SPECIAL REPORTS AND REVIEWS

Hepatitis C in African Americans: Summary of a Workshop

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In the 10 years since its discovery, the hepatitis C virus (HCV) has become recognized as a major cause of chronic liver disease, cirrhosis, and hepatocellular carcinoma (HCC) in most countries of the world. In the United States, HCV affects 1%–2% of the general population, is the most common newly diagnosed cause of liver disease, and is the most frequent reason for liver transplantation in adults.[1–3] Recent findings indicate that there are large racial and ethnic differences in the prevalence of HCV infection. Antibody to hepatitis C (anti-HCV) is 2–3 times more common among African Americans than whites in the United States,[1] and the complications of chronic hepatitis C, such as end-stage liver disease, death from cirrhosis, and liver cancer appear to be more common among African Americans than whites.[4,5] African Americans are also far less likely than whites to respond to standard therapy of HCV with interferon, and are seriously underrepresented in clinical trials of new antiviral therapies.[6] To evaluate these issues and to develop strategies to address the health discrepancies related to HCV in African Americans, the National Institutes of Health (NIH) held a 1-day research workshop on December 2, 1999, entitled "Hepatitis C in African Americans." This conference was organized by the National Institute of Diabetes and Digestive and Kidney Diseases and cosponsored by the National Cancer Institute, the National Institute on Drug Abuse, the National Institute of Allergy and Infectious Diseases, and the Office for Research on Minority Health. This review provides a summary of the conference.

Epidemiology of HCV

Miriam Alter, M.D. (Epidemiology Section, Hepatitis Branch, Centers for Disease Control and Prevention, Atlanta, Georgia) reported that the prevalence of HCV infection in the United States has recently been estimated based on testing of stored serum samples from the third National Health and Nutrition Evaluation Survey (NHANES III), conducted from 1988 to 1994. In this survey, 1.8% of the adult, civilian, noninstitutionalized U.S. population had anti-HCV. Strikingly, rates of anti-HCV were higher among African American (3.2%) than white populations (1.8%) (Figure 1), a difference that was found in all age groups. After adjusting for socioeconomic status and prevalence of high-risk behaviors, the racial differences were not significant. The peak prevalence of anti-HCV was found in the 4th and 5th decades in African Americans, but peaked in the 4th decade in whites, declining thereafter. African American men between 40 and 49 years of age had the highest prevalence of anti-HCV (9.8%).

Testing for HCV RNA by polymerase chain reaction (PCR) showed that 76% of anti-HCV–positive samples had detectable viremia.[1] The rate of viremia varied by gender and racial groups. Thus, 86% of African Americans with anti-HCV had HCV RNA compared with only 68% of whites ($P < 0.05$), and rates of viremia were higher in African American men (98%) than African American women (70%). These findings suggest that African Americans, and particularly African American men, have a lower rate of viral clearance after acute infection. Extrapolations from these rates of anti-HCV and HCV RNA positivity indicate that 1.5 million whites and 588,000 African Americans in the United States have chronic HCV. African Americans, who represent 12%–13% of the population, account for 22% of the estimated 2.7 million people in the United States with chronic HCV.

Abbreviations used in this paper: anti-HCV, antibody to hepatitis C virus; HAI, histologic activity index; HIV, human immunodeficiency virus; IFN-α, interferon alfa; NHANES, National Health and Nutrition Evaluation Survey; NIH, National Institutes of Health; PCR, polymerase chain reaction; Peg-IFN, pegylated interferon; SVR, sustained virologic response; UNOS, United Network for Organ Sharing; VAMC, Veterans Administration Medical Center.

0016-5085/00/$10.00
doi:10.1053/gast.2000.19582

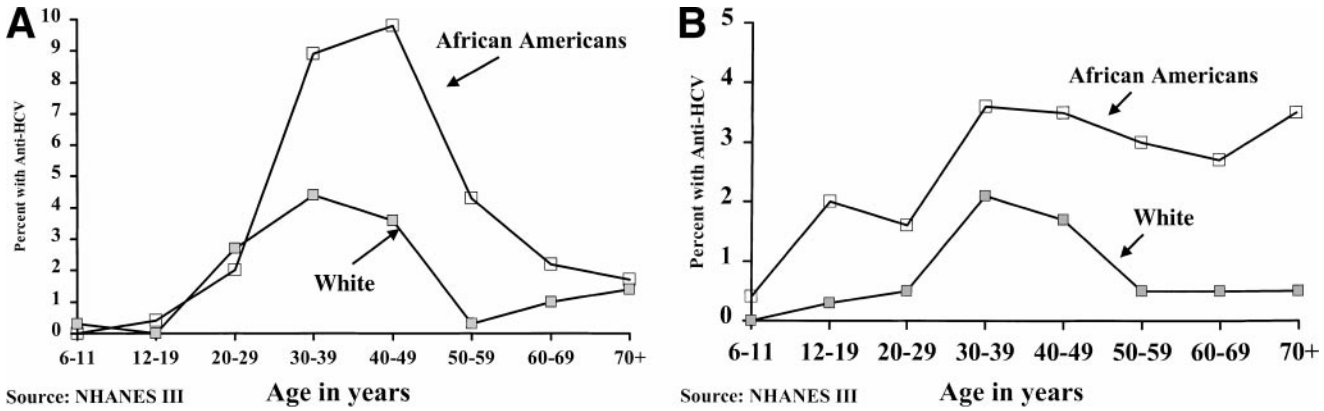

Figure 1. Prevalence of anti-HCV by decade of age and racial group among (*A*) men and (*B*) women as determined in the NHANES III, based on serum samples collected between 1989 and 1994.[1]

In the NHANES III survey, HCV genotypes were also found to differ among racial groups.[1] Genotype 1 accounted for 91% of cases of HCV infection among African Americans but only 67% among whites. Genotype 1b appeared to be particularly overrepresented in African Americans (36%) compared with whites (18%), whereas genotype 3a was underrepresented (in 6% of whites but <1% of African Americans).

Data from the Centers for Disease Control Sentinel County Study have documented a marked decline in acute HCV in the United States since 1989, from an estimated 242,000 per year between 1985 and 1989 to 36,000 per year in 1996.[7] This 80% decrease in acute HCV cases was mostly caused by a general decrease in cases of HCV among injection drug users. The decrease in acute HCV occurred in all racial and ethnic groups. Overall, 12% of acute hepatitis cases between 1991 and 1996 were attributable to HCV. African Americans accounted for 12% of the United States population and 10% of acute HCV cases. African Americans and whites with acute HCV had similar clinical features, including rates of jaundice (73% and 73%), alanine aminotransferase (ALT) levels increasing above 600 IU/L (65% vs. 65%), hospitalization (9% vs. 16%), and death (2% vs. 2%).

The prevalence and etiology of chronic liver disease has been estimated in a population-based surveillance study performed in Jefferson County, Alabama, in 1988–1989 (in which most patients were white), and a retrospective hospital record review done in Harlem, New York, in 1991–1992 (in which most patients were African American).[8] Chronic HCV represented 40% of newly diagnosed cases of chronic liver disease identified in Jefferson County (26% related to HCV alone, 14% related to HCV and alcohol) and 59% of cases in Harlem Hospital (11% HCV alone; 46% HCV and alcohol; 2% HBV, HCV, and alcohol). Thus, chronic but not acute hepatitis appears to be more common among African American than white populations in the United States. Furthermore, African Americans with anti-HCV are more likely to be viremic and to have genotype 1 than whites. The reasons for these differences remain to be defined.

Clinical Features and Natural History of Chronic HCV

Thelma Wiley, M.D. (Department of Gastroenterology, University of Illinois at Chicago Medical School, Chicago, Illinois) reported that most prospective studies on the natural history of HCV have included too few African Americans for meaningful comparisons of outcomes.[9–11] Cross-sectional studies have included more African American patients.[12] However, these studies suffer from ascertainment biases, being based on patients referred to tertiary medical centers. In recent, large, controlled trials of antiviral therapy, comparisons of African American and white patients at entry have shown no differences in risk factors for acquiring HCV, clinical symptoms, laboratory tests, or histologic features.[6,12,13] A reliable comparison of disease severity and progression would require population-based screening to identify all cases regardless of severity, thorough follow-up to insure inclusion despite economic or cultural restrictions in obtaining medical care, and a suitably large population observed for an adequate period of time.[9] No HCV cohort of this type is available.

In an attempt to assess the natural history of HCV in African Americans, a retrospective chart review was done on all patients undergoing liver biopsy at the University of Illinois Medical Center between 1996 and 1999.[14] The presumed date of initial exposure to HCV was based on

the date of transfusion or needlestick, or age of initiation of injection drug use. Histological features were then compared on the basis of race and duration of infection.[15] A total of 288 cases of chronic HCV were identified, including 195 whites and 93 African Americans. On average, African American patients were older than whites (49 vs. 45 years) and had a longer duration of infection (27 vs. 23 years) at the time of liver biopsy. The source of infection, average body weight, mean serum ALT, and HCV RNA levels were similar in the 2 groups. Genotype 1 was more common among African Americans (88%) than whites (65%), whereas genotype 3 was less common (0% vs. 9%). There were no differences in histologic activity index (HAI) by racial group. However, when categorized by decade of infection, mean ALT levels were lower and cirrhosis was less common in African American than white patients. After 2 decades of infection, cirrhosis was present in 0% of African Americans vs. 26% whites. These differences persisted in both the third (18% and 31%) and fourth decade (33% and 47%) of infection.

Similar results were presented by Bonacini et al. (University of Southern California, Los Angeles, personal communication, December 1999). Among 291 patients who underwent liver biopsy, the estimated rate of fibrosis progression was lower in the 53 African Americans (0.055 stages per year) than 116 whites (0.096 stages per year). Progression of fibrosis was also more rapid among human immunodeficiency virus (HIV)-coinfected patients, but this did not account for the racial and ethnic differences.

There are many shortcomings of retrospective analyses of disease progression based on presumed time of exposure, particularly when the date of exposure is several decades before clinical presentation. Nevertheless, these 2 analyses suggest that liver fibrosis evolves more slowly in African American than in white patients with HCV.

HCV Among Injection Drug Users

David Thomas, M.D. (Division of Infectious Diseases, Johns Hopkins University School of Medicine, Baltimore, Maryland) described the outcomes of HCV infection in a cohort of 1667 persons infected by injection drug use (ALIVE Cohort). Patients were followed up at 6-month intervals since 1989, and data were available through 1997 (average follow-up of 8.8 years per patient). The mean age of the HCV-infected subjects was 34 years, 78% were men, 94% were African American, and 33% were coinfected with HIV.

Forty-three subjects were anti-HCV negative and subsequently developed antibody.[16] HCV RNA was detectable in 42 of 43 subjects, and 37 became persistently viremic. Thus, the chronicity rate after seroconversion was 86% overall, yet 95% (35 of 37) of the African Americans developed chronic infection compared with only 33% (2 of 6) among whites. The patients who cleared HCV RNA had lower quasispecies complexity and a higher rate of HCV genetic mutations that altered the amino acid sequences of viral peptides.[17] However, these factors did not explain the higher rate of persistent infection among African Americans.

Viral clearance was also assessed in a subset of 919 subjects who were already anti-HCV positive when they enrolled. Ninety-five patients had cleared HCV RNA. Factors associated with viral clearance in multivariate analysis were race not African American (odds ratio, 4.8), age <45 years (odds ratio, 1.7), and HIV infection, particularly in those with CD4 lymphocyte counts of <500 cells/mL. Female gender did not correlate with viral clearance.

Between 1988 and 1997, 40 of 1667 (2.4%) anti-HCV–positive patients developed end-stage liver disease (3.1 per 1000 patient-years). This rate of end-stage liver disease is similar to that reported among German children[9] and young Irish women[10] in recent cohort studies, but is less than the 7%–8% rates of cirrhosis per decade reported among predominantly white adults with post-transfusion hepatitis.[9] The development of end-stage liver disease was associated with patient age (>38 vs. ≤ 38 years) and excessive alcohol intake (>250 g per week). Although there was a trend toward less end-stage liver disease among African Americans (relative incidence, 0.43), this was not statistically significance. Gender, moderate alcohol intake, HCV genotype, hepatitis B surface antigen (HBsAg), and HIV status did not correlate with development of end-stage liver disease.

These findings suggest that African Americans are more likely to develop chronic infection after exposure to HCV, but that the disease tends to progress slowly in the majority of patients.

HCV in African American Veteran Populations

Lennox Jeffers, M.D. (Associate Professor of Medicine, University of Miami School of Medicine, Center for Liver Disease and Miami Veterans Affairs Medical Center, Miami, Florida) reported that HCV is a common problem among patients observed in Veterans Administration Medical Centers (VAMC). Serologic studies from the mid-1990s indicated that at least 20% of unselected veterans observed at the Washington, D.C., VAMC had

anti-HCV.[18] A similar study at the San Francisco VAMC reported an anti-HCV frequency of 10%.[19] Serosurveys for anti-HCV among special clinics in the VAMC system also indicated a high rate of infection. For example, 115 of 350 HIV-infected veterans (33%) studied in Atlanta had anti-HCV, including 83% of injection drug users, 14% of gay men, and 30% of all other groups.[20]

To better assess the prevalence of HCV among veterans, a survey was conducted on March 17, 1999, during which more than 24,000 United States VAMC patients were asked to undergo serologic testing for anti-HCV and complete a questionnaire regarding risk factors for hepatitis.[18] The point prevalence of anti-HCV was 8%–10%, suggesting that from 280,000 to 350,000 veterans are infected with HCV. There were marked geographical variations in rates of anti-HCV positivity, from as high as 14%–16% in Miami and San Francisco and as low as 2% in Idaho. In general, these findings indicate that HCV is 5 times more common among patients observed at VAMC than in the general population.

Among anti-HCV–positive patients identified in this serosurvey, 46% were white, 29% African American, and 5% Asian American (20% did not indicate race or ethnicity on the questionnaire). These proportions are similar to the overall racial and ethnic distribution in the VAMC system. The major risk factors for hepatitis and liver disease identified among anti-HCV–positive patients were injection drug use (54%), history of blood transfusion (24%), and excessive alcohol use (45%). Further analyses of risk factors and correlates with liver disease and anti-HCV positivity are now under way. In addition, the VAMC system plans an integrated and standardized approach to management and therapy of chronic HCV.[18]

HCC in African Americans

Hashem El-Serag, M.D. (Assistant Professor of Medicine, Baylor College of Medicine, Houston, Texas) reported that HCC is an uncommon form of cancer in the general population but is common among patients with liver disease, particularly hepatitis B and C. In recent years, HCC, unlike most malignancies, has been increasing in incidence in the United States. Between 1976 and 1995, the incidence of HCC increased by 71% and overall mortality from HCC by 45%.[5] Analysis of demographics of patients with HCC shows marked age, gender, and racial-related differences in rates. HCC is 2–3 times more common among men than women, and twice as common among African Americans than whites. The incidence of HCC increases with age, it rarely occurred before the age of 40 years, and peak incidence occurred in the 1970s (Figure 2). The recent increase in incidence of HCC has occurred in both men and women, African Americans and whites. There appears to be a shift in the age-related incidence of HCC to younger persons.

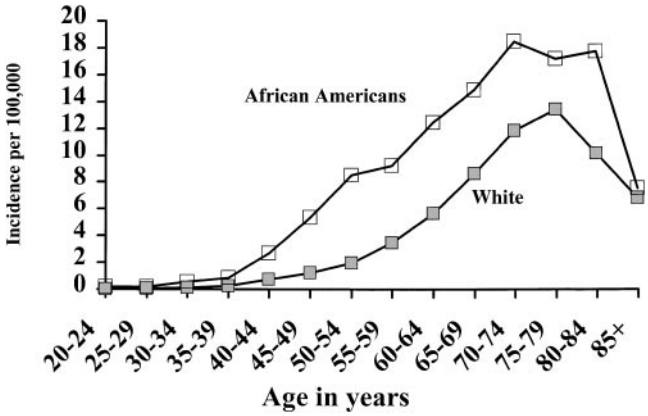

Figure 2. Incidence of HCC according to race and age from 1991 to 1995 (United States SEERS Data).[5]

Several observations suggest that the increase in HCC is caused by an increase in the prevalence of HCV. At present, the bulk of patients with HCC were born between 1940 and 1955. This cohort of patients were young adults in the 1960s and 1970s when peak rates of HCV transmission occurred, probably as a result of the spread of injection drug use.[1] This association is supported by recent information on the proportion of cases of liver cancer among hospitalized U.S. veterans caused by HCV, hepatitis B, and alcohol. Nevertheless, other factors may account for the rising incidence of HCC, including improved imaging and diagnostic tests for HCC, the availability of serologic tests for HCV, and an increased awareness of HCV and its complications. Furthermore, the recent increase in rates of HCC may also reflect the increased emigration of persons from areas of the world where HCC is common, such as Asia and Africa. Nevertheless, the rising incidence of HCC is disturbing. The fact that HCV is twice as common among African Americans than whites also suggests that African Americans will continue to experience twice the rate of HCC as whites.

Adrian M. Di Bisceglie, M.D. (Professor of Internal Medicine, St. Louis University School of Medicine, St. Louis, Missouri) reported that major risk factors for HCC include hepatitis B and C, alcoholic liver disease, and hemochromatosis. In most studies, a common denominator is the presence of underlying cirrhosis and duration

of liver disease. Indeed, in autopsy series, HCC is identified in 18%– 25% of patients who die with cirrhosis, regardless of etiology.[21,22] Furthermore, HCC is found at the time of liver transplantation in grafts in a high proportion of patients with end-stage liver disease.[3] For these reasons, the prevalence of hepatitis B virus (HBV) or HCV infection among patients with HCC generally reflects the relative rates of these 2 infections and liver disease in the populations studied. Previous studies from the United States have suggested that HCV represented 13%–53% of cases of HCC.[23,24]

In response to a recent conference on HCC, a national survey was done between July 1, 1997, and June 30, 1999, at 13 liver centers in the United States.[25,26] Of 661 patients with HCC, 51% had anti-HCV, 21% had HBsAg, and 33% were negative for both serologic markers. Ninety-nine patients (18%) with HCC were African American. African American HCC patients were more likely to have HCV than were whites (57% vs. 50%). These preliminary findings indicate that infection with HCV may now be the most common cause of HCC in the United States in both African Americans and whites.

Liver Transplantation for HCV in African Americans

Andrea E. Reid, M.D. (Associate Professor of Medicine, Massachusetts General Hospital, Boston, Massachusetts) reported that although African Americans represent 12.8% of the U.S. population and are more likely to have chronic liver disease than whites, they are less likely to undergo liver transplantation. Thus, analysis of data from the United Network for Organ Sharing (UNOS) indicates that only 7% of patients currently on the waiting list for liver transplantation are African American.[3] Once on the waiting list, however, African Americans appear to be as likely to receive a liver transplant as persons of other ethnic background. Thus, between 1994 and 1998, 34,845 persons were placed on the liver transplant waiting list and 17,968 (51%) underwent transplantation.[3] The rate of transplantation was similar for African Americans (49.6%) as for whites (52.4%). Yet in every UNOS region analyzed, African Americans represented a lower proportion of transplants than their percentage of the population.

The major reason for liver transplantation in adults is HCV, but this diagnosis is less likely to be the etiology of the end-stage liver disease in African Americans (20%) than whites (31%). Although HCV and cirrhosis are both more common among African Americans than whites, African Americans are less likely to receive a liver transplant. The barriers to transplantation appear to occur before referral and listing and are likely to be economic as well as health-related.

Outcome of Liver Transplantation for HCV in African Americans

Michael R. Charlton, M.D. (Assistant Professor of Medicine, Department of Liver Transplantation, Mayo Clinic, Rochester, Minnesota) reported that in 1997, the major indications for liver transplantation in adults were HCV (31%), followed by alcoholic liver disease (16%), cryptogenic cirrhosis (12%), primary biliary cirrhosis and sclerosing cholangitis (both 8%), and fulminant hepatic failure (6%).[3] The proportion of transplants performed for HCV appears to be increasing, and may ultimately represent more than half of cases.

The National Institute of Diabetes and Digestive and Kidney Diseases Liver Transplantation Database is a study of 916 patients who underwent liver transplantation at 1 of 3 medical centers in the United States between 1991 and 1994.[27] In that study, only 44 patients (5%) were African American. Overall, there was no difference in survival after liver transplantation for African Americans vs. whites. However, survival among 42 non-whites (heterogeneous ethnic background) with HCV was lower than the 124 whites. The cause of death was recurrent HCV in 19% of whites compared with 44% of non-whites. There were too few African Americans in this study for meaningful further analyses. Thus, the complete explanation for poorer survival is unknown.

In an analysis of 20,880 patients with HCV undergoing liver transplantation as recorded by UNOS between 1987 and 1998, overall survival was lower in African Americans than whites.[3] The difference in survival was not present until more than 2 years after transplantation. Overall patient survival for African Americans and whites in this cohort was 82% vs. 85% at 1 year and 71% vs. 77% at 4 years. Multivariate analysis on this cohort showed African American race to be independently associated with an increased risk of death (relative risk, 1.4; 95% confidence interval, 1.2–1.5; $P < 0.001$).[3] The etiology of death in these studies has not been well characterized. These findings require further analysis controlling for age, severity of illness, UNOS status, comorbid conditions, and other confounding features. However, in the aggregate these results suggest that African Americans with chronic HCV are less likely to undergo liver transplantation than white patients, and that posttransplant survival is lower, caused in part by severe recurrent HCV.

Therapy of Chronic Viral Hepatitis in African Americans

Jay Hoofnagle, M.D. (Director, Division of Digestive Diseases and Nutrition, NIDDK, Bethesda, Maryland) reviewed the outcomes of treatment for chronic hepatitis B and C in African American patients managed at the Clinical Center of the NIH.

The data on therapy of hepatitis B were derived from analyses of 3 controlled trials of interferon alfa (IFN-α) conducted between 1984 and 1991.[28] A treatment response was defined as a sustained loss of hepatitis B e antigen (HBeAg) and HBV DNA within 1 year of starting therapy. Of the 103 subjects, 6 were African American. Overall, 31 (30%) subjects achieved a treatment response. Strikingly, the response rate in African Americans (5 of 6 or 83%) was 3 times higher than in whites (26 of 97 or 27%). In addition, 67% of African Americans ultimately became HBsAg negative compared with only 25% of whites. Other features that correlated with a response were higher initial aminotransferase levels, lower pretreatment HBV DNA concentrations, and higher HAI scores, but these other predictive factors did not fully explain the differences noted between African Americans and whites.

In contrast to the higher rate of response to therapy for HBV among African American patients was a lower rate of response to therapy of chronic HCV. In a trial of escalating doses of interferon, patients were started on the standard dose of 3 million units (MU) 3 times per week. Patients who did not become HCV RNA negative by 3 months were treated with a higher dose: 5 MU daily, 6 days a week. Forty-two patients were enrolled, of whom 15 (36%) became HCV RNA negative on the standard dose and another 9 (21%) at the higher dose (total initial response rate, 57%), whereas only 9 patients (21%) had a sustained response. In this study, 7 patients were African American, 2 were Hispanic, and 33 were non-Hispanic whites. No African American patient achieved either an on-therapy or sustained response, whereas 57% of whites had an on-therapy and 26% a sustained virologic response (SVR) (Table 1, study 1). The other predictors of on-treatment and SVRs were HCV genotype and initial HCV RNA levels. All 7 African American patients had genotype 1 HCV infection as compared with 76% of whites. Yet, viral levels were similar between the 2 groups.

Monitoring of serum HCV RNA during therapy showed that levels decreased by 1.7 logs among 25 whites with genotype 1 (from 2.7 million to 53,000 copies/mL) but by only 0.3 logs among 7 African Americans (from 4.8 to 2.5 million copies/mL) with the standard interferon dose. At the higher dose, HCV RNA levels decreased by an average of 3.1 logs among whites (to 2300 copies/mL), but by only 0.6 logs among African Americans (to 1.3 million copies/mL). Overall, HCV RNA levels decreased by more than 1 log in 20 of 25 whites, but in none of the 7 African American patients. Thus, African American patients with HCV were more resistant to interferon than whites with similar genotype and viral levels. The reasons for this lack of virologic response to interferon were not clear. The increased responsiveness to interferon therapy among African Americans with hepatitis B suggests that features specific to HCV such as viral strain rather than racial and genetic factors play an important role.

Consensus Interferon Therapy of HCV in African Americans

K. Rajender Reddy, M.D. (Professor of Medicine, University of Miami, School of Medicine, Miami, Flor-

Table 1. Response Rates in Trials of IFN-α for HCV by Racial Group

Study	Therapy	Race	No. of patients	HCV RNA level (*million copies/mL*)	HCV genotype 1	ETVR	SVR
I	IFN-α2b in escalating doses	White	35	2.7	66%	57%	26%
		African American	7	4.8	100%	0%	0%
II	IFN-α2b vs. consensus IFN (9 μg)[6]	White	380	3.0	66%	33%	12%
		African American	40	3.6	88%	5%	2%
III	IFN-α2a vs. 4 doses of Peg-IFN-α2a[29]	White	142	NA	61%	NA	25%
		African American	13	NA	92%	NA	8%
IV	IFN-α2a vs. 2 doses of Peg-IFN-α2a[30]	White	260	NA	NA	NA	17%
		African American	11	NA	NA	NA	9%
V	IFN-α2b vs. IFN-α2b and ribavirin[13]	White	1600	4.7	65%	44%	27%
		African American	53	5.6	96%	15%	11%
Total		White	2417		65%	42%	24%
		African American	124		92%	10%	7%

NA, not available; ETVR, end-of-treatment virological response (HCV RNA negative at the end of treatment); SVR, sustained virological response (HCV RNA negative at least 6 months after stopping treatment).

ida) reviewed the results of a multicenter, randomized controlled trial comparing consensus interferon (9 μg) and IFN-α2b (3 MU) administered 3 times weekly for 24 weeks in respect to ethnicity of the participants.[6] Of the 472 patients analyzed, 40 (8%) were African Americans and 380 (80%) were non-Hispanic whites. Clinical features and pretreatment serum HCV RNA levels were similar in the 2 groups. However, African Americans were more likely to be infected with genotype 1 (88% vs. 66%; $P = 0.004$) and had a lower prevalence of cirrhosis (5% vs. 12%) than whites.

Both the end-of-treatment and the SVR rates were lower in African American than in white patients (Table 1, study 2).[6] Indeed, only 2 of 40 African American subjects (5%) became HCV RNA negative during treatment compared with 127 whites (33%; $P = 0.04$), and only 1 African American remained negative during follow-up compared with 46 whites (2% vs. 12%; $P = 0.07$). Among genotype 1 patients, 17 of 250 whites (7%) with genotype 1 had a sustained response compared with 1 of 35 African Americans (3%). The most significant independent predictors of both end-of-treatment and sustained responses were HCV genotype and initial HCV RNA levels. In multivariate analyses, race and ethnicity were not independent predictors of treatment response. The total interferon doses, frequency of side effects, dose modifications, and dose interruptions were similar among African Americans and whites. Nevertheless, African American patients were more likely to have neutropenia during therapy than whites (18% vs. 8%), reflecting the well-known constitutional neutropenia that is common in African Americans.

There were striking differences in the HCV RNA kinetics in African American and white patients during treatment. Among African Americans, median HCV RNA levels were decreased by an average of 50% (0.5 logs, from 3.6 to 1.8 million copies/mL) at the end of the 24 weeks of treatment, compared with 99.5% (2.5 logs, from 3.0 to 0.012 million copies/mL) among whites matched for genotype. Thus, these results indicated that African Americans were either more resistant to the antiviral effects of interferon or were more frequently infected with an interferon-resistant strain of HCV.

Pegylated Interferon Therapy of HCV in African Americans

Mitchell Shiffman, M.D. (Chief, Hepatology Section, Medical College of Virginia, Virginia Commonwealth University, Richmond, Virginia) presented data from 2 multicenter, randomized controlled trials comparing pegylated IFN-α2a (Peg-IFN) to regular IFN-α2a in chronic HCV.[29,30] Peg-IFN can be administered once weekly and theoretically provides a longer duration of action and a more sustained interferon response than regular interferon. Altogether, 426 patients were enrolled, but only 24 were African Americans (5%). Ninety-two percent of African Americans were infected with genotype 1, compared with 66% of whites.

In the first study, 4 doses of Peg-IFN were compared with standard doses of regular interferon (3 MU 3 times per week) administered for 48 weeks (Table 1, study III).[29] The sustained response rate for standard interferon was 3%, compared with 10%–36% for Peg-IFN. Only one of 13 African Americans (7%) had a sustained response, the only patient who did not have genotype 1. Restricting analysis to the patients who received the 3 highest doses of Peg-IFN, the sustained response rates were 33% (33 of 100) in whites and 18% (1 of 6) in African Americans.

In the second study (Table 1, study IV), only patients with advanced liver fibrosis or cirrhosis were enrolled.[30] Patients were randomized to receive standard IFN-α2a 3 times per week for 48 weeks or Peg-IFN in doses of either 90 or 180 μg administered once weekly for 48 weeks. The sustained response rate was only 6% with standard interferon, compared with 13% and 29% for Peg-IFN. None of 5 African American patients treated with standard interferon and only 1 of 6 treated with Peg-IFN achieved an SVR, the latter patient also having non-1 genotype. Thus, response rates to interferon in these 2 trials were low among African Americans, but the numbers of patients treated were too small for meaningful assessment of whether Peg-IFN provided a higher rate of response than standard interferon among African American patients with HCV.

Combination Therapy With Interferon and Ribavirin in African Americans

John G. McHutchison, M.D. (Medical Director, Liver Transplantation, Scripps Clinic and Research Foundation, La Jolla, California) reported outcomes of treatment in African Americans and white participants in 2 large, multicenter, randomized trials comparing interferon alone to the combination of interferon and ribavirin for either 24 or 48 weeks.[31,32] Of the 1744 patients enrolled in these 2 trials, 1600 (92%) were white and 53 (3%) were African American. African Americans were somewhat older (mean, 45 vs. 42 years; $P < .01$), had higher body weight (mean, 90 vs. 79 kg; $P < .01$), and had higher mean HAI scores (7.8 vs. 7.1; $P = 0.04$). Importantly, 96% of African Americans had genotype 1

compared with only 65% of whites. There were no differences between the groups in mean serum ALT levels, HCV RNA levels, or in the prevalence of cirrhosis.

Both end-of-treatment and SVR rates were significantly lower in African Americans than white patients in both the combination and interferon monotherapy arms (Table 1, study V).[13] Furthermore, in both groups combination therapy led to higher virological response rates than interferon monotherapy. Thus, among whites, the sustained response rate was 13% with interferon alone compared with 37% with combination therapy. Among African Americans, no patient had an SVR with interferon monotherapy, but 21% responded to combination therapy. Information on the relative efficacy of 24 vs. 48 weeks of combination therapy in African Americans was not available.

The strongest predictors of an SVR to combination therapy were HCV genotype, initial level of HCV RNA, and to a lesser extent, degree of fibrosis and gender. Controlling for these factors by multivariate analysis, race was not an independent predictor of a response to combination therapy. In patients with genotype 1, the SVR to interferon monotherapy was 12% among whites, but 0% among African Americans. In contrast, the sustained response rate with combination therapy was 23% in whites and 21% in African Americans with genotype 1.

An analysis of the HCV RNA kinetics during therapy showed that African American patients with genotype 1 receiving interferon alone had little overall decrease in HCV RNA levels (<0.5 logs). However, with combination therapy, mean HCV RNA levels decreased to a similar degree in both whites and African Americans. Thus, analysis of these 2 large controlled trials of antiviral therapy of HCV confirmed the very low rate of response of African Americans to IFN-α therapy and suggested that this poor response was at least partially negated by combination therapy.

Results from retreatment trials have also shown lower response rate to combination therapy among African Americans than whites.[33] Clifford Brass (Schering Laboratories, Kenilworth, NJ) representing the collective "Rebetron" investigators presented information on retreatment of 536 patients with chronic HCV who did not have a sustained response to previous therapy with interferon.[34] SVRs occurred in 34% of 445 whites, but only 11% of 55 African Americans, a highly significant difference. Patients enrolled in these studies included both virological nonresponders as well as relapsed patients to previous interferon monotherapy. Nevertheless, these findings indicate that the overall response rate to retreatment with interferon and ribavirin is lower in African Americans than in whites.

HCV Kinetics During Antiviral Therapy in African Americans

Thomas Layden, M.D. (Professor of Medicine, Digestive and Liver Diseases, University of Illinois at Chicago, Chicago, Illinois) discussed HCV viral kinetics after single and multiple injections of IFN-α, comparing African American and white patients.[35–37] Following the first injection of IFN-α, there is an initial delay followed by a 2-phase decline in HCV RNA levels. The initial 8–10 hours probably represents the time required for interferon to induce gene expression and the intracellular antiviral state. The first decline in HCV levels (phase 1) occurs between 8 and 24 hours after the first injection, is dependent on interferon dose, and probably represents decrease in virion production by hepatocytes under the influence of the interferon-induced antiviral state. Thereafter, there is a slower decline in HCV levels (phase 2) between days 2 and 14, which is not dose-related, and which probably reflects the gradual death or clearance of HCV-infected hepatocytes. The phase 2 decline continues for weeks to months and is the best predictor of complete HCV RNA clearance.[37]

Although the viral kinetics of HCV clearance can be expressed mathematically using average HCV RNA levels, there is actually a heterogeneity of response, particularly in the second phase decline. The pattern of change in HCV RNA levels varies from patient to patient, some patients having a rapid reduction in HCV RNA and clearing virus within a month of therapy, and others having a slow decline clearing virus at a later point or never becoming HCV RNA negative. Other patients have no further decline in HCV RNA levels after the first phase despite daily interferon administration. The reasons for these differences in viral response in the second phase are unknown.

Recent studies have shown that the pattern of viral kinetics varies by viral genotype and other viral and host factors.[35,37] The viral kinetics during IFN-α therapy (15 MU daily) in 3 African Americans was compared with that in 4 whites with similar genotype and initial viral load. The phase 1 decline was similar in both groups, suggesting similar drug effectiveness in inhibiting viral production. In contrast, the phase 2 decline rate was significantly faster in the whites than in the African Americans. Two African American subjects had no decline (<0.5 log) in HCV RNA levels over the month of therapy. Although the number of patients studied was

small, these findings provide support to the clinical observations of low rates of response to IFN-α among African American patients and provide a means of early assessment and clinical investigation of the reason for the differences in responses.

In a poster session, Sherman et al.[38] analyzed HCV quasispecies complexity and diversity by race and ethnicity. Quasispecies analysis was based on heteroduplex assays combined with sequencing of the hypervariable region of the HCV E2 domain. The complexity of HCV quasispecies in 26 African Americans was greater than in 14 whites, matched for genotype, gender, age, and alcohol use. In previous studies, quasispecies complexity has correlated with severity of liver disease and lack of response to interferon. These results promise to provide insights into the relative resistance to interferon among African Americans with HCV.

Racial and Ethnic Issues in HCV Research

Claudia R. Baquet (Associate Professor of Epidemiology, Preventive Medicine Director, Cancer Prevention and Control Research, University of Maryland, Greenebaum Cancer Center, Baltimore, Maryland) discussed the racial and ethnic barriers to participation of African Americans in clinical research. In the United States, African Americans account for at least 22% of patients with HCV[1] but are usually underrepresented in clinical trials of antiviral therapy, comprising <5% of patients in the 5 large clinical trials discussed in this meeting (Table 1). The small participation of African Americans in these trials prevent meaningful assessment of the efficacy, safety, and utility of antiviral agents in African Americans.

The reasons for a lack of participation of African Americans in clinical research are multiple and interrelated.[39] There is a low awareness of the significance of liver disease and HCV among African Americans. Multiple socioeconomic limitations complicate participation in research, including low income, education level, and inability to lose the time from work to participate in medical research. Also, minority individuals have a general distrust of medical institutions and research, arising out of a long history of racial bias in academic medicine and clinical research.

The barriers to participation in clinical research can be categorized into 6 areas: patient, community, health care professionals, investigator, research institution, and health system. Patient barriers are personal attitudes toward such participation, mistrust of the research and the institution, fear of the consequences of research or what might be discovered, and cultural issues. There may be little administrative support for persons from lower socioeconomic conditions and lack of reimbursement for travel, loss of work, or per diem costs. Community barriers include fear of exploitation and poor relationships between the African American and the academic communities. For many African American communities, other priorities are more important, such as providing a safe environment, adequate housing, better education, and basic medical care. The community health care professional barriers include a lack of information on availability of clinical studies, negative personal views regarding research benefits and risks, and lack of understanding of research design. Community physicians may also be concerned about losing patients and reimbursement. Research investigator barriers include the failure to use culturally sensitive approaches and lack of awareness of fears and areas of distress of minority patients. Investigators also often fail to reach out to community groups and depend largely on referral from physicians who serve middle- or upper-socioeconomic communities. Research institutional barriers to wider minority participation in clinical research include rigidity in scheduling of visits, isolation, and lack of involvement in the community, and an inability to fund outreach efforts or provide reimbursement to patients in lower socioeconomic groups.

Approaches to overcoming barriers to wider involvement of minority individuals in clinical research can be classified into 4 strategies or models. In the medical-system participation model, health care professionals from underserved communities are active partners, recruiting and treating patients, gathering data, and providing results to the established research organization. This model is best used for diseases that are common and for therapies that are easily applied. In the medical-system referral model, health care professionals from underserved areas are actively recruited to help in the referral process. Patients are referred to a central research center and the investigators and support staff operate from these established research institutions. This model is best for the relatively uncommon disease and therapy that is complex or likely to have problematic adverse events. In the general community-direct model, the central research organization appeals directly to patients, not depending on referral from health care professionals. Typically, familiar media and community contacts such as churches, community centers, and radio talk shows are used. This model is best used for diseases or conditions that are common and generally understood by the patient. In the general community-indirect model, research organizations use intermediaries or brokers to reach pa-

tients. The intermediaries act as agents for recruitment between community residents and the established research organization. An excellent intermediary to reach African American patients are churches and ministers.

Recognition of the barriers to participation in clinical research is needed to lay the groundwork to overcome these barriers. A community outreach strategy can be helpful in correcting the lack of participation of minority individuals in clinical research.

HCV in African Americans: Summary and Conclusions

Charles Howell, M.D. (Director, Division of Hepatology, University of Maryland School of Medicine, Baltimore, Maryland) provided an analysis of large databases on the epidemiology, natural history, complications, and therapy of HCV for racial differences have provided several common themes that offer research challenges to understanding this important liver disease.

Clearly, chronic HCV is 2–3-fold more common among African American than white populations.[1] The higher rate correlates with the lower socioeconomic status among African Americans. Most studies have also shown that African Americans, once infected with HCV, are more likely to develop chronic infection.[1,16] In particular, African American men have a 90%–95% rate of chronicity, far higher than the 65%–75% rate for whites. The reasons for the higher chronicity rate are not known, but may be virological (genotype, stain, quasispecies diversity) or host-related (genetic, immunologic, behavioral). Interestingly, genotype 1 appears to be more common in African Americans than whites, and genotype 3 is less common. The high rate of genotype 1 is a major reason why African Americans have a low response to current therapy. Whether the differences in genotypes are also responsible for differences in chronicity is not clear.

Although chronicity is more common, the rate of progression of liver disease to cirrhosis may be slower in African Americans than in whites. Yet because of the higher rate of infection, African Americans have a higher rate of cirrhosis, HCC, and death from HCV-related liver diseases than whites.[3–5] The apparent discrepancy between the estimated progression rate of liver fibrosis and morbidity among African Americans with HCV may be explained by the limited size, retrospective nature, and patient-selection bias of current studies. The issue of rate of progression can be addressed adequately only by prospective studies of African American and white cohorts with HCV.

Of enormous importance is the finding of a poor rate of virological response to IFN-α therapy among African Americans.[6] This low rate of response is partially attributable to the high prevalence of HCV genotype 1. However, one is still left with a dismally low rate of response to interferon among African Americans compared with whites. Indeed, in the 5 trials of IFN-α therapy for HCV reviewed here, the total number of African American patients with genotype 1 who had an SVR to IFN-α monotherapy was one. It is doubtful that IFN-α would have been approved for use in HCV, had the initial clinical trials used a predominantly African American population. Furthermore, it is doubtful that any physician would recommend interferon monotherapy for an African American patient with HCV outside of the 5%–10% who have non-1 genotype infections.

Preliminary evaluation of 2 large clinical trials has shown that the combination of interferon and ribavirin yields a higher rate of response in both African Americans and whites, but the overall rate is still somewhat low.[13] The low response rate may be caused by viral genotype, rather than actual racial differences. However, it should be stressed that $<5\%$ of the participants in these trials were African Americans. Thus, 9 years after IFN-α was approved for use in chronic HCV and 2 years after approval of combination therapy in the United States, there remains inadequate information on the response rate of African Americans to licensed therapies for this disease. These findings emphasize the need for active outreach to achieve adequate representation of all ethnic groups in clinical trials.

The analysis of kinetics of HCV RNA clearance during therapy with interferon has provided important clues to the basis of racial differences in response to therapy in HCV. African Americans are more likely to have an interferon-resistant phenotype, with either no response or a flat response of HCV RNA levels during treatment. These findings suggest a host-related defect in interferon signal transduction or a viral-related interference with interferon action. An important priority is for further research on the biological basis for this lack of response to interferon, evaluating all steps in interferon receptor occupancy, signal transduction, and gene expression, as well as cytokine production and activity during therapy, serum and intrahepatic HCV RNA levels, HCV strain differences, HCV sequence variations such as in the interferon-sensitivity determining region, immune responsiveness to HCV antigens, antibody levels to HCV epitopes, iron and antioxidant status, and other biomarkers.[37,38,40]

What also is clearly needed is a greater participation of African Americans in both clinical investigation and clinical trials in HCV. The use of community outreach models and direct approaches to decreasing barriers to patient participation should be the first priority in approaching the issue of HCV in African Americans and decreasing the health disparities for this important and common form of liver disease.

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Received February 29, 2000. Accepted June 21, 2000.

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The authors thank all the participants in the workshop "Hepatitis C in African Americans," Lister Hill Auditorium, National Institutes of Health, December 2, 1999. Speakers included Drs. Miriam Alter, Claudia R. Baquet, Michael R. Charlton, Adrian M. Di Bisceglie, Hashem B. El-Serag, Jay H. Hoofnagle, Charles Howell, Lennox Jeffers, Thomas J. Layden, John McHutchison, K. Rajender Reddy, Andrea E. Reid, Mitchell Shiffman, David Thomas, and Thelma Wiley. Moderators included Drs. Lynt B. Johnson, Frederick Nunes, Victor F. Scott, Leonard B. Seeff, Doris Strader, and Bruce Trotman.