Published in final edited form as:

AIDS. 2010 July 17; 24(11): 1689–1695. doi:10.1097/QAD.0b013e32833a2a32.

Hepatitis C Infection in HIV-1 Natural Viral Suppressors

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INTRODUCTION

We have recently described a cohort of HIV-1 infected individuals, Natural Viral Suppressors (NVS), who have the ability to naturally suppress HIV-1 to undetectable levels.^{1,2} Although a number of studies attempting to determine the mechanisms involved in the control of HIV-1 have been performed in similar cohorts (alternatively referred to as elite suppressors, elite controllers, natural controllers),^{3–5} little is known about the ability of these individuals to control other viral infections. Given the shared transmission routes of both HIV and hepatitis C virus (HCV) and relatively high rates of co-infection seen in populations such the NVS cohort, we sought to characterize HCV infection in the context of HIV-infected individuals with low HIV-1 viral loads. Specifically, we sought to determine whether these individuals had the ability to control HCV (another virus capable of causing persistent infection), and whether the presence of HCV within the NVS affected specific HIV-related parameters (CD4 cell count and HIV-1 viral load).

METHODS

Study patients

The NVS cohort has been described in detail elsewhere.^{1,2} Briefly, after informed consent was obtained, NVS patients had to be confirmed HIV-1 positive by Western Blot and proviral DNA, and have demonstrated viral loads <400 copies/ml for a 2 year time period without the use of antiretroviral therapy (one viral load > 400 copies/ml in a 2 year period was allowed provided the subsequent values were < 400 copies/ml). All patients in the NVS cohort were required to have a Hepatitis C antibody test performed. For those with a positive Hepatitis C antibody, a follow-up PCR (quantitative or qualitative) was required.

Two race-control cohorts were created for comparison with the NVS cohort. The first control group was comprised of HIV/HCV co-infected patients and was defined by non-NVS status with a positive serology for both HIV and HCV. The second control group was comprised of HCV mono-infected patients (negative HIV but positive HCV serology). Data for both control groups were extracted retrospectively by performing a chart review at the

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Conflict of Interest: M.M.S., N.S., R.T., and R.R.R. report no conflict of interests.

Author roles:

M.M.S. – Study design, data collection, data analysis, manuscript preparation.

N.S.- Data collection, manuscript preparation.

R.T.- Data analysis, manuscript preparation.

R.R.R.- Study design, data analysis, manuscript preparation.

Baltimore VA's Clinical Case Registry (CCR) database. The HIV/HCV cohort included all HIV-1/HCV co-infected patients in the CCR database between 2/16/1997 and 2/16/2009 and the HCV mono-infected group included an equal number of randomly selected HCV mono-infected patients from the same time period in the same database.

Demographic and laboratory data collected

The following demographic data were collected: Age, sex, race, date of diagnosis of HCV and/or HIV, estimated date of infection of HCV acquisition, risk factor for HCV, history of HCV treatment. The following laboratory data was collected: HCV antibody and HCV viral load results (in the event of treatment history, pre-treatment values were used for analysis), HCV genotype, Hepatitis B serologies (Surface Ab and Ag, Core Ab, E Ab and Ag), AST, ALT, Albumin, AFP, and liver biopsy results (when available). Additionally, for patients in the NVS group, CD4 count, CD4%, CD4/CD8 ratio, HIV-1 viral load, and HIV-1 proviral copy number were performed as described previously.¹

Statistical analysis and definitions

"Chronic HCV infection" was defined as having a positive HCV antibody and PCR for HCV. "Cleared HCV infection" was defined as having a positive HCV antibody but negative PCR without the use of anti-HCV treatment. "HCV negative" was those individuals who had a negative HCV antibody test. For data with normal distribution Student's *t* test was performed; otherwise, the Mann-Whitney test was used. Fischer's exact test was used for contingency table testing. All *p* values were two-tailed and considered significant if $< .05$. All data were analyzed with GraphPad Prism software (San Diego, CA).

RESULTS

Comparison of HCV clearance in the NVS, HIV/HCV, and HCV cohorts

Of the 47 NVS, 30 were HCV antibody positive and 17 were HCV antibody negative. Seven of these 30 NVS with positive HCV antibodies had negative HCV PCRs (minimum of 2 per subject were performed). Clearance rates of HCV infection was determined in 30 NVS with positive HCV antibodies, 350 HIV/HCV cohort, and 350 individuals in the HCV cohort. The demographic information of these cohorts is given in Table 1. NVS patients had a 23.3% (7 of 30) HCV clearance rate compared to 6.5% (23 of 350) in the HIV/HCV co-infected and 9.1% (32 of 350) in the HCV mono-infected groups. These results were statistically significant ($p=.005$ and $p=.024$, respectively). These results were still significant when controlling for female sex in the VA cohorts ($p=.011$ and $p=.023$, respectively). The above results are described in Table 2.

Comparison of Chronic HCV in the NVS, HIV/HCV, and HCV cohorts

HCV-related parameters were compared in patients from the 3 cohorts with chronic HCV infection (those with a positive HCV PCR). Twenty-three NVS, 327 HIV/HCV co-infected, and 318 HCV mono-infected patients were compared.

Mean HCV viral loads were 1.92×10^6 IU/ml for the NVS, 2.55×10^6 IU/ml for the HIV/HCV, 1.45×10^6 IU/ml for the HCV group. For patients with detectable HCV viral load, there was no significant difference in the HCV viral load between the NVS and HIV/HCV or HCV groups ($p=.670$ and $p=.075$, respectively), although there was a significant difference between the HIV/HCV and HCV groups ($p=.003$) (Figure 1).

Seven NVS, 88 HIV/HCV, and 112 HCV patients had a liver biopsy. The NVS had a median Grade 2 and Stage 1, the HCV/HIV had a median of Grade 2 Stage 2, and the HCV group a median of Grade 1 Stage 1 liver disease. These results were only statistically

significant between the HIV/HCV and HCV groups for grade ($p=.002$) and stage ($p=.048$). None of the NVS had cirrhosis, while 9.2% of the HIV/HCV and 6.6% of the HCV groups had cirrhosis. These results were not statistically significant between any of the groups. There was no significant difference in AST, ALT, or AFP values between the 3 cohorts (data not shown). None of the NVS cohort had a history of treatment for HCV. HCV clearance rates with treatment was 12% (4 of 33) in the HIV/HCV cohort and 17% (8 of 48) in the HCV cohort. A summary of the above is described in Table 2.

Effect of HCV upon HIV infection in the NVS: CD4 count and HIV viral load

HIV-1 related parameters were studied within the NVS cohort, dividing the NVS to those with chronic HCV (a positive HCV PCR) and those without chronic HCV infection (negative HCV PCR). The demographics of these 2 groups within the NVS cohort are shown in Table 3. Within the entire NVS cohort, individuals without chronic HCV had a median CD4 count of 949 cells/ul, while those with chronic HCV had a median CD4 cell count of 654. The elevated CD4 count in the non-chronic HCV group was statistically significant ($p=.029$). There was a similarly statistically significant elevation in the CD4% and a trend toward significance in the CD4/CD8 ratio in those without chronic HCV compared to the chronic HCV group ($p=.046$ and $p=.062$, respectively). The above results are shown in Figure 2. There was no correlation between HIV-1 proviral copy number and chronic HCV status ($p=.49$). There was also no correlation between HIV-1 viral blips to >400 copies/ml in the past 2 years and chronic HCV status ($p=.41$).

DISCUSSION

HIV-1 Natural Viral Suppressors are a unique cohort of patients who are able to suppress HIV-1 viral replication to extremely low levels.¹ Although there have been some studies on HCV infection in LTNP (none in the NVS or Elite controllers), these have mostly focused on response to HCV treatment and effects of a specific HCV genotype on HIV progression.⁶⁻⁷ The goal of this study was to characterize HCV infection in the NVS cohort, a cohort of patients all that have already demonstrated the ability to control one chronic viral infection.

Our results indicate that the NVS, as a group, demonstrate better control of HCV infection than the controls in that they had significantly higher rates of spontaneous clearance compared to race-matched historical controls of both HIV/HCV co-infected and HCV mono-infected patients. Spontaneous HCV clearance rates in various studies range from 6–80%, with a calculated mean of 26%.⁸⁻¹² In African-Americans, another Baltimore-based cohort with a male preponderance reported a 9.3% clearance rate,¹³ which is similar to the clearance rate of 9.1% in our HCV mono-infected cohort. The NVS cohort is comprised of patients with variables traditionally associated with lower rates of spontaneous clearance of HCV, i.e. male gender, African American race, intravenous drug use, and HIV infection.¹⁴ Despite this, the rates of HCV clearance in the NVS cohort was 23.3%, significantly higher than both the HIV/HCV co-infected (6.5%) and HCV mono-infected cohorts (9.1%). Recently, IL28B polymorphisms have been shown to be associated with clearance of HCV, and it remains to be seen whether this could be a potential mechanism involved in the elevated HCV clearance in the NVS group.¹⁵ Nevertheless, the ability of some NVS to successfully control 2 agents of chronic viral illness (HIV-1 and HCV), implies that a common genetic factor (controlling either innate or adaptive immunity) is responsible for the viral control in these individuals.

The only dissimilarity in the demographics of the 3 cohorts was male/female ratio (over-representation in the NVS compared to the other 2 cohorts). This is a potentially important confounder as studies have shown significantly higher clearance of HCV in females compared to males.⁸⁻¹² However, when controlling for female sex, the findings of a higher

clearance rate in the NVS was still statistically significant when compared to the HIV/HCV and HCV groups.

Besides the difference in HCV clearance rates, we were unable to detect any differences in HCV infection between NVS and the controls. Those NVS who developed chronic HCV infection did not control the infection better than the control groups, nor did they have less disease progression than the controls. The results demonstrated a difference between the HCV mono-infected and HIV/HCV co-infected cohorts in terms of HCV viral load and severity of liver disease by biopsy, with the NVS having values between the two groups. Although none of the results comparing the NVS to the other groups were significant, the trend implies that the NVS may have slightly less control of the HCV infection than the HCV mono-infected group, these findings tend to agree with previous studies that have shown increase HCV viral loads and HCV-related disease in HIV/HCV co-infected patients, 16-23 which is presumably because of a decrease in HCV-specific CD4+ and CD8+ response in co-infected patients.²⁴

Within the NVS cohort, there was a significant association between chronic HCV infection and immunological impairment. The CD4 count, CD4%, and CD4/CD8 ratios were lower in those with circulating Hepatitis C virus than those without. The median CD4 cell difference was 294 cells/ul (with an 11% difference in CD4%). However, it should be noted that we were unable to demonstrate a difference in the HIV-1 proviral copy numbers or frequency of viral “blips” between those NVS with and without chronic HCV. Testing with HIV-1 viral load assays with a limit of detection of 1 copy/ml may help answer this question.²⁵

Whether this degree of immunologic impairment associated with HCV infection in the NVS will eventually have clinical significance is unknown; however, these findings add to the growing body of literature regarding the detrimental effects of HCV in patients infected with HIV. The chronic engagement of B lymphocytes by HCV in chronic infection can cause non-specific antibody production such as cryoglobulins, but it is uncertain if this may impact the course of HIV infection. Recently, one large study has shown HCV infection is a risk factor for developing AIDS-defining illness.²⁶ Previous studies have shown a blunted CD4 response to HAART in patients with HCV infection;¹⁶⁻²⁷ however, this association has not been consistently demonstrated in other studies.²⁸ Our study may be the first to correlate the direct impact of HCV on CD4 cell count in HIV-infected patients. Although low CD4 counts in HIV negative cirrhotic patients are thought to occur secondary to splenic sequestration,²⁹ none of the NVS have a clinical or pathologic diagnosis of cirrhosis. In addition, in the former case CD4% are preserved, but the NVS with HCV have lower CD4% and CD4/CD8 ratios, suggesting loss of CD4 rather than sequestration. The mechanism involved in the decrease in CD4 cells seen in the NVS is likely to be an increase in naive CD4 apoptosis as has been described by Nunez et al.³⁰ In typical co-infected patients, the impact of HCV on cellular immunity may be masked by the much greater HIV-induced immunosuppression, thus cohorts such as the NVS may be more suitable for demonstrating subtle HCV-induced effects on the immune system.

Because of the inherent difficulty in identifying NVS with acute HCV, this study was cross-sectional and this has to be considered in interpreting the results. However, the NVS cohort was similarly matched to the other 2 cohorts, which strengthens the findings. All three cohorts were composed of African-Americans only, closely matched for age, route of infection (majority IDU), estimated date of infection for HCV, and HCV genotype (see Table 1). Importantly, the median estimated date of HCV infection was similar for all three cohorts (between 1973–1975), predating potential exposure to HIV-1. Given that our cohorts were entirely composed of African-Americans, these findings may not pertain to other

ethnic groups, which can have a different genetic and immunologic makeup. Further studies are needed to confirm our findings in African-Americans and other groups of patients.

CONCLUSION

Individuals within the NVS cohort, which are defined based HIV viral control, appear to clear HCV infection at elevated rate compared to controls. NVS patients had a 23.3% clearance rate for HCV, which was significantly higher than HCV mono-infected (9.1%) and HIV/HCV co-infected (6.5%) patients. For individuals in the NVS who are able to spontaneously control HIV and HCV, a common genetic factor linked to either the adaptive or innate immune system likely accounts for this finding. Within the NVS cohort, there is evidence that chronic HCV infection can have a detrimental effect on the immune system. NVS patients with chronic HCV infection had statistically significant lower CD4 count and CD4%. Further studies are needed to elucidate the potential mechanisms involved in HIV/HCV clearance in the NVS, as well as the immune suppressive effects of HCV within the NVS.

Acknowledgments

We would like to thank members of the NVS cohort and Becky Boyce, RN, the study coordinator.

Funding: M.M.S. supported by award number NIH K12RR023250 (PI: Alan R. Shuldiner).

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Figure 1.

Comparison of HCV viral loads in the NVS, HIV/HCV, and HCV cohorts. Mean HCV viral loads were 1.92×10^6 IU/ml for the NVS, 2.55×10^6 IU/ml for the HIV/HCV cohort, 1.45×10^6 IU/ml for the HCV cohort. For patients with detectable HCV viral load, there was no significant difference in the HCV viral load between the NVS and HIV/HCV or HCV groups ($p=.670$ and $p=.075$, respectively), although there was a significant difference between the HIV/HCV and HCV groups ($p=.003$). NVS cohort = HIV-1 infected individuals with HIV-1 viral loads <400 copies/ml without therapy. HIV/HCV cohort = HIV and HCV co-infected patients. HCV cohort = HCV mono-infected patients.

Figure 2.

HIV immunological parameters in the NVS cohort based on chronic HCV infection. 1A) A higher CD4 count was noted in the NVS in the absence of chronic HCV ($p=.029$). The difference between the median values was 294 cells/ul. 1B) A higher CD4 percent was noted in the NVS in the absence of chronic HCV ($p=.046$). The difference between the median values was 11 percentage points. 1C) A higher CD4/CD8 ratio was noted in the NVS in the absence of chronic HCV ($p=.062$). The difference between the median values was 0.68. NVS = HIV-1 infected individuals with HIV-1 viral loads <400 copies/ml without therapy. NVS patients were divided into 2 groups: chronic HCV - (HCV PCR negative) and chronic HCV + (HCV PCR positive).

Table 1

Demographic information on the NVS, HIV/HCV, and HCV cohorts

Characteristic	NVS n=30	HIV/HCV n=350	HCV n=350
Age	55	55	55
Race	100% AA ^a	100% AA	100% AA
Sex	33% Female	3% Female*	5% Female*
Median HIV diagnosis date	1995	1994	Not applicable
Median EDI ^b for HCV	1973	1975	1977
HCV risk factor	80% IDU ^c	82% IDU	80% IDU
HCV Genotype (1a and 1b)	90%	91%	89%
Hepatitis B Sag positive	0%	5.4%	1.3%

NOTE.-NVS cohort=HIV-1 infected individuals with HIV-1 viral loads <400 copies/ml without therapy. HIV/HCV cohort=HIV and HCV co-infected patients. HCV cohort=HCV mono-infected patients.

^a AA=African-American

^b EDI=estimated date of infection

^c IDU=intravenous drug use

* P<.05 (p values are given in relation to the NVS cohort only)

Table 2

Comparison of HCV infection between the NVS, HIV/HCV, and HCV cohorts

Characteristic	NVS	HIV/HCV	HCV
Cleared HCV	23.3%	6.6% (p=.005)*	9.1% (p=.024)*
HCV viral load (IU/ml)	1.92 × 10 ⁶	2.55 × 10 ⁶ (p=.670)	1.45 × 10 ⁶ (p=.075)
Median Liver bx Grade	2	2 (p=.363)	1 (p=.872)
Median Liver bx Stage	1	2 (p=.601)	1 (p=.852)
Cirrhosis	0%	9.2% (p=.238)	6.6% (p=.381)

NOTE.-NVS cohort=HIV-1 infected individuals with HIV-1 viral loads <400 copies/ml without therapy. HIV/HCV cohort=HIV and HCV co-infected patients. HCV cohort=HCV mono-infected patients. 7 NVS, 88 HIV/HCV, and 112 HCV had liver biopsies performed. All p values are given in relation to the NVS cohort only.

* P<.05

Table 3

Demographic information of NVS based on chronic HCV status

Characteristic	NVS without chronic HCV	NVS with chronic HCV
Age	48	51
Race	100% AA	100% AA
Sex	35% M 65% F	65% M 35%F
HIV diagnosis date	1995	1995
Median CD4 cell count (cells/ul)	949	654
Median CD4 %	43	36
Median CD4/CD8 ratio	1.53	.85

NOTE.-AA=African-American, M=male, F=female.