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A Case-Control Study of Factors associated with Resolution of Hepatitis C viremia in Former Blood Donors

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Abstract

Background/aims—NAT is performed on blood collected in the United States allowing for the classification of HCV antibody positive donors into resolved and chronic hepatitis C infections. We report a case-control study of factors associated with HCV resolution.

Methods—Blood donors with resolved (HCV Ab+, RNA- defined as “cases”) or chronic (HCV Ab+, RNA+ defined as “controls”) based on their index donation HCV test results were enrolled. Participants completed a risk factor, symptoms and treatment questionnaire followed by HCV antibody, RNA and liver biochemical testing.

Results—We enrolled 100 cases and 202 controls. In a multivariate logistic regression model, significant independent effects for spontaneous viral clearance were observed for African American (inverse) (OR = 0.11, 95% CI: 0.01-0.87), autologous blood donation (OR = 4.70, 95% CI: 2.02-10.94), alcohol intake (OR=2.39, 95% CI: 1.13-5.03), and transfusion prior to May 1990 (inverse) (OR = 0.36, 95% CI: 0.14-0.91). Cases admitting injection drug use (IDU) had shorter time since first injection than did controls. Forty-nine index RNA+ controls received antiviral therapy and 25 (51%) were RNA- at enrollment; surprisingly several RNA- cases received liver biopsies and/or antiviral treatment.

Conclusions—We document the role donor screening plays in the identification, subsequent medical evaluation and treatment among individuals who presumable did not know they were at risk for HCV infection. Additionally, we confirmed race/ethnicity as a determinant of clearance and suggest infectious dose and route of infection may play a role in clearance.

INTRODUCTION

HCV is the most prevalent pathogenic blood-borne infection in the United States. At least 4 million persons are infected with the virus and worldwide it is estimated that 170 million persons are chronically infected, representing a viral pandemic.^{1,2} In the US, chronic HCV infection is the primary cause of end-stage liver disease resulting in liver transplantation.³ Since transfusion-transmitted HCV infection has been virtually eliminated in the US due to blood donor screening, injection drug use (IDU) is the primary route of infection. The epidemic continues among those who share needles and drugs.

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A systematic review of 31 longitudinal studies of acute HCV found that rates of spontaneous viral clearance ranged from 0% to 80%.⁴ Clearance is more likely to occur in white non-Hispanics, females, acute symptomatic hepatitis with lower peak viral titer and in re-infected IDU with a previously resolved HCV infection.⁵⁻¹⁰ Recent immunological data suggest protective immune responses in seronegative individuals engaging in high risk behavior.¹¹ Biological mechanisms underlying observations of spontaneous clearance and possible protection from HCV reinfection have not been clearly illuminated.

In 1999, NAT screening of blood donors was implemented in the United States under a Food and Drug Administration-approved investigational new drug protocol.^{12,13} This new technology allowed for direct detection of HIV-1 and HCV RNA and was implemented for the testing of multiple donation samples in small pools.¹² In addition to detecting rare early phase infections prior to the development of antibody, minipool-NAT has resulted in the classification of HCV antibody confirmed positive donors into RNA-positive (~80% viremic) and RNA-negative (~20% presumptive resolved) subcategories, allowing their clinical study. We report a case-control study of factors associated with presumptive HCV resolution compared to chronically infected donors. By comparing index donation and subsequent study enrollment NAT results, we also describe the persistence of RNA negative and positive status with and without antiviral treatment.

METHODS

Study design and population

We performed a case-control study among serologically confirmed HCV positive blood donors identified within our large blood bank network with either presumptive resolved (Ab positive (confirmed by RIBA), RNA negative donors, defined as “cases”) or persistent infection (Ab positive, RNA positive donors, defined as “controls”) at the time of their index blood donation. This blood bank network consists of 17 collection sites in the western and southern United States, with annual blood collections of over 1.3 million donations.

As part of the donation process, a donor's health is assessed on the day of donation by a private face-to-face interview. A standardized questionnaire including questions about deferral risk factors for HIV/AIDS and HCV is administered. In addition blood pressure, pulse, temperature and hemoglobin/hematocrit are measured. A donor answering “yes” to either set of risk factor questions as well as either currently taking antibiotics or a temperature above 99.6° F is excluded from donating. In donors with a positive HCV result(s) notification and counseling was achieved with a letter containing the HCV test results, a deferral and counseling message, an 800 counseling phone number, as well as a HCV information sheet.

The main objective of the current study was to evaluate virologic and epidemiologic factors associated with RNA negative status and presumed HCV resolution. Study personnel contacted confirmed HCV antibody positive, RNA negative consecutive donors (cases) with sufficient residual volume after NAT screening for further virologic testing, and offered them enrollment in our study. Controls were selected based on age (+/- 2yrs) and sex matching, from a database of serologically confirmed, minipool viremic donors in the same blood bank network. Study design called for a ratio of one case to two controls. If a potential subject did not respond to routine contact attempts at their address of record, address information was updated using online resources and/or a professional tracing specialist. When new information was acquired, new contact attempts were made. Successful enrollment included consent; completion of a risk factor, symptom and treatment questionnaire; and phlebotomy for HCV serology, RNA testing and a liver biochemical panel. Autologous blood donors who reported HCV antiviral treatment were excluded since

such treatment generally preceded their index blood donation. The Committee on Human Research at the University of California, San Francisco, approved the study protocol.

Questionnaire

Questionnaires were self-administered at the time of enrollment to gather information on measureable lifestyle factors and health indicators that might predict evolution either towards resolved or chronic HCV infection (see online Appendix).

Laboratory methods

Subjects were enrolled in the study based upon confirmed HCV antibody and NAT results at their index blood donation regardless of subsequent HCV test results. Serology was established using HCV 3.0 ELISA Test System (Ortho Clinical Diagnostics, Raritan, NJ) and confirmed by RIBA HCV 3.0 SIA (Novartis, Emeryville, CA); while HCV RNA status was established using nucleic acid amplification testing (NAT) of minipools representing sixteen donation samples (Procleix HIV-1/HCV Assay, Gen-Probe, San Diego/Novartis, Emeryville, CA). A reactive minipool result triggered HIV-1/HCV NAT of the individual donations comprising the pool in order to identify the NAT-reactive donation, followed by discriminatory HCV (dHCV) NAT to confirm HCV viremia. Residual volume after NAT screening from all cases was retested by duplicate undiluted HCV RNA testing using dHCV Transcription-Mediated Amplification (TMA) (Gen-Probe Incorporated, San Diego, California). ALT testing was a component of donor screening throughout most of the donor accrual period of our study, but was discontinued on November 7, 2005 due to its declining value.¹⁴

At enrollment, another phlebotomy specimen was evaluated using the laboratory methods previously described with one exception, namely all HCV RNA results were obtained by duplicate undiluted dHCV TMA testing. Additionally, a liver biochemical evaluation, including ALT, AST, alkaline phosphatase, total bilirubin with a breakdown into direct and indirect bilirubin, and total protein with a breakdown into albumin and globulin, was performed by a licensed clinical laboratory. Quantification of HCV RNA was determined using reverse transcription-PCR combined with real-time fluorescent detection (Abbott Molecular Inc., Abbott Park, IL).¹⁵

Clinical Data

We requested subject permission to obtain pathology records of all reported liver biopsies. These were evaluated using the Metavir scoring system. We grouped scores in the following manner: an F0 – F1 score was considered absent to mild fibrosis, an F score of >1 and <3 was considered moderate fibrosis, and an F score ≥ 3 was considered advanced fibrosis.

Statistical analysis

First, cases and controls were compared regarding frequencies of demographic characteristics and either first-time or repeat allogeneic and autologous blood donor status. Next, behavioral and medical risk factors that might influence resolution of infection were compared between the two groups using a bivariate analysis with calculation of unadjusted odds ratios (OR) and 95% confidence intervals (CI) using SAS PROC LOGIST. We estimated duration of infection for injection drug users by subtracting the year of first reported drug injection from the year of index donation, and compared the distribution of these durations between the RNA negative and RNA positive groups after excluding autologous donors. Significance of trends was analyzed using a Cochran-Armitage trend test. Flow diagrams showing medical diagnostic procedures and treatment were constructed

by sorting RNA negative and RNA positive subjects hierarchically according to self-reported medical information and duplicate TMA results at enrollment.

Finally, we constructed a multivariate logistic regression model to simultaneously compare predictors of HCV resolution and account for confounding. Case (Ab+/RNA-) versus control (Ab+/RNA+) status was the dependent variable, and variables found to be associated with RNA status in the bivariate analysis were entered into the model as independent variables. A final reduced model was obtained by sequentially removing variables that were not associated with an HCV RNA status of $p > 0.20$. The matching variables age and gender as well as interaction terms between IDU and transfusion and between IDU and sex with an IDU were forced into the model.

RESULTS

Recruitment letters were sent to 389 deferred blood donors [180 (46%) females and 209 (54%) males] with presumptive resolved (RIBA+/minipool RNA negative) HCV infections with enough residual volume for duplicate TMA testing of index donation plasma after routine minipool NAT testing. These blood donors were derived from a pool of 1,324 RIBA positive, minipool RNA negative donors detected by NAT screening from June 16, 1999 through November 7, 2007. A total of 124 (32%) consented to participate in the study and 112 (90%) successfully completed their enrollment visit at a mean of 2.1 years (0.2 – 6.0 years) post index donation. Successful recruitment resulted in a slight enhancement of females in the final target population (56% vs. 46%). Additionally, recruitment letters were sent to 986 RIBA positive, minipool viremic (RIBA+/RNA+) deferred blood donors [464 (47%) females and 506 (51%) males] in an effort to achieve the minipool RNA negative (case) to minipool viremic (control) ratio of one to two. A total of 246 (25%) consented to participate in the study and 205 (83%) successfully completed their enrollment visit. Mean time from index donation to enrollment was 2.7 years (0.5 – 11.0 years). At analysis, a total of 15 autologous donors (12 Ab+/RNA- and 3 Ab+/RNA+) reporting antiviral treatment prior to their index donation were removed from the study group resulting in 100 cases and 202 controls.

Demographic and lifestyle characteristics of cases (Ab+/RNA-) and controls (Ab+/RNA+) are presented in Table 1. Even though the cases and controls were only matched for age and sex, cases and controls were also similar for country of origin, education, and income. African American non-Hispanic donors represented a smaller proportion of presumptive resolved infections compared to HCV chronic infection (1 percent vs. 7 percent). First-time donors were the primary donor type for allogeneic cases and controls. Cases were more likely to be autologous donors (22%) than controls (8%). Additionally, 8 (10%) cases were repeat allogeneic blood donors while 10 (5%) controls were repeat allogeneic donors. Date of previous blood donation was available for 17 of these 18 participants. The average time from their index donation to their previous donation was 5 years (0.21 – 18.8 years).

Table 2 shows a comparison of potential risk factors. Cases and controls self-reported similar proportions of lifetime IDU. Cases (Ab+/RNA-) self-reported heavier current alcohol intake and were less apt to report heavier drinking in the past. Among all subjects, cases were less likely to report sex with an IDU, but this difference diminished when the analysis was restricted to non-IDU. On the other hand, fewer cases than controls reported a blood transfusion prior to 1990, and this difference increased when the analysis was restricted to non-IDU. Cases reported more Rhogam treatment than did controls. There were only minimal differences with respect to smoking, BMI, tattoo and IgG history. Among those reporting IDU, we estimated the interval between HCV infection (year of first reported IDU)

and enrollment excluding autologous donors (Figure 1). IDU cases had shorter intervals since infection than did IDU controls (two-sided p -value = 0.008).

Table 3 shows results from the multivariate logistic regression model. Significant, independent effects for spontaneous viral clearance were observed for race, donor type, drinking, and receiving a transfusion prior to May 1990. African Americans had only one tenth the odds of HCV clearance compared to non-Hispanic whites. Autologous donors were 4.7 times more likely to be HCV RNA negative than were allogeneic community donors. Current alcohol consumption was significantly associated with HCV RNA negative status compared to non-consumption; there did not seem to be a dose effect with similar odds ratios for the three levels of weekly drinks consumed. Past alcohol consumption was not independently associated with RNA status. Finally, having received a blood transfusion prior to May 1990 (when HCV antibody screening was introduced in US blood banks) was associated with 0.36 the odds of HCV clearance compared to donors who had not received a transfusion.

Seventy-seven out of 97 cases (79%) and 186 out of 200 controls (93%) first learned of their HCV infection due to blood bank notification, while 20 (21%) cases and 14 (7%) controls were told by their physician. Among the donors who first learned of their infection due to blood bank notification, 58 (75%) cases and 169 (91%) controls were first-time donors. Of these first-time donors, 44 (76%) cases and 149 (88%) controls contacted a physician. Data on clinical treatment of HCV infection are reported in the flow diagrams separately for cases (Figure 2A) and controls (Figure 2B). Nine (9%) of the RNA negative cases reported having a liver biopsy and pathology reports were available for six of these cases (Figure 2A). Using the Metavir scoring system for fibrosis, 4 (67%) had mild fibrosis and 2 (33%) had moderate fibrosis. Three RNA negative cases (1 after biopsy and 2 without biopsy) reported antiviral therapy. All three cases remained HCV RNA negative after treatment. Ninety-five cases (8 after biopsy and 87 without biopsy) reported no antiviral treatment. Of these, five (5%) were HCV RNA positive at their enrollment bleed either on duplicate ($n=4$) or one out of two TMA assays ($n=1$). IDU history was available for three of these donors, all of whom reported first injecting in the 1980's. The viral load for one of these donors' enrollment bleed (2.5 years post-index) was 10,715 IU/mL, with ALT increasing from 17 U/L at the index bleed to 56 U/L at the enrollment bleed. The viral loads from the enrollment visits of the four remaining cases were beneath the detection level of the quantitative viral load assay and their ALT values were within the normal clinical range.

Ninety-two (46%) of the HCV RNA positive controls reported having a liver biopsy (Figure 2B), and pathology reports were available for 71 (77%). Using the Metavir scoring system for fibrosis, 46 (65%), 14 (20%), and 11 (15%) had mild, moderate and advanced fibrosis, respectively (Chi-squared trend = 0.31 compared to HCV RNA negative cases). Forty-nine controls (44 after liver biopsy and 5 without biopsy) reported antiviral treatment. Of these, 25 (51%) were HCV RNA negative at their enrollment bleed indicating sustained viral response (SVR). Finally, three controls without biopsy or antiviral treatment were RNA negative in duplicate at enrollment. Two of the three reported past injection drug use (one autologous and one first-time donor) with usage beginning in 1964 and 1986. One of the three's ALT was 164 U/L at index and 18 U/L at enrollment 0.7 years later, while the other two had normal ALT values both at their index bleeds and 1.5 to 2.6 years later at enrollment.

A review of liver biochemical parameters (Table 2) revealed the mean ALT for HCV RNA positive female controls was 40.9 U/L (8-240 U/L) compared to 19.9 U/L (4-64 U/L) for HCV RNA negative female cases ($p < 0.0001$). In comparison the mean ALT for male controls was 53.6 U/L (12-239 U/L) compared to 26.3 U/L (7-84 U/L) for male cases

($p < 0.0001$). Albumin levels were significantly lower ($p = 0.0065$) in RNA positive controls than in cases, and 3.47% of HCV RNA positive controls had albumin levels beneath the lower normal range of 3.5 g/dL.

DISCUSSION

This study has confirmed the previously reported inverse association with African American race/ethnicity and HCV clearance. We also provide novel evidence that route of infection may determine likelihood of clearance, with those reporting previous blood transfusion significantly less likely to spontaneously clear HCV and suggestive data that a history of more recent injection drug use could predispose to clearance. The data illustrate the effectiveness of donor counseling and give a snapshot of the clinical care these HCV seropositive donors received after donation related diagnosis. Reassuringly, antiviral treatment was successful in proportion to previous reports (30%-54%).¹⁶⁻¹⁸ Intriguing were rare apparent cases of spontaneous viral clearance and low-level viral recrudescence in the absence of treatment. Finally, we were dismayed to find that several HCV RNA negative donors reported receiving liver biopsies and/or antiviral therapy.

In our study, African American participants were significantly less likely to resolve their HCV infection compared to whites. Thomas and coworkers¹⁹ reported a prospective study wherein 9.3% of 729 seropositive African American IDUs resolved HCV infection compared to 36% of 44 non-African American IDU's. Subsequently, Busch and coworkers⁶ reported that 14.4% of African Americans compared to 20.7% of Caucasians blood donors were HCV Ab+/RNA- in a cross-sectional analysis. Even though the current study is smaller, the lower frequency of resolved HCV infection among African American blood donors was detectable. To elucidate the basis for these racial differences, investigators have begun to correlate HLA and other immune response polymorphisms with HCV clearance.²⁰⁻²⁴

Our data raise intriguing questions about the effects of HCV infectious dose and immunological status at the time of infection on subsequent viral clearance. Subjects reporting blood transfusion prior to 1990 were significantly less likely to resolve their infections. Although most blood units containing HCV virus also contain neutralizing antibodies, receipt of a high infectious dose via blood transfusion could overwhelm the initial immune response. Studies have demonstrated that a strong, broad immune response favors viral clearance compared to one that is weak or narrowly focused.^{25,26} Data from transfusion-transmitted HCV indicates that the viral strain and the amount of inoculum influence the course of acute hepatitis C, but only very modestly.²⁷ Furthermore, these studies support the idea that variability in the host is much more important than the virus in determining the course of infection. On the other hand, frequent re-exposure to smaller inocula among IDUs might favor resolution of HCV viremia. It has been shown that previously infected IDUs are twelve times less likely to develop chronic infection with subsequent re-infection and viremia usually lasted less than 12 week upon re-infection.^{7,28} Although our data did not show any difference between cases and controls in the prevalence of past injection drug use, IDU cases had shorter intervals since they began injecting than did IDU controls (Figure 1), suggesting either that resolution of viremia occurred soon after infection and/or that because resolvers lose antibody they are less apt to be captured by donor testing. Finally, the immune impact of the circumstances surrounding a transfusion also needs to be considered. Pain, surgical stress, and tissue injury are known to modulate the complex immune response leading to temporary immunosuppression potentially diminishing HCV clearance.²⁹

Although the intended purpose of donor screening is to keep the blood supply safe from transfusion-transmissible diseases, our data would indicate that an important public health goal is also being met. Our data illustrates that universal donor screening with subsequent donor notification, plays a significant role in the identification, seeking of medical attention and ultimate treatment of HCV positive individuals identified during the screening process who believed they were healthy. HCV is a major cause of liver disease and a potential cause of substantial morbidity and mortality.^{2,30} Early detection is important because HCV-related complications may be altered substantially by the removal of effect modifiers such as alcohol and the institution of appropriate treatment.³¹ Therefore, the donor notification process probably represents the single largest setting in which asymptomatic adults are informed for abnormal test results related clinically significant infectious agents.³²

We found higher current alcohol intake to be associated with Ab+/RNA- status. We suspect that RNA positive controls were cautioned to avoid alcohol consistent with current practice guidelines to limit HCV-related liver damage. In contrast, many HCV RNA negative cases were probably told that they no longer had HCV infection and were not cautioned regarding alcohol intake.

Our data on liver biopsy and antiviral treatment were both expected and troubling. In accordance with the literature, roughly 50% of antiviral treated RNA positive controls were non-viremic at the time of their enrollment bleed and most were treated after a liver biopsy.¹⁸ On the other hand, 9 HCV RNA negative cases reported liver biopsies and 3 were given antiviral treatment. Based upon recommended practice guidelines,³³ viremic status should be established before pursuing a liver biopsy and/or HCV treatment. It is unclear whether the treating physician performed an HCV viral load measurement that may have shown viremia, or whether no viral load assessment was performed. These inconsistencies may be a reflection of poor access to good medical care due to predominantly rural residence and lower socioeconomic status or lack of medical insurance among study participants. In any case, reinforcement of HCV treatment guidelines among primary care physicians seems warranted starting with confirmation of NAT results as well as communication letters and information sheets sent to donors and their physicians.

Because of the interval between the index donation and the enrollment bleed, we were able to monitor the time course of HCV viremia in our subjects, and demonstrate rare cases of presumable spontaneous viral clearance, re-infection and low-level recrudescence of viremia. Three non-treated controls that were RNA positive at their index donation were RNA negative in duplicate 0.7 to 2.6 years later at enrollment. It is generally accepted that for the majority of persons spontaneous clearance occurs early in infection.^{5,34,35} Although the donors' self-report of no treatment could have been erroneous, it is unlikely considering the considerable side effects and cost of current HCV treatment strategies.

The one case of possible re-infection consisted of a repeat donor classified as a case (Ab+/RNA-) with negative minipool HCV NAT and duplicate negative TMA results at index donation, who then presented with a viral load of 10,715 IU/mL and an ALT of 56 U/L at enrollment 2.5 years later. During the donation process and at enrollment, this participant repeatedly denied IDU but we suspect IDU as the cause of this viral load. Additionally, the four other initially RNA- cases developed very low level viremia that was only detectable by the TMA assay. We feel this represents a phenomenon of intermittent, very low-level HCV viremia which has been reported both during very early HCV infection and also among putative resolvers.^{36,37}

What are the implications of the study for transfusion safety? First, repeat blood donors are considered to be much safer than first-time blood donors because they undergo frequent

questioning and blood testing, but they still represented 10% of our cases and 5% of controls. The repeat donors who were enrolled in this study tended to have longer intervals since their last donation, suggesting that “lapsed” repeat donors should perhaps undergo scrutiny more similar to first-time donors. Second, the case of the first-time blood donor who presented for blood donation after having a liver biopsy for HCV infection points out the limitations of pre-donation exclusion questionnaires, as previously reported.³⁸ Finally, the case of HCV re-infection in a repeat donor underscores the necessity for permanent exclusion from donation of seropositive persons irrespective of previous RNA results, and for universal RNA and serology screening to effectively guard the blood supply.

A major strength of this study is that the participants are more representative of the general population of HCV infected persons in the U.S. than either studies of clinic patients or active IDU. Furthermore, we performed a standardized questionnaire to investigate risk factors and probable dates of infection, as well as additional laboratory studies to confirm viremic status or otherwise characterize (liver biochemical evaluation) the cases (Ab+/RNA-) and controls (Ab+/RNA+). All HCV testing was done using very sensitive and specific HCV assays in well monitored laboratories, assuring that assessment of HCV infection was accurate and complete.

There are several potential limitations of our study. Unlike a prospective cohort study, a case-control study can only retrospectively measure the risks associated with an individual's HCV infection evolving into either a chronic or spontaneously resolving infection. Furthermore, matching for gender in order to control for gender-specific risk behaviors prevented us from assessing any effect of this variable on spontaneous resolution. Several studies have shown that women are more likely to resolve HCV infection compared to men^{4,39-43}, but three others studies in U.S. IDU, U.S. blood donors and the Italian general population have shown no gender association after adjusting for confounding.^{6,19,44} Another limitation was the inclusion of autologous donors. To compensate for this, all autologous donors reporting antiviral treatment were removed from the analysis minimizing the effect of participants being misclassified as cases (Ab+/RNA-). Finally, because our data was obtained primarily by self-administered questionnaire, recall bias or inaccurate responses may have affected its accuracy.

In conclusion, we were able to confirm race ethnicity as a risk factor for HCV clearance. Our new findings pointing to the possible importance of infectious dose, route of infection and circumstances surrounding receiving a transfusion are intriguing but require replication by other studies. Finally, we provide useful biopsy and treatment data among HCV-infected blood donors in the community as opposed to patients at clinics specializing in liver disease. Public health implications include the need for continued vigilance at safeguarding the blood supply against HCV, the role of blood screening in the identification of HCV infected individuals who presumably did not believe that they were at risk of infection and finally the need for consensus on treatment guidelines regarding the measurement of HCV viremia prior to liver biopsy and/or antiviral treatment.⁴⁵ All of these observations, illustrate the importance of follow-up studies among allogeneic blood donors deferred due to HCV infection.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Estimated years since HCV infection among allogeneic cases (n=37) and controls (n=82) based on year of first reported intravenous drug usage and year of index donation. Autologous donors were excluded from this analysis.

Figure 2.

A: Flow diagram of cases (Ab+/RNA-) sorted first by reported liver biopsy, followed by reported treatment (alpha-interferon treatment alone or in combination with other medications) and finally by RNA status at enrollment. Three autologous donors were among the biopsied non-treated group and an additional autologous donor was within the non-biopsied, non-treatment group.

*Data missing for two cases

B. Flow diagram of controls (Ab+/RNA+) sorted first by reported liver biopsy, followed by reported treatment (alpha-interferon treatment alone or in combination with other medications) and finally by RNA status at enrollment. Three controls not reporting either biopsy or treatment were RNA- in duplicate at enrollment. Two were first-time donors while one was an autologous donor. One first-time donor's ALT was 164 U/L at index and 18 U/L 0.7 years later, while the other two controls had normal ALT values (22-33 U/L) at enrollment.

*Data missing for 11 controls

Table 1Demographic and other characteristics of the study group^a

Characteristics	Ab+/RNA- (n=100)	Ab+/RNA+ (n=202)
Gender		
Female	56 (56%)	112 (55%)
Male	44 (44%)	90 (45%)
Age		
Mean (range)	50 (23-77)	49 (21-85)
21-30	11 (11%)	11 (5%)
31-40	9 (9%)	18 (9%)
41-50	33 (33%)	74 (37%)
51-60	36 (36%)	74 (37%)
>60	11 (11%)	25 (12%)
Race		
White	84 (84%)	152 (75%)
African American	1 (1%)	15 (7%)
Hispanic	10 (10%)	23 (11%)
Asian	1 (1%)	1 (0%)
Other	4 (4%)	11 (5%)
US Born		
Yes	95 (95%)	193 (97%)
No	5 (5%)	7 (4%)
Education		
Less than High School	4 (4%)	19 (9%)
High School/Some College	77 (77%)	136 (68%)
College graduate	19 (19%)	46 (23%)
Income		
\$15,000 or less	21 (21%)	31 (15%)
\$15,000-\$40,000	29 (29%)	69 (34%)
\$40,000-\$100,000	39 (39%)	75 (37%)
\$100,000 or more	10 (10%)	26 (13%)
Donation Type		
Allogeneic	78 (78%)	186 (92%)
First time donor	70 (89.74%)	176 (94.62%)
Repeat donor	8 (10.26%)	10 (5.38%)
Autologous	22 (22%)	16 (7.92%)

^aNumbers may not add to total because of missing data.

Table 2
Selected lifestyle and clinical characteristics of cases (Ab+/RNA-) and controls (Ab+/RNA+)

Characteristics	Ab+/RNA-(n=100)		Ab+/RNA+ (n=202)		Unadjusted Odds Ratio Estimate
	No. ^a	%	No. ^a	%	OR (95% CI)
Current Drinking					
Non-drinker	28	(28%)	87	(44%)	
0.25-1.99 drinks per week	21	(21%)	37	(19%)	1.19 (0.65-2.16)
2-6.99 drinks per week	25	(25%)	35	(18%)	1.65 (0.92-2.95)
≥7 drinks per week	26	(26%)	38	(19%)	1.52 (0.86-2.68)
Past Heavy Drinking					
Yes	66	(66%)	150	(75%)	0.66 (0.39-1.11)
< 1 year	7	(11%)	13	(9%)	1.09 (0.42-2.84)
1-5 years	26	(41%)	57	(38%)	0.89 (0.52-1.53)
> 5 years	31	(48%)	79	(53%)	0.70 (0.42-1.16)
Smoking					
Non-smoker	14	(14%)	43	(21%)	
0-15 pack per year	26	(26%)	65	(32%)	0.72 (0.42-1.24)
> 15 pack per year	51	(51%)	84	(42%)	1.49 (0.92-2.42)
BMI					
Underweight/Normal (<25 kg/m ²)	31	(31%)	62	(31%)	
Overweight (25-29.9 kg/m ²)	36	(36%)	85	(42%)	0.77 (0.47-1.27)
Obese (BMI ≥ 30 kg/m ²)	32	(32%)	53	(26%)	1.32 (0.78-2.24)
IDU ^b	51	(51%)	95	(48%)	1.15 (0.71-1.86) ^b
Blood transfusion before 1990	21	(21%)	60	(30%)	0.63 (0.36-1.11)
Sex with IDU	34	(34%)	89	(44%)	0.65 (0.40-1.08)
Tattoo history	48	(48%)	84	(42%)	1.30 (0.80-2.1)
IgG history	31	(31%)	67	(33%)	0.91 (0.54-1.52)
Rhagam history (females only)	8	(14%)	11	(10%)	1.51 (0.59-3.88)
Among non-IDU	49	(49%)	105	(53%)	
Blood transfusion before 1990	9	(18%)	40	(38%)	0.37 (0.16-0.83) ^b
Sex with IDU	6	(12%)	20	(19%)	0.593 (0.22-1.59) ^b

Characteristics	Ab+/RNA- (n=100)		Ab+/RNA+ (n=202)		Unadjusted Odds Ratio Estimate	
	No. ^a	%	No. ^a	%	OR (95% CI)	
Tattoo history	18	(37%)	30	(29%)	1.45 (0.71-3.0) ^b	
IgG history	15	(31%)	34	(32%)	0.92 (0.44-1.92) ^b	
Rhogam history (females only)	5	(15%)	5	(7%)	2.27 (0.63-8.25) ^b	
Liver Biochemical Data						
	Mean (range)		Mean (range)		p-Value (t-Test)	
Albumin	4.46 g/dL (3.8-5.4 g/dL)		4.34 g/dL (2.0-5.4 g/L)		0.0065	
Total bilirubin	0.58 mg/dL (0.2-1.7 mg/dL)		0.68 mg/dL (0.2-2.3mg/dL)		0.0064	
Direct bilirubin	0.15 mg/dL (0-0.4 mg/dL)		0.19 mg/dL (0-0.8 mg/dL)		0.0024	
Indirect bilirubin	0.42 mg/dL (0.1-1.3 mg/dL)		0.51 mg/dL (0.1-4.0 mg/dL)		0.0107	
ALT (women)	19.9 U/L (4-64 U/L)		40.9 U/L (8-240 U/L)		<.0001	
ALT (men)	26.3 U/L (7-84 U/L)		53.6 U/L (12-239 U/L)		<.0001	

^aNumbers may not add to total because of missing data.

^bAge-adjusted odds ratios

Table 3

Final multiple logistic regression model for factors associated with spontaneous resolution of hepatitis C infection

	Risk Factors	Odds Ratio	95% Conf. Interval
Age	<=30	1.0	
	Each subsequent decade	0.77	0.59-1.02
Sex	Male	1.0	
	Female	1.14	0.60-2.14
Race or ethnicity	White	1.0	
	African American	0.11	0.01-0.87
	Hispanic	0.61	0.25-1.51
	Other	1.12	0.34-3.69
US-born	No	1.0	
	Yes	0.54	0.13-2.19
Donor type	Allogeneic, first-time	1.0	
	Allogeneic, repeat	2.59	0.89-7.55
	Autologous	4.70	2.02-10.94
Current drinking	Non-drinker	1.0	
	>0- <2 drinks per week	2.29	1.05-5.00
	2- <7 drinks per week	2.62	1.22-5.62
	>7 drinks per week	2.39	1.13-5.03
Past heavy drinking	No	1.0	
	Yes	0.79	0.42-1.48
BMI	Underweight or normal (<25 kg/m ²)	1.0	
	Overweight (25-29.9 kg/m ²)	0.97	0.49-1.90
	Obese (> 30 kg/m ²)	1.40	0.68-2.89
Received Rhogam	No	1.0	
	Yes	1.75	0.58-5.31
Transfusion prior to May 1990	No	1.0	
	Yes	0.36	0.14-0.91
IDU	Never	1.0	
	Ever	1.88	0.79-4.50

	Risk Factors	Odds Ratio	95% Conf. Interval
Sex with IDU	No	1.0	
	Yes	0.77	0.19-3.22
Both IDU and Transfusion prior to May 1990	No	1.0	
	Yes	3.05	0.83-11.15
Both IDU and sex with IDU	No	1.0	
	Yes	0.46	0.14-1.5