Evaluation of Hepatitis C Virus as a Risk Factor for HIV-Associated Neuroretinal Disorder

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Background. Both hepatitis C virus (HCV) and human immunodeficiency virus (HIV) penetrate the central nervous system. HIV-associated neuroretinal disorder (HIV-NRD), a visual impairment of reduced contrast sensitivity and reading ability, is associated with cytokine dysregulation and genetic polymorphisms in the anti-inflammatory interleukin 10 (IL-10) signaling pathway. We investigated associations between HCV and HIV-NRD and between HCV and single-nucleotide polymorphisms (SNPs) in the IL-10 receptor 1 (*IL10R1*) gene.

Methods. Logistic and Cox regression analysis were used to analyze risk factors for HIV-NRD in 1576 HIV-positive patients who did not have an ocular opportunistic infection at enrollment. Median follow-up was 4.9 years (interquartile range, 2.4–8.8 years). Four *IL10R1* SNPs were examined in a subset of 902 patients.

Results. The group included 290 patients with chronic HCV infection, 74 with prior infection, and 1212 with no HCV markers. There were 244 prevalent cases of HIV-NRD and 263 incident cases (rate = 3.9/100 person-years). In models adjusted for demographics, HIV treatment and status, liver function, and immune status, both the prevalence and incidence of HIV-NRD were significantly higher in patients with chronic HCV infection (odds ratio = 1.54; 95% confidence interval [CI], 1.03–2.31 and hazard ratio = 1.62; 95% CI, 1.13–2.34, respectively), compared to patients with no HCV markers. Chronic HCV was associated with rs2228055 and 2 additional *IL-10R1* SNPs expected to reduce IL-10 signaling. HIV-NRD was not significantly associated with these SNPs.

Conclusions. HCV is a possible risk factor for HIV-NRD. Genetic analysis suggests that alterations in the IL-10 signaling pathway may increase susceptibility to HIV-NRD and HCV infection. Inflammation may link HCV and HIV-NRD.

Keywords. AIDS; hepatitis C virus; HIV-associated neuroretinal disorder; cytomegalovirus retinitis; HIV-1.

In the era of combination antiretroviral therapy, survival of human immunodeficiency virus (HIV)–positive individuals has increased; however, patients continue to have central nervous system (CNS) abnormalities that reduce quality of life. HIV-associated presumed neuroretinal disorder (HIV-NRD) is a visual abnormality that occurs in about 10%–15% of patients with AIDS who do not have ocular opportunistic infections. HIV-NRD is characterized by reduced contrast sensitivity [1–3], reduced color sensitivity [4–6], and deficits in visual fields [7, 8] in the absence of impaired visual acuity. HIV-NRD may also compromise reading speed and reduce quality of life [9].

The etiology of HIV-NRD is unknown, but cytokine dysregulation and chronic inflammation are considered likely cofactors. Genetic studies show that risk in European Americans is associated with mutations that are expected to decrease production of interleukin 10 (IL-10), an anti-inflammatory cytokine. Genetic markers include single-nucleotide polymorphisms (SNPs) in introns of the IL-10 receptor and an IL-10 receptor 1 (*IL10R1*) haplotype [10]. The nongenetic risk factors for HIV-NRD

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include age, race, a history of injection drug use (IDU), lower hemoglobin, decreasing Karnofsky score, and low $CD4^+$ T-cell count [3].

Due to shared routes of transmission, many HIV-positive patients are also infected with the hepatitis C virus (HCV). Chronic HCV infection causes systemic inflammation [11] and increases mortality in HIV-positive patients by 35%–50% [12]. Both cell culture studies [13] and analysis of patient specimens indicate that HCV is present within the CNS and replicates there [14–18]. HCV is reported to have CNS effects that include reduced learning and memory abilities [14, 19–22]. These deficits may improve in patients who clear HCV infection [23]. Despite successful HIV management, patients coinfected with HCV have an increased risk of neurocognitive dysfunction [24–26] and HIV-associated dementia [20].

Because HCV is proinflammatory and penetrates the CNS, this study examined the impact of HCV infection on the prevalence and incidence of HIV-NRD in a large cohort of AIDS patients enrolled in the Longitudinal Studies of the Ocular Complications of AIDS (LSOCA). LSOCA is one of only a few cohort studies limited to persons diagnosed with AIDS, but without further exclusion criteria. It focuses exclusively on the era following the introduction of combination antiretroviral therapy. Because of the associations between HIV-NRD and the IL-10 signaling pathway, genetic associations between 4 *IL10R1* SNPs and HCV risk were also examined.

METHODS

Study Subjects and Design

At enrollment, subjects in LSOCA were aged ≥13 years with a diagnosis of AIDS according to the 1993 definition of the Centers for Disease Control and Prevention (CDC). The LSOCA population is similar in age, race, and sex to the US AIDS population, except it has a lower percentage of patients with a history of IDU [27, 28]. At enrollment, demographic information and past medical history were obtained and physical and ophthalmologic examinations were performed by a LSOCA-certified ophthalmologist [28]. Ophthalmologic examinations were conducted at each visit.

Follow-up occurred every 3 months for patients with an ocular opportunistic infection (eg, cytomegalovirus retinitis [CMV-R]) and every 6 months otherwise. Most HIV type 1 (HIV-1) RNA assays were performed using the Roche Amplicor system. All baseline samples were tested for anti-HCV antibodies using the third-generation enzyme immunoassay version 2.0 (Abbott). HCV RNA testing was performed on all samples that tested positive for anti-HCV antibodies and on all samples from injection drug users, using the Roche COBAS AMPLICOR Hepatitis C Virus Test, version 2.0 (lower limit of detection, 50 IU/mL), except as noted previously; we estimate that this testing strategy identified about 93% of the patients with HCV RNA in serum [12]. Patients with HCV RNA were considered to have chronic infection, and patients with anti-HCV antibodies but without detectable HCV RNA were considered to have cleared a previous infection. The liver fibrosis stage was estimated in 451 subjects for whom data were available by calculating the aspartate aminotransferase platelet ratio index (APRI) score; a score ≥1.45 was used to distinguish minimal from advanced fibrosis/cirrhosis [29]. Polymorphisms in the *IL10R1* gene that occur at relatively high frequency (minor allele frequency ≥3% in the general population) and are predicted to change amino acids and thus to influence IL-10 signaling were determined in 902 patients, as previously described [10]. The genotyping success rate was at least 95% for each SNP examined. This study was approved by the institutional review board at each center, and all patients gave written informed consent.

Data Analysis

Data available as of 31 December 2011 were included. HIV-NRD was defined as <1.50 log contrast sensitivity units. Among the 2393 subjects enrolled in LSOCA, 1576 were included in the analyses of HIV-NRD prevalence and 1220 were included in the analyses of HIV-NRD incidence (Supplementary Figure 1). Because decreased visual acuity (eg, from an ocular infection or from media opacities) decreases contrast sensitivity and does not indicate HIV-NRD, 815 patients were excluded from the analysis carried out to determine HIV-NRD prevalence (Table 1) and from the analysis carried out to analyze the factors associated with HIV-NRD prevalence (Table 2) because they had ocular opportunistic infection(s) (n = 536), visual acuity <20/40 (n = 18), or lacked data regarding HCV status (n = 261). An additional 356 were excluded from the analysis of factors associated with HIV-NRD incidence (Table 3) because they had HIV-NRD at baseline or lacked follow-up data.

The population characteristics at enrollment were calculated by HIV-NRD status. Race/ethnicity was analyzed as white/non-Hispanic versus all others. The associations between each characteristic and HIV-NRD status were assessed using χ^2 tests. Unadjusted and adjusted logistic regression was used to identify factors associated with prevalent HIV-NRD at enrollment. The adjusted model included all baseline risk factors shown in Table 2: HCV serostatus, age (dichotomized at the median age of 43 years), sex, race, HIV exposure category (dichotomized as IDU vs all others), $CD4^+$ T-cell count, HIV load, highly active antiretroviral therapy use, HIV retinopathy status, and platelet count.

The cumulative incidence (1 – survival) Kaplan-Meier curves were compared for HCV uninfected, cleared, and chronic. Unadjusted and adjusted Cox regression was used to identify factors associated with incident HIV-NRD. Follow-up time was calculated as the time from study entry to first HIV-NRD event in either eye or censoring (death, 31 December

Table 1. Characteristics of the Population at Enrollment by HIV-Associated Neuroretinal Disorder Status

Characteristic (at Enrollment)	Prevalent HIV-NRD (n = 244)		No prevalent HIV-NRD (n = 1332)		*P* Value[a]
	%	No.	%	No.	
HCV status					
Uninfected	68	167	78	1045	<.001
Cleared	3	8	5	66	
Chronic	28	69	17	221	
Age					
<43 y	44	107	47	620	.438
≥43 y	56	137	53	712	
Sex					
Male	74	181	82	1094	.004
Female	26	63	18	238	
Race					
White	36	89	49	652	<.001
Nonwhite	64	155	51	680	
Intravenous drug use					
No	80	195	87	1154	.006
Yes	20	49	13	178	
$CD4^+$ T-cell count					
0–100 cells/μL	34	84	27	363	.024
>100 cells/μL	66	160	73	965	
HIV load, log_{10} copies/mL					
<2.60	34	77	35	450	.577
≥2.60–4.00	29	64	31	398	
>4.00–5.00	21	46	17	215	
>5.00	17	37	17	216	
HAART					
No	19	47	15	197	.071
Yes	81	196	85	1135	
HIV retinopathy in either eye					
No	97	236	98	1301	.379
Yes	3	8	2	31	
Platelet count, cells/μL					
≤60 000	3	8	2	29	.298
>60 000	97	236	98	1301	
APRI					
≥1.45	2	6	1	19	.24[b]
<1.45	27	65	27	361	
Missing	71	173	71	952	

Neuroretinal disorder was defined as <1.50 log contrast sensitivity units. Participants without ocular opportunistic infections, with at least 1 eye with visual acuity of 20/40 or better and without cataract, and with available HCV data are included.

Abbreviations: APRI, aspartate aminotransferase platelet ratio index; HAART, highly active antiretroviral therapy; HCV, hepatitis C virus; HIV-NRD, human immunodeficiency virus–associated neuroretinal disorder.

[a] χ^2 test.

[b] *P* value for comparison among those with APRI data.

2011, or to the date of the last study contact for patients who were lost to follow-up). Sensitivity analyses were performed to examine the hazard ratio (HR) for the first 3 years of follow-up versus later time points, and to determine the impact of censoring data when both eyes had <20/40 acuity and/or developed cataract. During the study, the Pelli-Robson charts were replaced at the clinics due to wear. The manufacturing process for the charts was changed in 2005, which resulted in patients' ability to read up to 6 additional letters. The new version was not in universal use until May 2010. Sensitivity analyses were performed to determine the impact of censoring data at December 2006 and at 2010. Censoring of the data at 2006 or at 2010 resulted in no substantive changes in interpretation and therefore results are shown not making any adjustments for manufacturing changes in the chart. Statistical analyses were performed with SAS software, version 9.2 (SAS Institute Inc, Cary, North Carolina) and R software version 2.13.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Risk Factors for HIV-NRD at Baseline

The study group included 244 patients with HIV-NRD and 1332 patients without HIV-NRD (Table 1). Patients with HIV-NRD at baseline were more likely to have chronic HCV infection ($P < .001$), to be female ($P = .004$), to be nonwhite ($P < .001$), to have a history of IDU ($P = .006$), and to have a $CD4^+$ T-cell count ≤100 cells/μL ($P = .024$). In an adjusted multivariable logistic regression model, prevalent HIV-NRD was significantly positively associated with 3 factors: chronic HCV infection (odds ratio [OR], 1.54; 95% confidence interval [CI], 1.03–2.31); female sex (OR, 1.54; 95% CI, 1.09–2.18); and nonwhite race/ethnicity (OR, 1.49; 95% CI, 1.09–2.05). Prevalent HIV-NRD was negatively associated with a $CD4^+$ T-cell count >100 cells/μL (OR, 0.66; 95% CI, .46–.94; Table 2). A subset analysis was performed on 476 subjects for whom data were available to assess the impact of liver fibrosis stage on the association between HIV-NRD and chronic HCV infection. In a logistic regression model of HIV-NRD that controlled for APRI ≥1.45, the magnitude of the association between HIV-NRD and HCV for chronic versus no markers of HCV was similar to the original analysis (OR, 1.64; 95% CI, .88–3.05; $P = .16$), although no longer statistically significant with this reduced sample size. HIV-NRD was not significantly associated with APRI ≥1.45 (OR, 1.50 [95% CI, .56–4.01; $P = .43$; Supplementary Table 1).

Risk Factors for the Development of HIV-NRD

The development of HIV-NRD was analyzed in 1220 subjects with a median follow-up of 4.9 years (interquartile range

Table 2. Logistic Regression of Risk Factors Associated With HIV-Associated Neuroretinal Disorder at Enrollment

	Unadjusted[a]			Adjusted[a]		
Risk Factor (at Enrollment)	OR	95% CI	*P* Value	OR	95% CI	*P* Value
HCV status						
Uninfected	Ref			Ref		
Cleared	0.76	(.36–1.61)	.110	0.62	(.27–1.41)	.092
Chronic	1.95	(1.42–2.68)	.001	1.54	(1.03–2.31)	.011
Age						
<43 y	Ref			Ref		
≥43 y	1.11	(.85–1.47)	.438	1.31	(.95–1.80)	.101
Sex						
Male	Ref			Ref		
Female	1.60	(1.16–2.20)	.004	1.54	(1.09–2.18)	.015
Race						
White	Ref			Ref		
Nonwhite	1.67	(1.26–2.21)	<.001	1.49	(1.09–2.05)	.014
Intravenous drug use						
No	Ref			Ref		
Yes	1.63	(1.15–2.31)	.006	1.21	(.78–1.89)	.398
$CD4^+$ T-cell count						
0–100 cells/μL	Ref			Ref		
>100 cells/μL	0.72	(.54–.96)	.024	0.66	(.46–.94)	.022
HIV load, $\log_{10}$ copies/mL						
<2.60	Ref			Ref		
≥2.60–4.00	0.94	(.66–1.34)	.398	0.91	(.63–1.31)	.913
>4.00–5.00	1.25	(.84–1.86)	.183	1.04	(.67–1.61)	.392
>5.00	1.00	(.65–1.53)	.788	0.76	(.46–1.25)	.245
HAART						
No	Ref			Ref		
Yes	0.72	(.51–1.03)	.072	0.83	(.56–1.24)	.359
HIV retinopathy in either eye						
No	Ref			Ref		
Yes	1.42	(.65–3.13)	.381	1.18	(.50–2.81)	.707
Platelet count, cells/μL						
≤60 000	Ref			Ref		
>60 000	0.66	(.30–1.45)	.300	0.75	(.32–1.79)	.522

HIV-associated neuroretinal disorder was defined as <1.50 log contrast sensitivity units. Participants without ocular opportunistic infections, with at least 1 eye with visual acuity of 20/40 or better and without cataract, and with available HCV data are included.

Abbreviations: CI, confidence interval; HAART, highly active antiretroviral therapy; HCV, hepatitis C virus; HIV, human immunodeficiency virus; OR, odds ratio.

[a] Unadjusted and adjusted logistic regression results, *P* value calculated using Wald χ^2. Adjusted model includes all risk factors.

[IQR], 2.4–8.8). There were 263 incident cases of HIV-NRD. In an adjusted Cox proportional hazards regression model, incident HIV-NRD was significantly associated with 4 factors: chronic HCV infection (hazard ratio [HR], 1.64; 95% CI, 1.14–2.37), age ≥43 years (HR, 1.59; 95% CI, 1.22–2.06), female sex (HR = 1.65; CI, 1.22–2.24), and HIV load >10 000 copies/mL (Table 3). The association between chronic HCV infection and HIV-NRD remained significant in sensitivity analyses that investigated the impact of (1) censoring data when both eyes have <20/40 acuity and/or developed cataract, (2) censoring data at December 2006, (3) censoring data at 2010 (Supplementary Table 2).

Kaplan-Meier curves of the cumulative incidence of HIV-NRD are shown in Figure 1. These data show the positive association between chronic HCV infection and the development of HIV-NRD expected based on the data in Table 3 and suggest that cleared HCV infection might increase the risk of HIV-NRD in a time-variant manner. This possibility was investigated through a sensitivity analysis of the Cox regression results (Supplementary Table 2). For patients with cleared HCV

Table 3. Cox Regression of Risk Factors Associated With Incident HIV-Associated Neuroretinal Disorder During Follow-up

			Unadjusted[a]			Adjusted[a]		
Risk Factor (at Enrollment)	Rate/100 PY	Events/No.	HR	95% CI	*P* Value	HR	95% CI	*P* Value
HCV status								
Uninfected	3.4	188/959	Ref			Ref		
Cleared	5.0	13/59	1.38	(.79–2.42)	.262	1.30	(.73–2.31)	.372
Chronic	6.7	62/202	1.81	(1.36–2.41)	<.001	1.62	(1.13–2.34)	.010
Age								
<43 y	3.1	99/558	Ref			Ref		
≥43 y	4.6	164/662	1.45	(1.13–1.86)	.004	1.62	(1.24–2.11)	<.001
Sex								
Male	3.5	197/998	Ref			Ref		
Female	6.2	66/222	1.70	(1.28–2.24)	<.001	1.67	(1.23–2.26)	.001
Race								
White	3.3	114/595	Ref			Ref		
Nonwhite	4.5	149/625	1.31	(1.03–1.68)	.029	1.13	(.86–1.48)	.378
Intravenous drug use								
No	3.7	222/1059	Ref			Ref		
Yes	5.6	41/161	1.37	(.98–1.92)	.063	0.80	(.58–1.09)	.155
$CD4^+$ T-cell count								
0–100 cells/μL	5.2	75/309	Ref			Ref		
>100 cells/μL	3.6	188/907	0.73	(.56–.95)	.021	0.92	(.62–1.39)	.706
HIV load, $\log_{10}$ copies/mL								
<2.60	2.8	69/429	Ref			Ref		
≥2.60–4.00	3.4	76/366	1.24	(.89–1.72)	.197	1.22	(.88–1.69)	.244
>4.00–5.00	6.3	60/196	2.16	(1.53–3.06)	<.001	2.11	(1.47–3.04)	<.001
>5.00	5.4	45/187	1.80	(1.23–2.62)	.002	1.61	(1.05–2.46)	.029
HIV retinopathy in either eye								
No	3.8	255/1195	Ref			Ref		
Yes	7.9	8/25	1.89	(.93–3.82)	.077	1.51	(.73–3.11)	.264
Platelet count, cells/μL								
≤60 000	8.0	7/24	Ref			Ref		
≥60 000	3.9	256/1194	0.51	(.24–1.09)	.082	0.52	(.24–1.12)	.095

HIV-associated neuroretinal disorder (HIV-NRD) was defined as <1.50 log contrast sensitivity units. Participants without ocular opportunistic infections or HIV-NRD at enrollment and with at least 1 eye with visual acuity of 20/40 or better and at least 1 follow-up visit are included.

Abbreviations: CI, confidence interval; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HR, hazard ratio; PY, person-years.

[a] Unadjusted and adjusted Cox proportional hazards regression results, *P* value calculated using Wald χ^2. Adjusted model includes all risk factors.

infection, in an unadjusted model that allowed the HR to change at 3 years after enrollment, the HR for the first 3 years was 2.07 (95% CI, 1.14–3.74; $P = .017$), whereas the subsequent HR was 0.33 (95% CI, .05–2.37; $P = .269$). The interaction between cleared HCV infection and time had a *P* value of .08, showing a trend toward a time-variable effect of HCV infection and subsequent clearance. For comparison, the interaction between chronic HCV infection and time had a *P* value of .65, indicating that the risk associated with chronic infection was less variable over time.

A subset analysis was performed on 342 subjects to assess the impact of liver fibrosis stage on the association between the development of HIV-NRD and chronic HCV infection. In a regression model that controlled for APRI ≥1.45, the HR was 1.42, similar to the HR in the main analysis (1.64); however, the 95% CI and *P* value (.74–2.74 and $P = .30$, respectively) did not show a statistically significant relationship between HIV-NRD and chronic HCV infection. Incident HIV-NRD was significantly associated with APRI ≥1.45 (HR, 4.72; 95% CI, 2.22–10.01; $P < .01$), raising the possibility that advanced liver disease, some factor associated with advanced liver disease such as inflammation, or some factor associated with HIV/AIDS such as pancytopenia/thrombocytopenia increases the risk of HIV-NRD (Supplementary Table 1).

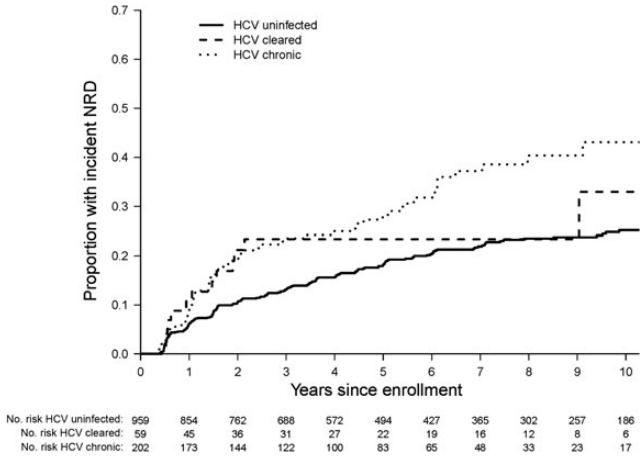

Figure 1. Kaplan-Meier curve of the cumulative incidence of human immunodeficiency virus–associated neuroretinal disorder (NRD). The proportion of subjects (n = 1220) with incident NRD over time since enrollment is shown by hepatitis C virus (HCV) status. Patients never infected with HCV (solid line) had a lower incidence of NRD compared to patients with previous HCV infection (dashed line) and patients with chronic HCV infection (dotted line).

IL10R1 Polymorphisms Are Associated With HCV Infection

Four SNPs in the *IL10R1* gene were examined for associations with chronic HCV infection using Fisher exact test. The number of patients who were eligible for this analysis and had data for at least 1 SNP was 902. The availability of data varied from 860 to 887 for the 4 SNPs analyzed (Supplementary Table 3). Of these patients, 140 had prevalent NRD at baseline. Three of the 4 SNPs had significant associations with chronic HCV infection in 1 or more of the populations examined. The rs2228055 SNP was associated with HCV infection in the total study group ($P = .02$) and in white patients ($P = .01$); rs2229113 trended toward significance in the total study group ($P = .07$) and was significant in white patients ($P = .04$); and rs3135932 was significant in white patients ($P = .01$) (Table 4). The similar trend of HCV association observed for rs2229113 and rs3135932 may be due to the strong linkage disequilibrium they have with each other in European Americans (Supplementary Table 3). The rs2229114 SNP was not associated with HCV. None of the 4 SNPs was associated with baseline HIV-NRD ($P > .10$; data not shown). The distribution of allele frequencies of *IL-10R1* SNPs was very different between European Americans and African Americans (Supplementary Table 3). Among African Americans, the frequencies of variant alleles were much lower, resulting in greatly reduced statistical power to detect any association with HCV susceptibility. In addition, the linkage disequilibrium pattern observed in European Americans was not observed in African Americans.

Table 4. Allelic Distribution and Association of *IL10R1* With Baseline Hepatitis C Virus

	All Races				White Race Only			
Allelic Distribution	HCV			*P* Value[a]	HCV			*P* Value[a]
rs3135932	Uninfected (n = 692)	Cleared (n = 40)	Chronic (n = 148)		Uninfected (n = 441)	Cleared (n = 22)	Chronic (n = 43)	
A/A	565 (81.7%)	31 (77.5%)	121 (81.8%)	.44	332 (75.3%)	14 (63.6%)	23 (53.5%)	.01
A/G	117 (16.9%)	8 (20.0%)	27 (18.2%)		99 (22.4%)	7 (31.8%)	20 (46.5%)	
G/G	10 (1.4%)	1 (2.5%)	0 (0.0%)		10 (2.3%)	1 (4.6%)	0 (0.0%)	
rs2228055	Uninfected (n = 697)	Cleared (n = 40)	Chronic (n = 150)		Uninfected (n = 444)	Cleared (n = 22)	Chronic (n = 45)	
A/A	653 (93.7%)	35 (87.5%)	144 (96.0%)	.02	410 (92.3%)	17 (77.3%)	44 (97.9%)	.01
A/G	43 (6.2%)	3 (7.5%)	6 (4.0%)		33 (7.4%)	3 (13.6%)	1 (2.2%)	
G/G	1 (0.1%)	2 (5.0%)	0 (0.0%)		1 (0.2%)	2 (9.1%)	0 (0.0%)	
rs2229113	Uninfected (n = 677)	Cleared (n = 39)	Chronic (n = 144)		Uninfected (n = 431)	Cleared (n = 21)	Chronic (n = 43)	
A/A	51 (7.5%)	2 (5.1%)	14 (9.7%)	.07	40 (9.3%)	2 (9.5%)	7 (16.3%)	.04
G/A	230 (34.0%)	13 (33.3%)	54 (37.5%)		161 (37.3%)	7 (33.3%)	23 (53.5%)	
G/G	396 (58.5%)	24 (61.5%)	76 (52.8%)		230 (53.4%)	12 (57.1%)	13 (30.2%)	
rs2229114	Uninfected (n = 695)	Cleared (n = 39)	Chronic (n = 151)		Uninfected (n = 440)	Cleared (n = 21)	Chronic (n = 45)	
C/C	653 (94.0%)	38 (97.4%)	147 (97.4%)	.48	402 (91.4%)	20 (95.2%)	42 (93.3%)	1.00
C/T	39 (5.6%)	1 (2.6%)	4 (2.6%)		35 (7.9%)	1 (4.8%)	3 (6.7%)	
T/T	3 (0.4%)	0 (0.0%)	0 (0.0%)		3 (0.7%)	0 (0.0%)	0 (0.0%)	

Abbreviation: HCV, hepatitis C virus.

[a] Fisher exact test for any association between rows and columns.

DISCUSSION

In a large cohort of patients with CDC-defined AIDS, this study demonstrated that chronic HCV infection increased the risk of having HIV-NRD at enrollment and the risk of developing HIV-NRD over time. In addition to having chronic HCV infection, patients with HIV-NRD at enrollment were more likely to be female, to be of nonwhite race, to have a history of IDU, and to have $CD4^+$ T cells ≤100 cells/μL. The risk of developing HIV-NRD was higher in patients aged >43 years (the median of the population). It was also higher in females and in patients with detectable HIV load.

Several of the risk factors for prevalent and/or incident HIV-NRD are consistent with prior evidence that inflammation and cytokine dysregulation play an etiological role in the development of this impairment. Low $CD4^+$ count, higher HIV load, age, and HCV infection are all associated with increased inflammation and/or decreased adaptive immune responses; females are predisposed to autoimmune disorders, which often involve proinflammatory cytokines.

IL-10 is an important anti-inflammatory cytokine. *IL-10R1* is the subunit of the IL-10 receptor complex that binds IL-10, mediating its biological effects. The 4 SNPs in the *IL10R1* gene examined in this study were chosen because they cause an amino acid substitution. Three of the 4 SNPs were associated with chronic HCV infection in 1 or more populations. The variant rs2228055 allele leads to an isoleucine to valine mutation at residue 203, which lies close to the cell membrane where the loss of the additional methyl group present on isoleucine may decrease receptor function [30]. The rs2229113 allele replaces an arginine with glycine at residue 330 in the cytoplasmic domain of the receptor, causing a loss-of-function mutation [31]. Similarly, the variant rs3135932 allele replaces serine-138 with glycine, leading to a conformational change in the extracellular domain of the protein and reduced function [32]. The rs2228055 SNP was significantly associated with chronic HCV infection in the total study group, whereas rs3135932 and rs2229113, which are in strong linkage disequilibrium with each other, were significantly associated with HCV infection in white patients only. Although the same variants may have a similar effect in African Americans, we did not have sufficient statistical power to detect such an association. These findings support earlier studies showing associations between rs2228055 and HCV viral persistence [33] and between rs3135932 and rs2229113 and HCV progression [34]. Polymorphisms in the IL-10 receptor leading to decreased IL-10 signaling and therefore increased inflammation may promote HCV persistence and disease progression. IL-10 promoter region variants associated with reduced IL-10 signaling have already been shown to increase susceptibility to HIV-NRD [10], indicating the importance of regulation of inflam- mation in HIV-NRD susceptibility. Reduced IL-10 signaling can decrease TNF-α suppression [35], increasing the risk of inflammatory myelin damage in the optic nerve, which leads to a visual dysfunction similar to that observed in patients with HIV-NRD. We did not find an association between the *IL-10R1* SNPs and HIV-NRD. It is possible that these SNPs are associated with HIV-NRD, but the limited sample size prevented us from observing this association.

The strengths of this study include the long and detailed follow-up of a large cohort of patients, the use of both antibody and viral RNA testing to establish HCV infection status, and the use of trained and expert ophthalmologists to detect HIV-NRD and other visual impairments. In addition, genetic testing was focused on a single gene, *IL10R1*, reducing the probability of detecting associations based on chance. The study also had some limitations, including the reliance of baseline testing to establish HCV infection status, the lack of complete data about liver fibrosis markers and *IL10R1* genotype, and manufacturing changes during follow-up in the eye charts used to assess contrast sensitivity.

In summary, HCV infection increases the risk of HIV-NRD. Inflammation may be the mechanistic link between HCV infection and HIV-NRD, although it is also possible that HCV contributes more directly by infecting ocular tissues, thereby reducing their integrity. Adequate vision is important for maintaining a high quality of life. Reducing systemic infections such as HCV infection, by treating appropriately selected patients, may decrease HIV-NRD and benefit patients with HIV/AIDS.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (http://cid.oxfordjournals.org). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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Roche Pharmaceuticals, GlaxoSmithKline, Alcon Laboratories, Corcept Therapeutics, and Genentech; has received past research support from Roche Laboratories; and currently acts as a data and safety monitoring board member for Applied Genetic Technologies Corporation. All other authors report no potential conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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