Hepatitis B and C in African Americans: Current Status and Continued Challenges

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Viral hepatitis remains a public health concern in the United States, resulting in excess morbidity and mortality for the individual and representing a burden to societies as evidenced by billions of dollars in health care expenditures. As with many chronic diseases, race and ethnicity influence various aspects of disease pathogenesis, including mechanisms of persistence, disease progression, disease sequelae, and response to therapy. For hepatitis B and C infections, African Americans disproportionately bear a large burden of disease in the United States. The role and importance of African American race, however, have been less well-characterized in the literature among the population of viral hepatitis–infected individuals. The differences in epidemiology, manifestations of liver disease, response to therapy, and differential trends in liver transplantation in African Americans compared with other racial and ethnic groups deserve special attention. This review will address the current status of hepatitis B and C infection in African Americans in the United States and identify some of the remaining challenges in diagnosis, characterization of natural history, and treatment. For the purposes of this review, the terms *African American* and *black* will be used interchangeably throughout the text.

Keywords: Hepatitis B; Hepatitis C; African American; Black; Disparities.

Hepatitis B Infection

Epidemiology of Hepatitis B Infection

Globally, more than 2 billion persons have evidence of hepatitis B virus (HBV) infection, and nearly 200–375 million of those have serologic evidence of chronic infection.[1] Although prior estimates of HBV infection in the United States have ranged from 800,000 to 1.4 million, emerging data suggest that this is an underestimate of disease burden, with infection in 2.2 million persons being proposed and of which immigrants bear the heaviest burden.[1–3] Furthermore, an estimated 1.4 million HBV-infected individuals are unaware of their infectious status, and important opportunities for treatment of chronic infection and surveillance for hepatocellular carcinoma (HCC) are being missed.[4]

In the United States, an estimated 35,000 new diagnoses of acute HBV infection were established in 2010.[5] This represents a decline of nearly 80% when compared with the rate of new HBV infections in the early 1990s before implementation of HBV vaccination programs. When examining incidence rates stratified by race and ethnicity, African Americans have the highest incidence of acute HBV infection, with 1.7 cases per 100,000 persons reported in 2010. This is in contrast to a rate of 0.6 per 100,000 persons in Asian Pacific Islanders and Hispanics, groups in the United States with the lowest HBV incidence.[5] The incidence rate of acute HBV infection for blacks has consistently been higher than that of other racial and ethnic groups since 2000.

Data from the National Health and Nutrition Examination Survey (NHANES) II and III suggest that the age-adjusted prevalence of chronic infection or serologic markers of past exposure to HBV in blacks was 5.5% and 4.9%, respectively; these rates failed to change during the years of study.[6] In this group, rates of chronic infection ranged from 0.33% to 0.42%. In addition to identifying foreign-born status as a risk factor for increased HBV prevalence, as defined by hepatitis B surface antigen (HBsAg) or hepatitis B core positivity, African American race was associated with an age-adjusted prevalence of 15.8% for 1976–1980 and 11.9% for 1988–1994. Furthermore, being black was associated with a 3.9-fold increase in odds of HBV positivity in comparison to whites.[6] Additional analyses in NHANES data found that differences in HBV prevalence rates between African Americans and other groups persisted after adjustment for important risk factors including demographic, socioeconomic, and behavioral characteristics.[7] These data suggest that factors other than socioeconomics and other risk factors account for

Abbreviations used in this paper: HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; IFN, interferon; IL, interleukin; MELD, Model for End-Stage Liver Disease; NHANES, National Health and Nutrition Examination Survey; PEG-IFN, peginterferon; RBV, ribavirin; SNP, single nucleotide polymorphism; SVR, sustained virologic response.

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an increased prevalence of HBV infection in African Americans.

Natural History of Hepatitis B Infection

The natural history of hepatitis B infection, including its incubation period, symptomatology, and chronicity, has been well described.[8] No studies to date have examined differences in the natural history of HBV in African Americans or made comparisons to other racial and ethnic groups.

Chronic HBV infection may be asymptomatic or result in a range of manifestations of liver disease including chronic hepatitis, cirrhosis, or HCC. With regard to HCC, African Americans assume a greater burden of disease, with a notable increase in both HCC incidence and HCC-related mortality when compared with whites.[9,10] Yu et al[11] compared HCC risk factors in African Americans and whites. They found that African Americans had higher rates of viral hepatitis, coinfection with HBV and hepatitis C virus (HCV), and metabolic risk factors such as diabetes mellitus that increased their risk of HCC. In addition, because of the high prevalence of genotype A HBV infection in blacks, a genotype associated with a 4-fold to 5-fold increase in risk of HCC in black Africans,[12] African Americans may have risk factors for HCC that result in a markedly elevated and additive risk of HCC. Unfortunately, comparison data were not available for other racial groups such as Asians and Hispanics in the above study. Clearly, more research is required to further elucidate these aspects of HCC risk in African American patients with chronic HBV infection.

Because of the high risk of HCC in the context of viral hepatitides for many patient populations, surveillance for HCC is now recommended in select groups.[13] One such group, sub-Saharan Africans, tend to have not only a high incidence of HCC but also a high incidence of HCC at a younger age.[14] In a cohort of Africans with HCC, HBV serologies including HBsAg and hepatitis B e antigen (HBeAg) were more prevalent in patients younger than 30 years of age.[15] Although there are several studies of Africans that have examined their risk of HCC and demonstrated the importance of HCC surveillance in this group, such data are not available for blacks from other regions including the United States.[15–17] However, because of the increase in HBV infection in African Americans and their higher risk of HCC, it may be prudent to extend surveillance recommendations to this high-risk population.

Viral Genotype and Host Genetic Diversity in Hepatitis B Infection

Hepatitis B virus genotypic variability. HBV genotype is an important determinant of disease progression with a notable influence on disease severity and response to HBV-directed therapy.[18–23] A review of HBV genotypes suggested that there are differences in HBV genotype distribution by race and ethnicity and place of birth. With respect to African Americans, 84% were infected with genotype A, followed by genotypes C and D at 6% and 4%, respectively.[19] In whites, genotypes A and D were most prevalent, as seen in 71% and 21% of the cohort, respectively. In comparison, genotypes B and C were observed most frequently in Asians. In the study, genotypes A and C were associated with HBeAg-status, and non–genotype B infection was an independent risk factor for abnormal alanine aminotransferase levels and decompensated cirrhosis. Although data are limited, it can be gleaned that there may be differences in disease progression that are mediated by differences in viral genotype distribution.

Host genetic diversity. Interleukin (IL)-10 promoter polymorphisms have been associated with HBV infectious outcomes, including spontaneous HBV clearance, HBeAg seroconversion, development of chronic liver disease, and incidence of HCC.[24,25] In addition, foci near the IL-19 and IL-20 genes have been associated with regulation of proinflammatory cytokine production early in viral infections. To further explore racial differences in response to acute HBV infection, Truelove et al[26] examined the effect of single nucleotide polymorphisms (SNPs) in the IL-10, IL-19, and IL-20 genes in African Americans and whites in a nested case-control study. It was found that African Americans who were heterozygotes at the rs1518108 locus of IL-20 were more susceptible to chronic HBV infection. This locus is also of importance in the genetics of host response in HCV infection.[27] Furthermore, polymorphisms in the IL-10 promoter region were observed to be an important determinant of HBV infection. In African Americans, SNP variants at the IL-10 and IL-20 loci determined the establishment of HBV infection, whereas in those of European ancestry, IL-20 variants solely influenced recovery. Although more work needs to be done to clarify the genetic and immunologic basis of the development of HBV infection stratified by race, differences in host genetics may contribute to the racial and ethnic differences observed in HBV prevalence.

Treatment and Outcomes in Chronic Hepatitis B Infection

There is a relative scarcity of data regarding treatment outcomes for chronic HBV infection in African Americans undergoing interferon (IFN) and/or nucleoside/nucleotide-based antiviral therapy. A long-term follow-up study of patients who had undergone therapy with IFN observed that African American patients were much more likely to respond to therapy.[28] Of note, all African American responders not only cleared HBeAg and HBV DNA from the serum, but all cleared HBsAg, a relatively rare milestone with HBV therapy that occurs in up to 7.8% of patients on therapy.[29] Unfortunately, there were few African Americans who

Table 1. African American Inclusion in Nucleotide/Nucleoside Analogue Clinical Trials

Author	Treatment	Treatment length (*wk*)	Total patients, N	African Americans, n	African Americans, %
Dienstag et al,[30] 1999	Placebo	52	71	13	18
	Lamivudine	52	66	10	15
Perrillo et al,[31] 2002	Placebo	52	196	13	7
	Lamivudine	52	406	16	4
	IFN	16	68	3	4
	IFN + lamivudine	16[a]	135	5	4
Marcellin et al,[32] 2003	Placebo	48	167	3	2
	Adefovir (10 mg)	48	171	8	5
	Adefovir (30 mg)	48	173	5	3
Hadziyannis et al,[33] 2003	Placebo	48	61	1	2
	Adefovir	48	123	5	4
Dienstag et al,[34] 2003	Lamivudine	144	40	1	3
Marcellin et al,[35] 2004	PEG-IFNα-2a + placebo	48	177	3	2
	PEG-IFNα2a + lamivudine	48	179	2	1
	Lamivudine	48	181	0	0
Kuo et al,[36] 2004	Tenofovir	48	9	1	1
Chang et al,[37] 2005	Lamivudine	76	45	0	0
	Entecavir (1.0 mg)	76	42	3	7
	Entecavir (0.5 mg)	76	47	1	2
	Entecavir (0.1 mg)	76	47	0	0
Hadziyannis et al,[38] 2006	Placebo/adefovir	97–240	55	1	2
	Adefovir/adefovir	97–240	70	3	4
Chang et al,[39] 2006	Lamivudine	52	355	8	2
	Entecavir	52	354	8	2
Lai et al,[40] 2006	Lamivudine	52	313	7	2
	Entecavir	52	325	8	2
Marcellin et al,[41] 2008	Adefovir	48	171	8	5
	Adefovir	240	65	3	3
Marcellin et al,[42] 2008	Adefovir	48	215	9	4
	Tenofovir	48	426	21	5
Leung et al,[43] 2009	Adefovir	52	32	2	6
	Entecavir	52	33	2	6
Liaw et al,[44] 2009	Lamivudine	104	687	8	1
	Telbivudine	104	680	4	1

[a]All subjects were treated with 8 weeks of lamivudine prior to starting IFN + lamivudine.

participated in the study (n = 6), and these observations have yet to be further explored. With respect to use of nucleotide/nucleoside analogues, there are inadequate data about the efficacy and safety of these agents in African American patients with chronic HBV infection (Table 1[30–44]).

Likewise, there are limited data on the number of treatment-eligible African Americans with HBV infection who are initiated on therapy. A small study including subjects from an urban medical center found that only 7% of a predominantly African American and Hispanic population had been initiated on therapy.[45] The study also highlighted potential barriers to therapy including lack of insurance, history of nonadherence, and ongoing drug and alcohol abuse.

Liver Transplantation in Hepatitis B Infection

Sentinel work has demonstrated that disparities exist for those African American patients awaiting liver transplantation. In addition to being more likely to die and becoming too sick for liver transplantation, African Americans are less likely to undergo transplant once listed.[46] Subsequent to this work in the pre–Model for End-Stage Liver Disease (MELD) era, Moylan et al[47] demonstrated an improvement in racial disparities in liver transplantation that coincided with implementation of the MELD-based allocation system for liver transplantation that was adopted in 2002. Although these data would seem to suggest a more equitable allocation of organ donation since implementation of the MELD score, the work also demonstrated that blacks are listed at higher MELD scores and their waiting times are shorter than whites, suggesting that access to care may still be a barrier for African Americans. In addition, although there is a high prevalence of liver disease in African Americans, they represented a smaller proportion of those listed for liver transplantation than expected.

Shifting the focus to liver transplantation for HBV infection, the data on outcomes for African Americans are conflicting. In a review of outcomes after liver transplantation for HBV in the United States, Kim et al[48]

Table 2. Unmet Needs in African Americans With Hepatitis B Infection

Understanding of high prevalence of HBV infection
Understanding of differences in natural history of HBV infection in African Americans compared with other racial/ethnic groups
Understanding of host genetics and how it affects establishment of chronic HBV infection
Comparison of disease progression in African Americans and other racial/ethnic groups
Focused studies of safety and efficacy of HBV antiviral therapies in African Americans
More data on post-transplant patient and allograft outcomes in African Americans requiring liver transplantation for chronic HBV infection

found that African Americans had a 35% increase in mortality compared with whites in the pre-MELD era. However, Bzowej et al[49] failed to demonstrate race-based differences in HBV waitlist or post-transplant outcomes. This discrepancy in results, likely resulting from the limitations of observational studies and limited inclusion of African Americans, speaks to the need for more research to address this and other questions regarding racial disparities in transplantation.

Challenges and Future Directions

Racial disparities exist in prevalence of chronic HBV infection in the United States, and there are unmet needs in those African Americans with chronic HBV (Table 2). Although those who are foreign-born bear the majority of the burden of HBV infection in the United States, African Americans have a high prevalence of infection. In addition, there remain differences in acquisition of infection, with African Americans having the highest rates of incident infection. Data presented also suggest that there are racial differences in genetic polymorphisms that are important in the establishment of chronic infection and modulation of disease course. There are also vast differences in viral genotypic distribution by race and likely differences in response to therapy, a relationship that is not yet delineated. Continued research is needed to identify and address areas of disparity in chronic HBV infection and treatment, and an improvement in enrollment of African Americans in clinical trials is essential for achievement of this goal.

Hepatitis C Infection

Epidemiology of Hepatitis C Infection

Although African Americans remain a minority in the United States, HCV infection is highly prevalent in this population compared with other racial groups,[50–53] and thus African Americans represent a group disproportionately affected by this disease. In NHANES III data, inclusive of years 1988 through 1994, it was estimated that approximately 3.9 million Americans, or 1.8% of the U.S. population, had been exposed and 2.7 million, or 74%, chronically infected with HCV.[52] Blacks had the highest prevalence of HCV exposure, equating to 3.2% of the population screened.

The NHANES III survey, as well as a follow-up study examining HCV prevalence in the United States from 1999 through 2002, highlighted the tremendous HCV disease burden in those born between 1945 and 1965. Of note, the highest prevalence, 9.4%, was observed in black men 40–49 years old.[53] Because of the potential complications of chronic HCV infection, including cirrhosis, hepatic decompensation, and HCC, it is this cohort of patients that is expected to have HCV-related complications. Mathematical modeling studies have suggested that the proportion of cases with advanced hepatic fibrosis as a result of HCV infection will continue to rise during the next decade, with the number of cases of cirrhosis and hepatic decompensation peaking at 2020 and 2022, respectively.[54] Unfortunately, because of the burden of HCV infection in African Americans and other racial and ethnic minorities, these groups are likely to have increased rates of HCV-related death. Mortality data from 1999–2007 obtained from the National Center for Health Statistics suggest that the effect of HCV on mortality is already being seen. The mortality rate for HCV-related disease surpassed that of death among human immunodeficiency virus–infected patients, a rate on the decline, and HBV-related death, a rate that has been relatively constant. This study also demonstrated racial and ethnic disparities in death rates for HCV infection, with African Americans having a 2-fold higher rate of death than expected.[55]

Natural History of Hepatitis C Infection

Longitudinal studies addressing the natural history of HCV infection in African Americans are lacking. However, cross-sectional and retrospective studies have observed a lower prevalence of cirrhosis among African Americans when compared with other groups.[56–59] In addition, most studies found a lower alanine aminotransferase level and less piecemeal necrosis and hepatic fibrosis in African Americans.[56,57] In contrast, a more recent study that used mathematical modeling of disease progression suggested that there is little difference on the basis of race in progression of hepatic fibrosis in HCV infection.[60] Hence, data on racial differences in hepatic fibrosis remain inconclusive. The rationale for differences in HCV natural history and disease progression that are based on race and ethnicity are not completely understood, and further research is necessary to determine mechanisms underlying these potential differences.

Because of the differences suspected in the natural history of HCV infection in African Americans, it would be expected that they would have fewer disease-related complications including hepatic decompensation and a

lower incidence of HCC. No studies to date have explored differences in rates of hepatic decompensation stratified by race. However, there are race-based disparities noted in incidence of HCC. Recent data suggest that the incidence rate of HCC is 2-fold to 3-fold higher among blacks than whites.[61] Moreover, African American men bear the highest burden of HCC, with an incidence rate of 5.4% per year noted, surpassing incidence rates for whites, Hispanics, and women.[54,62,63]

Viral Genotype and Host Genetic Diversity in Hepatitis C Infection

Hepatitis C virus genotypic variability. HCV genotype is one of the major determinants of response to antiviral therapy. Genotype 1 infection has been recognized as being difficult to treat and is more frequent in the United States, Europe, and Japan.[64] Genotype 1 is the predominant genotype among African Americans and whites. However, it is more prevalent in African Americans, affecting up to 91% of those infected, in comparison to only 70% of whites.[52,53,65] On the basis of data from NHANES, African Americans are twice as likely as whites to be infected with genotype 1b.[52,53,65] Moreover, among genotype 1–infected patients, African Americans clear the virus at approximately half the rate of their white counterparts.[66–69] The Study of Viral Resistance to Antiviral Therapy of Chronic Hepatitis C (Virahep-C) examined factors associated with non-response to peginterferon alfa (PEG-IFNα) and ribavirin (RBV) therapy in patients infected with HCV genotype 1a or 1b. In the study, African Americans were found to have a poor response to treatment, a finding not explained on the basis of clinical factors including viral load, disease severity, or cumulative dose of therapy received.[69] As part of the Virahep-C study, an ancillary study on genetic variation in HCV genotype 1 strains found that higher interpatient HCV genetic diversity was associated with a robust treatment response at day 28 of therapy. This increase in genotypic diversity was limited to a few genes including those in the NS3 and NS5A regions in genotype 1a and the core and NS3 genes in genotype 1b.[70] In addition, those subjects achieving a marked response to therapy had more diverse HCV sequences than nonresponders. This finding may suggest that African Americans are infected with more homogenous and perhaps more difficult to treat strains of HCV. In addition, the relevance of subgenotypic variability that was less important in an era of IFN-based dual therapy may generate more interest going forward because of its importance in the context of protease inhibitor–based therapy. Genotype 1b is associated with a modestly improved sustained virologic response (SVR) with protease inhibitor–based therapy when compared with genotype 1a. This phenomenon is thought to be explained by genotype 1b's lower propensity for the development of viral resistance as compared with genotype 1a.[71]

Host genetic diversity. Genome-wide association studies were the first to identify SNPs near the IL-28B host gene that dictate the host's response to HCV infection. These SNPs not only predicted treatment-induced clearance and spontaneous recovery from HCV infection but also explained some of the differences in response rates between whites and African Americans to HCV therapy with PEG-IFNα and RBV.[72–74] The CC genotype at the rs12979860 locus of the IL-28B gene was shown to be associated with improved early viral kinetics and an increased likelihood of a rapid and early viral response, conferring approximately a 6-fold increased odds of achieving an SVR.[75–77] In addition, those with the CC genotype were noted to have a higher probability of clearing HCV infection spontaneously than those with either the TC or TT genotypes. Two of these studies included African Americans and, although the sample size was small, found that the rs12979860 locus was associated with a favorable treatment outcome in these individuals.[72,75] Ge et al[72] showed that there was variation in the odds of SVR among different racial groups with the CC genotype, with a 7.3-fold increase noted in whites, 5.6-fold increase in Hispanics, and 6.1-fold increase in African Americans. Thompson et al[75] demonstrated in multivariable analysis that African Americans with the CC genotype responded more favorably than whites with the non-CC IL-28B genotype, but that the CC genotype was far less prevalent in African Americans. Although IL-28B polymorphisms were the strongest pretreatment predictor of SVR to PEG-IFN and RBV therapy, these SNPs failed to explain all of the treatment-related variability observed in African Americans, with African American race remaining an independent negative predictor of outcome on multivariable regression analysis.[75]

Treatment and Outcomes in Chronic Hepatitis C Infection

Treatment of HCV genotype 1 infection has changed over time, with each incremental modification in therapy being associated with consistent improvements in SVR rates (Table 3). The rates of SVR were approximately 6%–12% with IFN monotherapy, 38%–42% with conventional IFN and RBV, and as high as 55% with PEG-IFN and RBV.[57,78–81] In African Americans, the response rates have been considerably lower and have ranged from 0% to 11% with IFN monotherapy[57,80,82] and 8% to 28% with PEG-IFN and RBV.[67–69,83] The introduction of 2 new direct-acting antiviral agents, telaprevir and boceprevir, approved by the Food and Drug Administration in 2011 for the treatment of chronic HCV genotype 1 infection, has brought with it the prospect of a shorter duration of therapy and an improvement in SVR rates. Although efficacy of therapy has increased during the last 20 years, there remain challenges including management of complexity of treatment, adverse events, tolerability, and

Table 3. Review of HCV Treatment Studies

Author, year of study	Treatment	Treatment length (*wk*)	Total patients, N	AA, n (%)	Non-AA SVR (%)	AA SVR (%)
Reddy et al,[57] 1999	IFNα-2b or consensus IFN	24	472	40 (8)	12	2
McHutchison et al,[83] 2000	IFNα-2b	24	230	12 (5)	6	0
	IFNα-2b	48	489	13 (3)	16	0
	IFNα-2b + RBV	24	497	15 (3)	34	20
	IFNα-2b + RBV	48	496	13 (3)	41	23
Theodore et al,[82] 2003	IFNα-2b (3 MU thrice weekly)	24	42	12 (29)	4	0
	IFNα-2b (5 MU daily)	24	32	8 (25)	10	11
Jeffers et al,[67] 2004	PEG-IFNα-2a + RBV	48	106	78 (74)	39	26
Muir et al,[68] 2004	PEG-IFNα-2b + RBV	48	200	100 (50)	52	19
Conjeevaram et al,[69] 2006	PEG-IFNα-2a + RBV	48	401	196 (49)	52	28
Hezode et al,[95] 2009	PEG-IFNα-2a + RBV	48	82	2 (2)	46	
	PEG-IFNα-2a + RBV + TVR	12	82	2 (2)	60	
	PEG-IFNα-2a + RBV + TVR/ PEG-IFNα-2a + RBV	12/12	81	1 (1)	69	
	PEG-IFNα-2a + TVR	12	78	1 (1)	36	
McHutchison et al,[96] 2009	PEG-IFNα-2a + RBV	48	75	9 (12)	41[a]	11
	PEG-IFNα-2a + RBV + TVR	12	17	3 (18)	35[a]	
	PEG-IFNα-2a + RBV + TVR/ PEG-IFNα-2a + RBV	12/12	79	7 (9)	61[a]	44[b]
	PEG-IFNα-2a + RBV + TVR/ PEG-IFNα-2a + RBV	12/36	79	8 (10)	67[a]	
McHutchison et al,[97] 2010	PEG-IFNα-2a + RBV	48	114	10 (9)	14	10
	PEG-IFNα-2a + RBV + TVR/ PEG-IFNα-2a + RBV	12/12	115	9 (8)	54	22
	PEG-IFNα-2a + RBV + TVR	24	111	10 (9)	27	0
	PEG-IFNα-2a + RBV + TVR/ PEG-IFNα-2a + RBV	24/24	113	11 (10)	53	55
Kwo et al,[98] 2010	Part 1					
	PEG-IFNα-2b + RBV	48	104	16 (15)	42	13
	PEG-IFNα-2b + RBV/PEG-IFNα-2b + RBV + BOC	4/24	103	15 (15)	59	40
	PEG-IFNα-2b + RBV/PEG-IFNα-2b + RBV + BOC	4/44	103	15 (15)	78	53
	PEG-IFNα-2b + RBV + BOC	28	107	18 (17)	57	39
	PEG-IFNα-2b + RBV + BOC	48	103	14 (14)	73	29
	Part 2					
	PEG-IFNα-2b + RBV + BOC	48	16	4 (25)	50	
	PEG-IFNα-2b + RBV (low dose) + BOC	48	59	16 (27)	36	
Bacon et al,[94] 2011	PEG-IFNα-2b + RBV	48	80	12 (15)	24	8
	PEG-IFNα-2b + RBV/PEG-IFNα-2b + RBV + BOC (PEG-IFNα-2b + RBV)	4/32 (12)	162	18 (11)	58	61
	PEG-IFNα-2b + RBV/PEG-IFNα-2b + RBV + BOC	4/44	161	19 (12)	68	53
Poordad et al,[87] 2011	PEG-IFNα-2b + RBV	48	363	52 (14)	40	23
	PEG-IFNα-2b + RBV/PEG-IFNα-2b + RBV + BOC (PEG-IFNα-2b + RBV)	4/20 (24)	368	52 (14)	67	42
	PEG-IFNα-2b + RBV/PEG-IFNα-2b + RBV + BOC	4/44	366	55 (15)	68	53
Jacobson et al,[99] 2011	PEG-IFNα-2a + RBV	48	361	28 (8)	46	25
	PEG-IFNα-2a + RBV + TVR/ PEG-IFNα-2a + RBV	12/12 or 36	363	26 (7)	75	62
	PEG-IFNα-2a + RBV + TVR/ PEG-IFNα-2a + RBV	8/16 or 40	364	40 (11)		
Sherman et al,[86] 2011	PEG-IFN α-2a + RBV + TVR/ PEG-IFNα-2a + RBV[c]	12/12	162	17 (10)	92	88
	PEG-IFNα-2a + RBV + TVR/ PEG-IFN2a + RBV[c]	12/36	160	17 (11)	87	88
	PEG-IFNα-2a + RBV + TVR/ PEG-IFN2a + RBV	12/36	118	20 (17)	64	65

AA, African American; BOC, boceprevir; TVR, telaprevir.

[a]Overall SVR.

[b]All telaprevir groups combined.

[c]Random drug regimen assignment in those subjects with an extended rapid virologic response.

Table 4. Differences in HCV Epidemiology, Natural History, Disease Progression, and Outcomes

Factor	African Americans	White Americans
Prevalence	High prevalence of HCV Increased rate of HCV-related death	High prevalence of HCV
Genotype	Virus: higher rate of genotype 1b More difficult to treat genotype 1 Host: lower prevalence of CC IL-28B genotype	Virus: higher rate of genotype 1a Host: higher prevalence of CC IL-28B genotype (non-CC genotype in whites responded to treatment less than CC genotype in blacks)
Disease progression	More frequent evolution to chronic state from acute infection Less severity and slower progression Lower ALT than other ethnic groups Lower prevalence of cirrhosis Hepatic fibrosis progression (inconclusive) High risk to disease sequelae	Less likely to evolve to chronic infection Higher prevalence of cirrhosis
Treatment response	Less responsive to IFN-based therapy, including use of a protease inhibitor Fewer patients represented in clinical trials	Better response rates than African Americans Better representation in clinical trials
HCC risk	Higher incidence rate of HCC HCC incidence rate of 5.4%	Incidence rates of HCC 1%–4% per year
Liver transplantation	Underrepresented on liver transplant list Lower survival rate after transplantation	More recipients and donors both pre-MELD and MELD era Higher survival rate after transplantation

ALT, alanine aminotransferase.

cost. This is further exaggerated among African Americans because of the relatively lower SVR rates achieved and their limited representation in clinical trials, resulting in a dearth of meaningful observations until the postmarketing phase of drug development.

African Americans represented 10.6% of total enrollment in the most recent phase 3 clinical trials of telaprevir or boceprevir.[84] Hence, data generated from these late-phase clinical studies are limited for this underrepresented population. In the case of boceprevir, however, because of lower treatment response rates in African Americans, a separate treatment group for African American subjects was created, resulting in the enrollment of 159 subjects in this group, which represented 15% of total study enrollment. The success of this targeted enrollment strategy may be a useful approach to increase African American enrollment going forward, and it was invaluable for providing data on differences in response rates and adverse events in this population. Regardless of the strategy used for enrollment, data suggest that many African Americans are more likely to be ineligible for trial enrollment. Melia et al[85] noted that African Americans were 65% less likely to be eligible for treatment. Reasons cited for ineligibility included leukopenia, anemia, and concomitant comorbid conditions such as diabetes mellitus and chronic kidney disease. The authors therefore suggest that further consideration should be given to eligibility criteria, including a decrease in neutrophil requirement, to allow for improved study inclusion and treatment rates in African Americans.

The introduction of triple therapy with boceprevir and telaprevir has demonstrated a substantial improvement in SVR rates for treatment-naive and treatment-experienced HCV patients. When comparing African American with non–African American patients, SVR rates in the ILLUMINATE study, inclusive of a telaprevir-based regimen, were 60% vs 74%, respectively, and the SPRINT-2 study, inclusive of a boceprevir-based regimen, resulted in SVRs of 53% vs 68%, respectively.[86,87] However, differences were still noted in overall treatment response rates in African Americans, a facet of this disease process that is not well understood. However, our hope is that the promise of new direct-acting antiviral agents will bring with it the ability to eradicate infection in all difficult-to-treat populations.

Liver Transplantation in Hepatitis C Infection

In addition to disparities noted in HCV prevalence, natural history, and treatment response, African Americans also have a higher disease burden and higher prevalence of HCC than other racial and ethnic groups.[53,88,89] Although the same eligibility criteria for liver transplantation apply, African Americans are more likely to have an advanced stage of HCC at presentation and thus be considered high risk or unsuitable for liver transplantation.[90] Regardless of the indication for listing, African Americans were found to be underrepresented on the liver transplantation waiting list even when matched to those with similar wait times. African Americans were also noted to be more likely to die while waiting for liver transplantation.[46]

A sentinel study compared pre-MELD and MELD-era liver transplantation survival in HCC patients with and

Table 5. Unmet Needs in African Americans With Chronic HCV Infection

Better understanding of natural history of HCV infection in African Americans compared with other groups
More understanding of viral and host genetic diversity to generate better tailored treatments
Better accessibility, affordability, and quality in both clinical trials and standard treatment
Determine mechanisms of differences in disease progression
Increase access to liver transplantation for racial and ethnic minorities
Improvement in allograft and patient survival in the post–liver transplantation setting

without HCV. These investigators demonstrated that in the MELD era, HCV patients without HCC experienced a decrease in 5-year graft and patient survival. Those with HCV and HCC had improved graft and patient outcomes at 1 and 3 years; however, this advantage nearly disappeared at 5 years. Not surprisingly, in both the pre-MELD and MELD eras, there were more white recipients and donors, regardless of HCV status. Another notable observation from this study was that African Americans with HCC had a 30% lower survival rate than other races after adjusting for other factors.[91] In a study of clinical outcomes of liver transplantation recipients, Nair et al[92] also showed that African Americans with HCV had higher rates of primary graft non-function, an almost 2-fold increase in graft failure that was due to chronic rejection, a higher 30-day mortality, and worsened 2-year survival than other races. Furthermore, recipient race has been noted to be an independent predictor of survival in recipients with HCV.[93] African American race was an independent predictor of patient survival after liver transplantation compared with whites.[90] Although the data speaking to racial disparities in liver transplantation are relatively robust, the possible reasons for this inequality remain underexplored.

Challenges and Future Directions

Many barriers remain before chronic HCV infection can be eradicated in African Americans and, more globally, all infected patients. Because of the silent nature of disease before the onset of late stage sequelae, many patients harbor infection without knowledge of their infectious status. This results in missed opportunities for treatment and preventative care. In addition, those at risk for disease-related complications have failed to be entered into surveillance programs such as those that exist for HCC. To facilitate improvements in outcomes in African Americans and, more broadly, all patients with chronic HCV infection, more effective screening must be provided, and more efficacious therapies must become available. Such strides undoubtedly can be facilitated through a promotion of awareness of HCV infection and its sequelae and additional research in difficult-to-treat populations, such as African Americans, to determine the basis of viral persistence, host viral responses, and differences in response to therapy (Tables 4 and 5). Our ability to overcome these HCV-specific factors will result in better outcomes for all patients with chronic HCV infection.

Conclusion

Viral hepatitides represent a public health concern whose impact on morbidity and mortality are only presently being recognized. As outlined in this review, there are many racial and ethnic disparities in the context of hepatitis B and C infection that have yet to be addressed in the literature. Attention to these disparities will not only increase our understanding of various aspects of disease but may also improve clinical outcomes for patients. Further understanding of these conditions, commitment to all-encompassing research efforts, and development of new, efficacious, and cost-effective treatment strategies will hopefully lead to eradication of these viral diseases in all, irrespective of race and ethnicity.

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Conflicts of interest
This author discloses the following: K. Rajender Reddy has served on the advisory boards for Merck, Genentech-Roche, Gilead, BMS, Idenix, Vertex, Janssen, and Abbvie and has conducted research with Merck, Genentech-Roche, Gilead, BMS, Vertex, Janssen, and Abbvie. The remaining authors disclose no conflicts.

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