Role of primary T-cell immunodeficiency and hepatitis B coinfection on spontaneous clearance of hepatitis C: The BC Hepatitis Testers Cohort

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ABSTRACT

T-cell host immune response against hepatitis C virus (HCV) has been suggested to play an important role in determining HCV infection outcome. However data from human studies are not available. This study examined the effect of primary T-cell deficiency along with other factors on the spontaneous clearance of HCV in a large population-based cohort in British Columbia, Canada. The BC Hepatitis Testers Cohort includes all individual tested for HCV in BC in 1990-2013 linked with data on their medical visits, hospitalizations, and prescription drugs. HCV positive individuals with at least one valid HCV-PCR test on/after HCV diagnosis (n=46,783) were included in this study. To examine factors associated with the spontaneous clearance of HCV, multivariable logistic regression was fitted on the full sample, and Cox proportional hazard model on the HCV seroconverters. Spontaneous clearance was observed in 25.1% (n=11,737) of those tested for HCV. After adjusting for potential confounders, the odds of spontaneous clearance of HCV was lower in people with primary T-cell immunodeficiency (adjusted odds ratio [aOR]: 0.55, 95% CI: 0.32-0.94), and higher in females (aOR: 1.61, 95% CI: 1.54-1.68), and in those co-infected with HBV (aOR: 2.31, 95% CI: 1.93-2.77). Similar results were observed in HCV- seroconverters except HBV co-infection was not significant. In conclusion, primary T-cell immunodeficiency is associated with a lower spontaneous clearance of HCV while female sex and co-infection with HBV are associated with a higher spontaneous clearance.

Key words: HCV; Spontaneous resolution; T-cell immune-deficiency; HBV; genotype

INTRODUCTION

More than 185 million people are living with Hepatitis C virus (HCV) globally. [1] While the majority of the HCV infected individuals develop persistent infection, about a quarter clear the virus spontaneously, without any treatment. [2-8] The exact mechanisms that determine these outcomes are not well-defined, [9, 10] even though host, viral, and environmental factors have been suggested to influence these outcomes. [3, 5, 11, 12] A growing body of evidence suggests that cellular, particularly T-cell, host immune response against HCV plays a critical role in determining the outcomes of the infection. [13-15] Moreover, spontaneous clearance (SC) of HCV has been found to be associated with sustained HCV-specific CD4+ and CD8+ T-cell responses. [14-16] However, epidemiological research that studied the factors associated with spontaneous clearance of HCV has not examined the role of primary T-cell deficiency in viral clearance. [3, 11, 12, 17, 18] Concurrent infection with hepatitis B virus (HBV) has also been suggested to be associated with spontaneous clearance of HCV in specific group of population such as hemophiliacs, [12, 19] and people who inject drugs (PWID). [3] Most studies on spontaneous clearance were of relatively small size, and were conducted in specific high risk population cohort such as PWID, hemophiliacs, or men who have sex with men (MSM). Thus these studies may not be generalizable to the broader population. We have conducted analysis of data from the BC Hepatitis Testers Cohort (BC-HTC) to assess spontaneous clearance at population level and assess relationship of primary T-cell deficiency and other factors with spontaneous clearance.

MATERIALS AND METHODS

Study Cohort

The data for this analysis is based on the BC Hepatitis Testers Cohort (BC-HTC) that includes all individuals tested for HCV or HIV at the BC Public Health Laboratory (BC-PHL) or reported case of HCV, HBV, or HIV, and linked with data on demographic characteristics,[20] medical visits,[21] hospitalizations,[22] and prescription drugs[23, 24] (Supplementary Table 1). BC-BC-PHL is the centralized laboratory for most serology (95%), all HCV-RNA (PCR), and genotype testing in the province, and thus provides a unique tool to monitor and assess the natural history of HCV infection. Details of the BC-HTC and epidemiology of HCV including creation, linkage, characteristics, and matching have been reported previously. [25, 26] Overall, the linkage rate of our HCV cohort with the administrative databases was >85%, which approached 90% after 2006.

Eligibility

This analysis included all HCV positive individuals who had at least one valid HCV-PCR (test for HCV RNA) test on or after HCV diagnosis. The HCV-PCR test results were available until December 31, 2013. Thus, the date of HCV diagnosis for this analysis was restricted to December 31, 2012 to allow sufficient follow-up time to observe spontaneous clearance.

Data preceding participants' birth dates have been excluded. Excluded were also the HCV-antibody test results in infants <18 months without further HCV RNA test results since the possibility of passive maternal antibody could not be ruled out.

Case Definitions

An HCV case is an individual who tested positive for either HCV antibody (HCV-Ab) or HCV-PCR or genotype, or who was reported as a case of HCV in the Integrated Public Health Information System (iPHIS). Individuals with a negative followed by a positive test were considered seroconverters.[25, 26]

Spontaneous clearance was defined as a negative HCV-PCR test following HCV diagnosis without treatment. As a sensitivity analysis, we further defined spontaneous clearance requiring two consecutive negative PCRs, at least 28 days apart.[27] Among seroconverters in which we assessed time to spontaneous clearance, HCV diagnosis date was the midpoint between the last negative HCV date and the first time they tested positive for HCV.

Primary T-cell Immunodeficiency was defined based on diagnostic codes for disease conditions [28] reported to the medical services plan or disease abstract database (Table 1).

HIV cases were identified based on reporting to the HIV/AIDS Information System (HAISYS) as per provincial guidelines and/or a reactive HIV lab test. [29] Additional HIV cases who tested without nominal information were identified through a previously validated algorithm based on medical visits and/or hospital admissions described elsewhere. [25] Diabetes, major mental health conditions, injection drug use (IDU), and problematic alcohol use were defined based on diagnostic codes from medical services plan or disease abstract database (details, including the International Classification of Disease [ICD]) codes have been provided in Table 1). To address the issue of temporality, all these conditions, including the primary t-cell immunodeficiency have been defined at baseline, i.e. if they were diagnosed on/before HCV diagnosis. Social and material deprivation quintiles were based on Québec Index of Material and Social Deprivation. [30]

Data analysis

The characteristics of the eligible individuals are presented by their spontaneous clearance status (yes/no). Bivariate relationships were explored by simple logistic regression, and the unadjusted odds ratios (OR) along with 95% confidence intervals (CI) are presented. Variables based on a-priori hypotheses,[31-33] and those significant at 0.10 in the univariate analysis were included in the multivariable models, and adjusted odds ratios (aOR) are reported with 95% CI. To avoid non-identification problem, we did not include age, birth cohort, and HCV diagnosis year in the same adjusted model.

As most HCV infections are asymptomatic, and people often do not test for HCV regularly, the onset of infection is not known raising the issue of temporality of risk factors. However, HCV onset date is relatively more accurate among seroconverters who are being repeatedly tested for high risk activities and have a negative test available preceding a positive test, and thus it is possible to calculate the follow-up time more accurately. To address this issue, we performed Cox proportional hazard [PH] models on seroconverters using the follow-up time from midpoint between last negative test and first positive test to spontaneous clearance (the midpoint between the last negative PCR post-diagnosis and first positive PCR), and adjusted hazard ratios (aHR) and 95% CI were reported. To further validate our findings, Cox PH model was fit among the seroconverters who had two PCRs available (n=4,610). In this sample, spontaneous clearance was defined as two consecutive negative PCRs. All the analyses

were conducted in [SAS/STAT] Software version [9.4]. All the tests were two-sided at a significance level of 0.05.

Ethics Approvals

Data linkage to establish the BC-HTC was performed under the BCCDC's public health mandate. This study was reviewed and approved by the Behavioral Research Ethics Board at the University of British Columbia (H14-01649).

RESULTS

Figure 1 demonstrates the selection of our final sample. In brief, of a total of 67,726 HCV positive cases identified in the BC-HTC, 46,940 individuals had at least one valid PCR test result on or after HCV diagnosis. Due to the possibility of data linkage error, 157 cases were excluded from the final analysis resulting in a final sample size of 46,783 (Figure 1).

Characteristics of the participants

Table 2 shows the characteristics of the sample population. In brief, the majority of the individuals were 35-44 years of age (31.5%), born between 1945 and 1964 (61.9%), male (63.6%), and from most-deprived neighborhoods (36.3%). Overall, 22.2%, 22.5%, and 16.7% of the participants had recent injection drug use, problematic alcohol use, and major mental health disorders, respectively. The proportions of people co-infected with HIV, HBV, and primary T-cell deficiencies were 3.1%, 1.1%, and 0.24%, respectively. Of 3,268 participants with known HCV genotype, most (62.6%, n = 2044) of them were of genotype-1 followed by genotype-3 (24.5%, n = 802) and genotype-2 (11%, n = 258); the rest were genotype- 4, 5, and 6 or mixed.

Spontaneous clearance

A quarter (25.1%, n=11,737) of all eligible participants spontaneously cleared their infection while it was 32.9% (2,054 of 6,238) among seroconverters. Females cleared more frequently (32%) than the males (21%), while people with primary T-cell immunodeficiency at baseline had much lower clearance rate (14%) compared to those without (25%). People co-infected with HBV at baseline had much higher rate of clearance (42%) compared to those without HBV (25%). Genotype-3 had much higher clearance rate (17%) than genotype-1 (8%) (Table 2).

Factors associated with spontaneous clearance in overall sample

Table 3 shows unadjusted and adjusted estimates of the effect of primary t-cell immunodeficiency on spontaneous clearance. In unadjusted analysis, all the variables except HIV, and diabetes at baseline were statistically significantly associated with spontaneous clearance. After adjusting for birth cohort, sex, year of HCV diagnosis, HCV genotypes, HBV, major mental illness, injection drug use, problematic alcohol use, and material deprivation at baseline, people with primary T-cell immunodeficiency had 45% lower odds (aOR: 0.55, 95% CI: 0.32-0.94) of spontaneous clearance of HCV compared to those without. People co-infected with HBV had 2.31 times the odds (95% CI: 1.93-2.77) of clearing the infection spontaneously, while HCV genotype-3 was found to have more than twice the odds (aOR: 2.23, 95% CI: 1.74-2.86) of spontaneous clearance compared to HCV

genotype-1, and females had higher odds (aOR: 1.61, 95% CI: 1.54-1.68) of spontaneous clearance of HCV compared to males (Table 3).

Factors associated with spontaneous clearance among seroconverters

Additional analysis on seroconverters (n=6,238), who had a relatively well-defined infection onset date, showed that primary T-cell immunodeficiency was associated with lower clearance (aHR: 0.25, 95% CI: 0.06-0.99) adjusting for all the variables mentioned above, while females were found to have higher likelihood of spontaneous clearance of HCV (aHR: 1.61, 95% CI: 1.48-1.76) (Table 4). These findings were similar in a sensitivity analysis (Supplementary Table 2) among the seroconverters with two PCRs (n=4,610) where 25.6% (n=1,182) cleared the infection spontaneously (defined as two consecutive negative PCR test, at least 28 days apart). Since the interval between the last negative and first negative HCV tests (in the seroconverters) was longer (median: 2, IQR: 0.9-4.4 years), additional analysis was conducted among the seroconverters who did so within 24 months (n=3,101). The rate of spontaneous clearance in this group was 34.6% (n=1,074). However, the effect of primary t-cell immunodeficiency could not be assessed due to insufficient cases (four cases of primary t-cell immunodeficiency; none spontaneously cleared the infection).

DISCUSSION

Using a large population-based cohort, we have shown that overall spontaneous clearance was 25%, similar to other published studies. [5, 34] Clearance was significantly lower among those with primary T-cell immunodeficiency and older birth cohorts but higher among women, younger age at diagnosis, genotype 3, and those with HBV infection. These findings have important implications for overall care and support programs.

We found association of primary T-cell immunodeficiency with lower likelihood of spontaneously clearance of HCV infection both in overall study population as well among seroconverters. These findings are supported by the results from immunological studies. [14-16] These studies showed that HCV-specific T-cell response is associated with successful clearance of HCV infection. The population-level prevalence of primary T-cell immunodeficiency is low, thus primary t-cell deficiency may not have substantial population level impact on HCV clearance. However, since clearance is low among these patients, they will require treatment to prevent progressive liver disease, which will be important when we move to treating people earlier in the course of illness.

Co-infection with HBV was found to increase the likelihood of spontaneous clearance of HCV which is consistent with previous findings in specific high-risk cohorts. [11, 31] The study on PWIDs by Grebely *et al.*[3] also reported similar trend but HBV did not reach statistical significance, which may be due to very small number of cases with viral clearance (n=9). Previous research suggested that HBV superinfection may supress the pre-existing HCV infections. [35] This is supported by in-vitro and in-vivo evidence that interferon-γ (IFNγ), interferon-α, and tumor necrosis factor-α, released by host inflammatory cells in response to superimposed HBV infection, have been found to inhibit HCV replication. [36] However, whether HBV infection interferes with the clearance of new HCV infection has not been clearly examined. In our analyses on seroconverters, where HBV infection preceded HCV infection, the HBV infection was not found to be a statistically significant predictor of spontaneous clearance. This

may largely be due to the fact that seroconverters are distinct group of people (Supplementary table 3). Compared to non-seroconverters, they are younger (>60% aged below 35 years vs. 22% among the non-seroconverters), more represented by females (45%% vs. 35%), with higher proportion of HIV positive (4.23% vs. 2.87%), injecting drug use (47% vs. 18%), alcohol use (36% vs. 20%), and major mental health illnesses (33% vs. 14%). However, further research is required to disentangle the consequence of co- and super-infection of HBV on the natural history of HCV.

HCV genotype-3 was found to have twice the odds of spontaneously clearing the infection compared to genotype-1. This finding is consistent with previous epidemiological studies,[37, 38] while other studies reported higher clearance for genotype-1.[39-41] However, caution should be exercised in interpreting this finding for the following reasons. First, it was no longer significant in the time-to-spontaneous-clearance analysis among seroconverters. Moreover, a vast majority of the genotype was 'unknown', which most likely consists of genotypes 1 and 3, as these are the dominant HCV strains in Canada. It is likely that genotype-1 clears faster, and thus remains untypable contributing highly to the 'unknown' category. Our analysis also found females to have higher likelihood of spontaneous clearance of HCV compared to males, which was maintained across the sensitivity analyses among seroconverters, and is consistent with the findings from other epidemiological studies. [3, 11] This disparity in spontaneous clearance of HCV has been suggested to be linked with sex hormones, particularly oestrogen. [42] For example, 17β-estradiol (the most potent physiological estrogen) was found to inhibit mature virion production in cultured hepatic cells. [43] Moreover, oestrogen was found to have supressed the expression of hepatic scavenger receptors, critical for viral entry, while testosterone was found to have enhanced the expression of the same thus facilitating viral entry. [44] Some epidemiological studies found that the effect of IL28B polymorphism on the spontaneous clearance of HCV is affected by sex [39, 45] while other found a null association emphasizing on the mode of HCV acquisition.[34] However, we were not able to assess this effect.

Of all the HCV positive individuals, 29% did not further test for HCV-PCR and ultimately were not eligible for our analysis. We compared these individuals to those who were included in the analyses. We found no significant difference between these two groups (Supplementary table 4).

We calculated the estimated date of HCV seroconversion by taking the midpoint of last negative and first positive PCR, and estimated date of HCV clearance by taking the midpoint of the last positive and first negative PCR following HCV diagnosis, as has been the standard practice in the HCV literature so far. [27, 46] In practice, this is actually a case of interval censoring, and thus regression models addressing the interval-censored data would appear to be a better fit. However, we did not do that as it would lessen comparability of our results with existing literature. Moreover, the non-informative censoring assumptions behind the standard methods for censored data are probably questionable in this context. Generally the assumption is independence of censoring times and event times given the covariates included in the model. But when the censoring times are testing times, there may be violation of this assumption.

The sensitivity of different HCV–PCR assays changed over time, and may impact classification of spontaneously cleared cases. Most of the quantitative HCV-PCR tests were validated by a more sensitive qualitative

test up until 2007, after which quantitative PCR assays were as sensitive (RNA detection level up to 10-15 IU/mL) as the qualitative test. Between 2000 and 2006, a small proportion (2.95% of those tested for RNA) of quantitative test results with lower limit of RNA detection of 615 IU/mL (all negative) were not verified by a qualitative test. In this analysis, 227 negative HCV-PCR test results (HCV RNA <615 IU/mL) were not confirmed by a qualitative test. While this was the test used in practice back then, and while potentially all of them could well be HCV negative, we attempted to estimate the maximum number of HCV cases (assuming all of them had RNA levels between 15 and 615 IU/mL) that might have been HCV positive but test results were negative due to inability of the less sensitive assays to detect them. Therefore, the lowest estimate of spontaneous clearance rate would be 24.6% (n=11,510).

To our knowledge, this is the largest population-based study with sufficient follow-up time to examine the effect of primary T-cell immunodeficiency, HBV co-infection, and other factors on the spontaneous clearance of HCV. We also defined the covariates at baseline to disentangle the temporal issues of comorbidities and other risk factors. Further, several sensitivity analyses were conducted to validate our findings. We have previously validated the variable injecting drug use against interview based data[47] while problematic alcohol use, diabetes, and mental health variables were derived based on administrative codes validated by others. However, since these variables were defined using health services utilization codes, there is a possibility of under estimation and misclassification depending on health care utilization patterns. Another limitation of this study is that we did not have access to ethnicity data. While ethnicity was reported to be associated with spontaneous clearance of HCV,[3] it was not found to be a significant predictor in other studies[31] including a systematic review and meta-analysis conducted earlier.[5]

In conclusion, 25% of HCV infected individuals cleared infection spontaneously. Those with primary T-cell immunodeficiency were less likely, while females and those co-infected with Hepatitis B infection were more likely, to spontaneous clear their HCV infections. While these findings lend support to existing theories of the role of immune system in HCV clearance, these will also be useful in informing follow-up and treatment decisions in the era of highly effective direct-acting antivirals as to who could be prioritized to receive HCV treatment.

Abbreviations: HCV: Hepatitis C; BC-HTC: BC Hepatitis Testers Cohort; PCR: Polymerase chain Reaction; PH: proportional hazard; aOR: adjusted odds ratio; PWID: people who inject drugs; MSM: men who have sex with men; BC-PHL: BC Public Health Laboratory; HBV: Hepatitis B virus; HIV: Human Immunodeficiency Syndrome; AIDS: Acquired Immunodeficiency Syndrome; iPHIS: Integrated Public Health Information System; IDU: injection drug use; ICD: International Classification of Disease; aHR: adjusted hazard ratios; CI: Confidence Interval; IFNγ: interferon-gamma.

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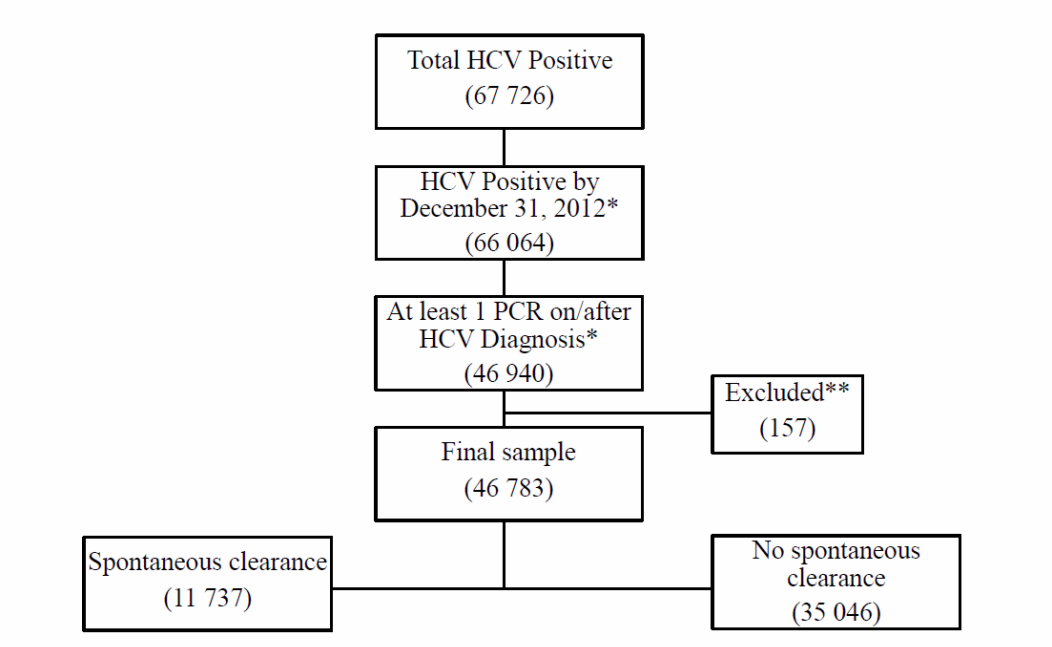
Figure 1: Schematic presentation of analytic sample for the study of spontaneous clearance in BC-HTC



** Date of HCV diagnosis was restricted to December 31, 2012 to allow sufficient time to observe spontaneous clearance.*

***Excluded are those who received treatment when they were HCV negative (possibly data linkage error)*

Abbreviations: HCV: Hepatitis C Virus; PCR: polymerase Chain Reaction

Table 1: Definitions for comorbid conditions for the BC Hepatitis Testers Cohort (BC-HTC) and current analysis

Primary T-cell immunodeficiency Primary T-cell immunodeficiency was diagnosed at the first occurrence of 1 MSP or 1 hospitalization codes for Combined immunodeficiencies, Wiskott–Aldrich syndrome, Di George's syndrome, Common variable immunodeficiency with predominant immunoregulatory T-cell disorders, Common variable immunodeficiency with autoantibodies to B- or T-cells, Lymphocyte function antigen-1 defect, Friedreich's ataxia, or Other spinocerebellar diseases inc. Ataxia-telangiectasia. Physician Billing Data: MSP ICD-9 diagnostic codes: starting with 2791, or exact codes 2792, 3340, 3348 Hospitalization Data: DAD1/ICD-9-CM: exact codes 27906, 27910-2, 2792, 3340, 3348; DAD2/ICD-10-CA: starting with D81, or exact codes D82.0, D82.1, D83.1, D83.2, D84.0, G11.1, G11.3, G11.8
Diabetes Diabetes was defined at the first occurrence of 2 MSP or 1 hospitalization codes for diabetes-specific diagnostic codes. Physician Billing Data: MSP ICD-9 diagnostic codes: starting with 250. Hospitalization Data: DAD1/ICD-9-CM: starting with 250; DAD2/ICD-10-CA: starting with E10-4
Major Mental Health Diagnosis Major mental illness was flagged at the first occurrence of either 1 hospitalization diagnostic code OR 2 MSP diagnostic codes from a psychiatrist visit for schizophrenic, bipolar, delusional, nonorganic psychotic, adjustment, anxiety, dissociative, personality and major depressive disorders Physician Billing Data: MSP ICD-9 diagnostic codes: starting with 295-298, 300-301, 308-309, 311 AND claim specialty = 3 Hospitalization Data: DAD1/ICD-9-CM: starting with 295-298, 300-301, 308-309, 311; DAD2/ICD-10-CA: starting with F20-F25, F28-F34, F38-F45, F48, F60-F61
Injection Drug Use Illicit Drug Use was defined at the first occurrence of 1 MSP or 1 hospitalization diagnostic codes for major drug-related diagnoses involving addiction, dependence, and drug-induced mental disorders; illicit drug use most likely to be injectables (e.g. excluding cannabis), or illicit use of prescribed drugs including: hallucinogens, barbituates/tranquillizers, sedatives, hypnotics, anxiolytics, opioids, cocaine, amphetamine, volatile solvents; or discharge to drug rehabilitation, counselling, surveillance or methadone/buprenorphine substitution treatment. **Physician Billing Data**: MSP ICD-9 diagnostic codes: starting with 292, 3040, 3042, 3044, 3046-9, 3054-7, 3059, 6483, 9650, 9697, 970, E8500, or exact codes V6542 or fee item = 39 **Hospitalization Data**: **DAD1/ICD-9-CM**: starting with 292, 3040, 3042, 3044, 3046-9, 3054-7, 3059, 6483, 9650, 9697, 970, E8500; **DAD2/ICD-10-CA**: starting with F11, F13-5, F18, F19, T42, or exact codes T401, T402, T404-6, T436, T438, T439, T507.
Problematic Alcohol Use Problematic alcohol use was defined at the first occurrence of 2 MSP or 1 hospitalization codes for major alcohol-related diagnoses including alcoholic mental disorders and dependence/abuse syndromes; alcoholic polyneuropathy, myopathy, cardiomyopathy; pseudo Cushing's syndrome; or discharge to alcohol rehabilitation, counselling, or surveillance Physician Billing Data: MSP ICD-9 diagnostic codes: starting with 291, 303, 3050, 3575, 4255 Hospitalization Data: DAD1/ICD-9-CM: starting with 291, 303, 3050,3575, 4255; DAD2/ICD-10-CA: starting with F10, E244, G312, G621, G721, I426, Z502, Z714

Table 2: Characteristics of HCV positive cases with at least one PCR test on/after HCV diagnosis in BC-HTC

Characteristics	Spontaneous Clearance		
	Yes 11,737 (25.1)	**No 35,046 (74.9)**	**% Spontaneous Clearance**
Age at HCV Diagnosis			
<25	1309 (11.2)	1969 (5.6)	39.9
25-34	2817 (24.0)	6454 (18.4)	30.4
35-44	3513 (29.9)	11220 (32.0)	23.8
45-54	2678 (22.8)	10199 (29.1)	20.8
≥55	1420 (12.1)	5204 (14.9)	21.4
Median age [Range]	39 [0 - 96]	43 [0 - 94]	
Birth Cohort			
<1945	710 (6.1)	2681 (7.7)	20.9
1945-1964	6370 (54.3)	22607 (64.5)	22.0
1965-1974	2678 (22.8)	6428 (18.3)	29.4
≥1975	1979 (16.9)	3330 (9.5)	37.3
Female	5366 (45.7)	11669 (33.3)	31.5
Year of diagnosis			
1990-1994	873 (7.4)	2327 (6.6)	27.3
1995-1999	3869 (33.0)	11793 (33.7)	24.7
2000-2004	2912 (24.8)	10004 (28.6)	22.6
2005-2009	2860 (24.4)	7647 (21.8)	27.2
2010-2013	1223 (10.4)	3275 (9.3)	27.2
HCV Genotypes			
Genotype 1	159 (1.4)	1885 (5.4)	7.8
Genotype 3	135 (1.2)	667 (1.9)	16.8
Genotype- other*	36 (0.3)	386 (1.1)	8.5
Genotype- unknown	11407 (97.8)	32108 (92.7)	26.2
HIV**	333 (2.8)	1096 (3.1)	16.4
Primary T-cell immunodeficiency**	16 (0.1)	98 (0.3)	14.0
Hepatitis B**	216 (1.8)	300 (0.9)	41.9
Diabetes (type-2)**	207 (1.8)	576 (1.6)	26.4
Major Mental Health**	2098 (17.9)	5721 (16.3)	26.8
Injection Drug Use**	2904 (24.7)	7491 (21.4)	27.9
Problematic Alcohol Use**	2782 (23.7)	7727 (22.1)	26.5
Material deprivation quintile**			
Q1 (most privileged)	1532 (13.1)	4677 (13.4)	24.7
Q2	1760 (15.0)	5476 (15.6)	24.3
Q3	2030 (17.3)	6282 (17.9)	24.4
Q4	2569 (21.9)	7954 (22.7)	24.4
Q5 (most deprived)	3522 (30.0)	9873 (28.2)	26.3
Unknown	324 (2.8)	784 (2.2)	29.2
Social deprivation quintile**			
Q1 (most privileged)	1213 (10.3)	3829 (10.9)	24.1
Q2	1492 (12.7)	4526 (12.9)	24.8
Q3	1927 (16.4)	5932 (16.9)	24.5
Q4	2423 (20.6)	7364 (21.0)	24.8
Q5 (most deprived)	4358 (37.1)	12611 (36.0)	25.7
Unknown	324 (2.8)	784 (2.2)	29.2

*: Other includes genotype 2, 4, 5, 6, and Mixed; **: on/before HCV diagnosis

HCV: Hepatitis C Virus; HIV: Human Immunodeficiency Virus

Table 3: Unadjusted and adjusted Odds Ratios for factors associated with spontaneous clearance in BC-HTC

Characteristics	Unadjusted OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Age at HCV Diagnosis		<0.0001		
<25	2.44 (2.22, 2.67)			
25-34	1.60 (1.49, 1.72)			
35-44	1.15 (1.07, 1.23)			
45-54	0.96 (0.90, 1.04)			
≥55	*Ref*			
Birth Cohort		<0.0001		<0.0001
<1945	0.45 (0.40, 0.49)		0.44 (0.40, 0.49)	
1945-1964	0.47 (0.45, 0.51)		0.50 (0.47, 0.54)	
1965-1974	0.70 (0.65, 0.75)		0.72 (0.67, 0.78)	
≥1975	*Ref*		*Ref*	
Female	1.69 (1.62, 1.76)	<0.0001	1.61 (1.54, 1.68)	<0.0001
Year of diagnosis		<0.0001		<0.0001
1990-1994	1.01 (0.91, 1.11)		1.23 (1.10, 1.36)	
1995-1999	0.88 (0.82, 0.95)		1.03 (0.96, 1.12)	
2000-2004	0.78 (0.72, 0.84)		0.87 (0.81, 0.94)	
2005-2009	1.00 (0.93, 1.08)		1.04 (0.96, 1.13)	
2010-2013	*Ref*		*Ref*	
HCV Genotypes		<0.0001		<0.0001
Genotype 1	*Ref*		*Ref*	
Genotype 3	2.40 (1.88, 3.07)		2.23 (1.74, 2.86)	
Genotype- other*	1.11 (0.76, 1.61)		1.13 (0.78, 1.66)	
Genotype/unknown	4.21 (3.58, 4.96)		4.19 (3.55, 4.94)	
HIV**	0.91 (0.80, 1.02)	0.1140		
Primary T-cell immunodeficiency**	0.49 (0.29, 0.83)	0.0076	0.55 (0.32, 0.94)	0.0292
Hepatitis B**	2.17 (1.82, 2.59)	<0.0001	2.31 (1.93, 2.77)	<0.0001
Diabetes (type-2)**	1.08 (0.92, 1.26)	0.3719		
Major Mental Health**	1.12 (1.06, 1.18)	<0.0001	0.98 (0.92, 1.04)	0. 4517
Injection Drug Use**	1.21 (1.15, 1.27)	<0.0001	1.03 (0.97, 1.09)	0. 3417
Problematic Alcohol Use**	1.10 (1.05, 1.15)	0.0002	1.09 (1.03, 1.15)	0. 0015
Material deprivation quintile**		<0.0001		0.0003
Q1 (most privileged)	*Ref*		*Ref*	
Q2	0.98 (0.91, 1.06)		0.97 (0.89, 1.05)	
Q3	0.99 (0.91, 1.07)		0.97 (0.90, 1.05)	
Q4	0.99 (0.92, 1.06)		0.96 (0.89, 1.03)	
Q5 (most deprived)	1.09 (1.02, 1.17)		1.05 (0.98, 1.13)	
Unknown	1.26 (1.10, 1.45)		1.25 (1.08, 1.44)	
Social deprivation quintile**		0.0025		
Q1 (most privileged)	*Ref*			
Q2	1.04 (0.95, 1.14)			
Q3	1.03 (0.94, 1.11)			
Q4	1.04 (0.96, 1.12)			
Q5 (most deprived)	1.09 (1.01, 1.17)			
Unknown	1.31 (1.13, 1.51)			

*: Other includes genotype 2, 4, 5, 6, and Mixed; **: on/before HCV diagnosis

HCV: Hepatitis C Virus; HBV: Hepatitis B Virus; HIV: Human Immunodeficiency Virus; OR: Odds Ratio: CI: Confidence Interval

Table 4: Cox proportional hazard model examining the factors associated with spontaneous clearance among HCV seroconverters in BC-HTC (n = 6,238)

Characteristics	Spontaneous clearance (N=2,054); N (%)	% spontaneous clearance	Adjusted HR (95% CI)	p-value
Birth Cohort				<0.0001
<1945	31 (1.51)	33.0	1.15 (0.8, 1.65)	
1945-1964	474 (23.08)	28.7	0.78 (0.69, 0.88)	
1965-1974	635 (30.92)	30.3	0.78 (0.7, 0.86)	
≥1975	914 (44.5)	38.1	*Ref*	
Female	1115 (54.28)	40.1	1.61 (1.47, 1.76)	<0.0001
Year of diagnosis				<0.0001
1990-1994	57 (2.78)	46.72	0.38 (0.28, 0.52)	
1995-1999	397 (19.33)	30.56	0.26 (0.21, 0.31)	
2000-2004	774 (37.68)	33.20	0.35 (0.3, 0.42)	
2005-2009	641 (31.21)	33.08	0.47 (0.4, 0.55)	
2010-2013	185 (9.01)	33.76	*Ref*	
HCV Genotypes				<0.0001
Genotype 1	48 (2.34)	16.96	*Ref*	
Genotype 3	46 (2.24)	25.84	1.43 (0.96, 2.15)	
Genotype- other*	8 (0.40	13.56	0.7 (0.33, 1.48)	
Genotype-/unknown	1952 (95.03)	34.14	2.4 (1.8, 3.2)	
Primary T-cell immunodeficiency**	2 (0.1)	7.69	0.25 (0.06, 0.99)	0.049
Hepatitis B**	47 (2.29)	30.32	1.02 (0.76, 1.37)	0.892
Major Mental Health**	637 (31.01)	30.80	0.91 (0.83, 1.01)	0. 085
Injection Drug Use**	930 (45.28)	31.72	0.91 (0.83, 1.00)	0. 048
Problematic Alcohol Use**	730 (35.54)	32.12	1.03 (0.94, 1.14)	0. 482
Material deprivation quintile**				0.258
Q1 (most privileged)	272 (13.24)	35.23	*Ref*	
Q2	276 (13.44)	30.80	0.84 (0.71, 1.00)	
Q3	336 (16.4)	34.11	0.94 (0.80, 1.10)	
Q4	465 (22.6)	31.31	0.86 (0.74, 1.00)	
Q5 (most deprived)	670 (32.6)	33.94	0.94 (0.82, 1.08)	
Unknown	35 (1.7)	27.78	0.88 (0.62, 1.25)	

*: Other includes genotype 2, 4, 5, 6, and Mixed; **: on/before HCV diagnosis

HCV: Hepatitis C Virus; PCR: Polymerase Chain Reaction; HR: Hazard Ratio: CI: Confidence Interval; Seroconverters: Who tested positive for HCV following at least one negative HCV test

Supplementary Table 1. Criteria and Data Sources for the BC Hepatitis Testers Cohort (BC-HTC)

Criteria for Inclusion in BC-HTC	
All individuals: • tested at the centralized provincial laboratory for HCV or HIV OR • reported by BC public health as a confirmed case of HCV OR • reported in BC enhanced surveillance system as a confirmed case of HIV or AIDS (all reports) OR • reported by BC public health as a confirmed case of HBV OR • included in BC Enhanced Strain Surveillance System (EHSSS) as an acute HBV or HCV case • All individuals meeting at least one the above criteria were linked internally across all their tests and case reports. Those with a valid personal health number (PHN) were then sent for deterministic linkage with province-wide Cancer and Ministry of Health (MoH) datasets	
Provincial Communicable Disease Data Sources:	**Data Date Ranges:**
BC-PHMRL HIV laboratory testing datasets (tests: ELISA, Western blot, NAAT, p24, culture)	1988–2013
BC-PHMRL HCV laboratory tests datasets (tests: antibody, HCV RNA, genotyping)	1992–2013
HIV/AIDS Information System (HAISYS) (public health HIV/AIDS case reports)	1980–2013
Integrated Public Health information System (iPHIS) (public health case reports of HCV, HBV, and TB)	1990–2013
Enhanced Strain Surveillance System (EHSSS) (risk factor data on a subset of acute HCV and acute HBV cases)	2000–2013
Cancer and MoH Administrative Data Sources:	**Data Date Ranges:**
BC Cancer Registry (BCCR) (primary tumour registry, excludes metastatic cancers)	1970–2012
Discharge Abstracts Dataset (DAD) (hospitalization records)[1]	1985–2013Q1
Medical Services Plan (MSP) (physician diagnostic and billing data)[2]	1990–2012
PharmaCare/PharmaNet (Pharma) (prescription drug dispensations)[3,4]	1985–2012
BC Vital Statistics (VS) (deaths registry)[5]	1985–2013
The final BC-HTC comprises all individuals successfully linked on PHN to the MoH Client Roster[6] (a registry of all BC residents enrolled in the publicly-funded universal healthcare system)	

HCV: Hepatitis C Virus; HBV: Hepatitis B Virus; HIV/AIDS: Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome; BC-PHMRL: BC Public Health Microbiology and Reference Laboratory: RNA: Ribonucleic Acid; PCR: Polymerase Chain Reaction.

Sources:

1. British Columbia Ministry of Health [creator]. Discharge Abstract Database (Hospital Separations). British Columbia Ministry of Health [publisher]. Data Extract. MOH (2013). 2014. http://www.health.gov.bc.ca/data/
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3. British Columbia Ministry of Health [creator]. PharmaCare. British Columbia Ministry of Health [publisher]. Data Extract. MOH (2013). 2014. http://www.health.gov.bc.ca/data/
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5. BC Vital Statistics Agency [creator]. Vital Statistics Deaths. BC Vital Statistics Agency [publisher]. Data Extract. BC Vital Statistics Agency (2014). 2014.
6. British Columbia Ministry of Health [creator]. Client Roster (Client Registry System/Enterprise Master Patient Index). British Columbia Ministry of Health [publisher]. Data Extract. MOH (2013). 2014. http://www.health.gov.bc.ca/data/

Supplementary Table 2: Cox proportional hazard model examining the factors associated with spontaneous clearance (defined as two consecutive negative PCR, at least 28 days apart) among HCV seroconverters in BC-HTC (n = 4,610)

Characteristics	Adjusted HR (95% CI)	p-value
Birth Cohort		<0.0001
<1945	1.1 (0.68, 1.76)	
1945-1964	0.71 (0.62, 0.82)	
1965-1974	0.74 (0.66, 0.83)	
≥1975	*Ref*	
Female	1.62 (1.46, 1.79)	<0.0001
Year of diagnosis		<0.0001
1990-1994	0.43 (0.3, 0.62)	
1995-1999	0.29 (0.23, 0.37)	
2000-2004	0.38 (0.31, 0.47)	
2005-2009	0.51 (0.41, 0.62)	
2010-2013	*Ref*	
HCV Genotypes		<0.0001
Genotype 1	*Ref*	
Genotype 3	1.42 (0.95, 2.13)	
Genotype- other*	0.71 (0.34, 1.51)	
Genotype-/unknown	2.34 (1.75, 3.12)	
Primary T-cell immunodeficiency**	0.77 (0.57, 1.03)	0.074
Hepatitis B**	0.99 (0.71, 1.39)	0.95
Major Mental Health**	0.92 (0.82, 1.03)	0. 015
Injection Drug Use**	0.88 (0.79, 0.98)	0. 02
Problematic Alcohol Use**	1.04 (0.93, 1.16)	0. 512
Material deprivation quintile**		0.18
Q1 (most privileged)	*Ref*	
Q2	0.82 (0.67, 0.99)	
Q3	0.88 (0.73, 1.07)	
Q4	0.85 (0.71, 1.01)	
Q5 (most deprived)	0.96 (0.81, 1.13)	
Unknown	0.87 (0.56, 1.34)	

*: Other includes genotype 2, 4, 5, 6, and Mixed; **: on/before HCV diagnosis

HCV: Hepatitis C Virus; PCR: Polymerase Chain Reaction; HR: Hazard Ratio: CI: Confidence Interval; Seroconverters: Who tested positive for HCV following at least one negative HCV test

Supplementary Table 3: Comparison between the seroconverters and non-seroconverters in BC-HTC cohort

Characteristics	Seroconverters (n = 6,238)		Non-seroconverters (n = 40,545)	
	% Total	% Spontaneous Clearance	% Total	% Spontaneous Clearance
Age at HCV Diagnosis				
<25	22.12	39.93	4.68	39.94
25-34	38.51	32.47	16.94	29.65
35-44	26.71	29.35	32.23	23.14
45-54	9.63	30.62	30.28	20.32
≥55	3.03	26.46	15.87	21.29
Birth Cohort				
<1945	1.51	32.98	8.13	20.59
1945-1964	26.43	28.74	67.40	21.57
1965-1974	33.62	30.28	17.29	29.15
≥1975	38.44	38.12	7.18	36.59
Female	44.63	40.05	35.15	29.83
Year of diagnosis				
1990-1994	1.96	46.72	7.59	26.51
1995-1999	20.82	30.56	35.42	24.17
2000-2004	37.37	33.20	26.11	20.2
2005-2009	31.07	33.08	21.13	25.9
2010-2013	8.78	33.76	9.74	26.28
HCV Genotypes				
Genotype 1	4.54	16.96	4.34	6.3
Genotype 3	2.85	25.84	1.54	14.26
Genotype- other/unknown*	92.61	33.93	94.12	24.85
HIV**	4.23	20.83	2.87	23.86
Primary T-cell immunodeficiency **	0.42	7.69	0.22	15.91
Hepatitis B**	2.48	30.32	0.89	46.81
Diabetes (type-2)**	1.51	31.91	1.70	25.69
Major Mental Illness**	33.15	30.80	14.18	25.4
Injection Drug Use**	47.00	31.72	18.41	26.45
Problematic Alcohol Use**	36.44	32.12	20.31	24.92
Material deprivation quintile**				
Q1 (most privileged)	12.38	35.23	13.41	23.17
Q2	14.36	30.80	15.64	23.41
Q3	15.79	34.11	18.07	23.12
Q4	23.81	31.31	22.29	23.28
Q5 (most deprived)	31.64	33.94	28.17	24.97
Unknown	2.02	27.78	2.42	29.43
Social deprivation quintile**				
Q1 (most privileged)	8.13	33.53	11.19	23
Q2	10.77	31.99	13.19	23.89
Q3	14.83	31.46	17.10	23.59
Q4	20.15	33.97	21.04	23.4
Q5 (most deprived)	44.10	33.30	35.07	24.21
Unknown	2.02	27.78	2.42	29.43

*: Other includes genotype 2, 4, 5, 6, and Mixed; **: on/before HCV diagnosis
HCV: Hepatitis C Virus; HIV: Human Immunodeficiency Virus

Supplementary Table 4: Characteristics of those who had a valid HCV-PCR on/after HCV diagnosis to those who didn't in BC-HTC

	PCR on/after HCV Diagnosis	
Characteristics	**Yes 46,783 (71.0)**	**No 19,124 (29.0)**
Age at HCV Diagnosis		
<25	3278 (7.0)	1092 (5.7)
25-34	9271 (19.8)	3986 (20.8)
35-44	14733 (31.5)	6385 (33.4)
45-54	12877 (27.5)	4406 (23.0)
≥55	6624 (14.2)	3255 (17.0)
Median age [Range]	42 [0 – 96]	42 [0 – 99]
Birth Cohort		
<1945	3391 (7.3)	2887 (15.1)
1945-1964	28977 (61.9)	11324 (59.2)
1965-1974	9106 (19.5)	3561 (18.6)
≥1975	5309 (11.4)	1352 (7.1)
Female	17035 (36.4)	5927 (31.0)
Year of diagnosis		
1990-1994	3200 (6.8)	2325 (12.2)
1995-1999	15662 (33.5)	9479 (49.6)
2000-2004	12916 (27.6)	4246 (22.2)
2005-2009	10507 (22.5)	2102 (11.0)
2010-2012	4498 (9.6)	972 (5.1)
HIV*	1429 (3.1)	602 (3.2)
Primary T-cell immunodeficiency *	114 (0.2)	29 (0.2)
Hepatitis B*	516 (1.1)	338 (1.8)
Diabetes (type-2)*	783 (1.7)	481 (2.5)
Major Mental Health*	7819 (16.7)	2761 (14.4)
Injection Drug Use*	10395 (22.2)	4080 (21.3)
Problematic Alcohol Use*	10509 (22.5)	4665 (24.4)
Material deprivation quintile*		
Q1 (most privileged)	6209 (13.3)	2216 (11.6)
Q2	7236 (15.5)	2856 (14.9)
Q3	8312 (17.8)	3150 (16.5)
Q4	10523 (22.5)	4016 (21.0)
Q5 (most deprived)	13395 (28.6)	5571 (29.1)
Unknown	1108 (2.4)	1315 (6.9)
Social deprivation quintile*		
Q1 (most privileged)	5042 (10.8)	1728 (9.0)
Q2	6018 (12.9)	2196 (11.5)
Q3	7859 (16.8)	2928 (15.3)
Q4	9787 (20.9)	3778 (19.8)
Q5 (most deprived)	16969 (36.3)	7179 (37.5)
Unknown	1108 (2.4)	1315 (6.9)

*: on/before HCV diagnosis

HCV: Hepatitis C Virus; HIV: Human Immunodeficiency Virus