such as illicit drug use or homosexual contact. Due to the sensitive nature of these activities and the stigmas that sometimes accompany them, patients may have chosen to withhold their histories from their physicians. Because of underreported and missing information, therefore, it is possible that our study underestimates the prevalence of many population characteristics. Second, our case definition for chronic liver disease (taken from the New Haven County Liver Study) had certain inherent limitations. Physicians in these clinics did not routinely order imaging studies, biopsies or collection

of liver function tests; therefore, our results may again be an underestimation of the prevalence of chronic liver disease in this population. Third, we studied a specific population of HIV-positive individuals in New Haven County, and our results may not be generalizable to other locales. Finally, given the fact that post-HAART LFTs were 50% higher than pre-HAART LFTs, the NHCLS definition may be overly sensitive in this population and affected by the impact of ART on LFT measurements.

In conclusion, the burden of chronic liver disease in HIV-infected populations is substantial and may even be underestimated in our study. A large number of these patients are coinfected with hepatitis C and/or have a history of alcohol abuse, and the majority of them are not followed by gastroenterology practices. Because HIV is known to accelerate the progression from hepatitis to cirrhosis [38-41], treatment for HCV with antivirals such as interferon and ribavirin must be considered a priority for coinfected patients and should be provided at the earliest possible time. Strategies aimed at the reduction of alcohol consumption are extremely important components of care, and particularly relevant in patients who have a history of intravenous drug use, given that they may be more prone to the abuse of substances. Although HAART-induced liver toxicity has been raised as a concern in this population, the benefits of antiretroviral therapy far outweigh the risks and should be considered in all patients.

Preventive care is also of utmost importance in this population. The United States Public Health Service (USPHS) and Infectious Diseases Society of America (IDSA) have made recommendations that should guide physicians in providing immunizations to HIV positive patients. The guidelines suggest that the pnemococcal vaccine should be provided to all adults and children at the time when CD4 count is greatest, with a single

revaccination after five years. Annual influenza vaccination is recommended in all HIV positive patients, regardless of CD4 count, and routine screening and immunization against HBV is recommended for all HIV-infected adults. With regards to the HAV vaccine, the current guidelines state that any patient with existing chronic liver disease or certain risk factors (chronic HBV or HCV, homosexual contact, IDU, or hemophilia) should be vaccinated either early in the course of HIV infection or following immune reconstitution on HAART.

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