## Title
Human leukocyte antigen B*57 does not fully explain hepatitis C clearance in HIV controllers



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# HLA B*57 Does Not Fully Explain Hepatitis C Clearance in HIV Controllers

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A small percentage (1-5%) of people living with HIV are able to intrinsically control their HIV infection over long periods of time without the use of antiviral therapy (ART) [1]. Two groups of "HIV controllers" have been described: (1) Elite controllers, who have HIV antibodies (anti-HIV), but plasma HIV RNA levels below the detection limits of commercially available assays, and; (2) Viremic controllers, who have measurable, but very low levels of HIV RNA (< 2000 copies/mL). HIV controllers represent "outliers" in the clinical HIV spectrum, and are considered very important for studies of host immunological and genetic factors that control viral replication, with the expectation that they will inform vaccine and drug development, or perhaps identify strategies to achieve a "functional cure [1, 2]."

Interestingly, HIV controllers may also be more likely to spontaneously clear hepatitis C virus (HCV) infection. While not observed in all studies [3, 4], most studies suggest a significantly higher rate of spontaneous HCV clearance in HIV controllers (23-39%) [5, 6] than in monoinfected groups (25%) [7] and HIV non-controllers (6.6%-10%) [1, 5]. This has led several groups to examine host genetic factors that might contribute to the control of both virus infections. For example, HLA B*57, the major histocompatibility class I allele, is highly enriched in HIV controllers and is also associated with spontaneous HCV clearance [8-10]. In contrast, HLA Cw*04 has been associated with faster progression of both HIV disease and chronic HCV infection [11, 12]. The *IL28B* CC genotype has been shown to be significantly associated with spontaneous control of HCV [13-16], conferring as much as 3.1 higher odds of clearance compared to CT and TT genotypes [17, 18].

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Whether the CC genotype of *IL28B* is also enriched in HIV controllers remains controversial. A relatively small Spanish study found that the CC genotype of *IL28B* was enriched in Caucasian HIV controllers relative to non-controllers [4], while other studies in primarily African-American cohorts have not observed this [6, 19]. Furthermore, none of the much larger genome-wide association studies have found an association between the *IL28B* (CC) genotype and HIV control, at least at the genome-wide level of significance [20-23]. In one study the *IL28B* CC genotype has been associated with higher all-cause mortality among all people living with HIV [24].

In this study, we investigated the degree to which spontaneous clearance of HCV could be explained by HLA B*57 and/or *IL28B* CC genotype in a well characterized cohort of HIV controllers.

## Methods

HIV-infected adults were sampled from the Study of the Consequences of the Protease Inhibitor Era (SCOPE), a clinic-based cohort of >1600 HIV-infected individuals at the University of California, San Francisco. This observational study has a large data and specimen bank of samples with carefully characterized clinical data, including HLA typing, and includes a large sample of HIV controllers [25]. For this study we included only anti-HCV positive participants, identified using a third generation enzyme immunoassay (EIA3) (Ortho Clinical Diagnostics®). Participants were classified as 'HIV controllers' if they were elite controllers or viremic-controllers. 'Non-controllers' had at least one HIV viral load > 10,000 copies/ml) as measured by bDNA (Quantiplex HIV RNA, version 3.0; Chiron Corporation) prior to or during ART.

HCV RNA was measured using discriminatory HCV transcription-mediated amplification (dTMA) assay component of the Procleix HIV-1/HCV assay, developed and manufactured by Gen-Probe (San Diego, CA) and marketed by Novartis Vaccines and Diagnostics. The 50% limit of detection of this assay is 12.1 copies/mL (95% confidence interval [CI], 11.1–13.2) of HCV RNA when using the recommended 0.5-mL plasma input volume. Participants were classified as having spontaneously cleared HCV infection if they had detectable anti-HCV but no detectable HCV RNA and had no history of HCV treatment. To evaluate whether any of the known host genetic determinants of HCV clearance were enriched in HIV controllers, we compared the genetic polymorphisms known to be associated with control of HIV and HCV in the HIV controller group to the HIV non-controllers.

Genetic testing for *IL28B* SNP polymorphism was conducted using real-time PCR amplification. The methodology of determining *IL28B* SNP polymorphism has been previously reported [26].

HLA typing was done using PCR-sequence-specific oligonucleotide probing [27]. Those positive for HBsAg or with a self-reported history of hepatitis treatment were excluded. The study was approved by the Committee for Human Subjects at the University of California San Francisco and all participants gave informed consent before undergoing any study-related procedures.

## Statistical analyses

The main outcome variable of this study is spontaneous HCV clearance, as defined above. The principal exposure of interest was HIV controller status: controller vs. or non-controller. Other covariates of interest included IL28-B (CC vs. non-CC (CT or TT)), HLA B*57, and HLA Cw*04 status. Bivariate associations between groups were assessed using *chi-square* and median tests for categorical and continuous variables, respectively. A multivariable regression model was fitted to assess genetic and immunologic predictors of HCV clearance; adjusted prevalence ratios (APR) were estimated using Poisson regression models with robust standard errors. All analyses were conducted using STATA version 12.1 (StataCorp, College Station, TX).

## Results

Of the 279 HIV/HCV-coinfected participants included in the analysis, 48 (17%) were HIV controllers. There was no difference in the sex, age or racial distribution between the HIV controller and non-controller groups (Table 1). HCV clearance did not appear to differ between HIV controllers and non-controllers in unadjusted analyses (35% vs. 27%, p=0.23).

HIV controllers were significantly enriched for HLA B*57 compared to HIV non-controllers (33% vs. 10%, p<0.001) (Table 2a). However, the HLA Cw*04 allele was similarly represented in controllers and non-controllers (26% vs. 17%, p=0.19), as was *IL28B* CC genotype (25% vs. 39% p=0.49). The only genetic factor significantly different by HCV clearance status, was *IL28B* CC: 59% of clearers were CC positive compared to 27% of non-clearers (p<0.001)(Table 2a). We next examined these associations stratified by sex (Table 2b). Male HIV controllers were significantly more likely to have HLA B*57 than male non-controllers (42% vs. 10%, p<0.001), but not female HIV controllers did not appear to be enriched for HLA B*57. Both females and males who cleared HCV were significantly more likely to be *IL28B* CC positive than non HCV clearers. The presence of HLA B*57 was not associated with HCV clearance among males or females.

To further evaluate whether HLA B*57 might explain the increased prevalence of HCV clearance on HIV controllers, we stratified our analysis by HLA B*57 status. Of the 24 HIV non-controllers positive for HLA B*57, 30% (n=7) spontaneously cleared their HCV infection compared to 27% (n=55) of the 207 HIV non-controllers without HLA B*57 (p=0.79). Similarly, among HIV controllers, 35% (n=11) of HIV controllers without HLA B*57 and 31% (n=5) of HIV controllers with HLA B*57 demonstrated HCV clearance (p=0.83).

The results of the multivariable analyses are shown in Table 3. After adjusting for HLA B*57, sex, age and race, two factors: HIV controller status (APR 1.78 (95% CI 1.06-3.00); p=0.0.032) and *IL28B* CC genotype (APR 2.76 (95% CI 1.85-4.11); p<0.001), were independently associated with spontaneous HCV clearance.

## Discussion

In the current study, we confirm prior studies demonstrating higher rates of spontaneous HCV clearance in HIV controllers [5, 6, 28]. We did not observe crude differences in the proportions of HIV controllers and non-controllers who cleared HCV, however, in multivariable analyses, HIV controller status was independently predictive of HCV clearance. Results also suggest that HLA B*57, a factor known to be associated with HIV controller status, is not explanatory of this association between controller status and HCV clearance. A recent study has suggested that HLA B*57 might be associated with promoting a more robust HCV-specific T cell response [29], however, the combined findings that HLA B*57 was not associated with HCV clearance, and the equally high proportions of HIV controllers with (31%) and without (35%) HLAB*57 who cleared HCV suggests that other mechanism or host factors are at play. The HLA Cw*04 allele also failed to explain the increased proportion of HCV clearance in HIV controllers. Given the lack of association of *IL28B* genotype and HIV controller status, these results suggest that other factors associated with HIV controller status and as yet unmeasured in this group are associated with HCV clearance.

As noted, a high proportion of HIV infected controllers and non-controllers in this cohort demonstrated a spontaneous HCV clearance. The 27% rate of spontaneously cleared HCV infection among HIV non-controllers is much higher than normally seen in HIV-infected populations [30]. It is likely that most of these patients experienced their HCV infection and subsequent clearance before their HIV infection [31]. Few, if any, were infected with HCV after ART-mediated immune recovery, although HCV reinfection cannot be ruled out [32]

Females have been shown to be almost three times more likely to clear HCV infection than males [18, 33]. However, we found no differences in HCV clearance rates by sex overall, or stratified by HIV controller status. We also did not observe differences in HCV clearance by sex and *IL28B* genotype, as others have recently reported [15, 18] There is little evidence that HCV risk differed by HIV controller group; injection drug use was reported equally. One study has suggested an association between sexually acquired HCV and HCV clearance, [34], but this association has not been seen prospectively, nor has this been observed in HIV+ men who have sex with men, a group well-represented within the SCOPE cohort [35]. There is no clear explanation for why males were equally likely to clear their HCV infection as women in this cohort.

There are some limitations to this study. We excluded those with a history of prior HCV treatment based on self-report. It is possible that there was underreporting of HCV treatment history; Medical record review was undertaken at our institution and failed to identify prior HCV treatment among any patients reporting no history of treatment. However, if misclassification of treatment did occur, the proportion of those who demonstrated spontaneous clearance would be smaller and the role of the genetic markers in these patients overestimated.

Understanding the shared and separate mechanisms that contribute to the control of HIV and HCV may shed light on future directions for treatment, prevention and vaccine development

for both viruses. Because HIV controllers are more likely to clear HCV infection than HIV non-controllers, this unique group may provide new insights into the mechanisms underlying viral control. Our study suggests that HLAB*57 a factor highly associated with HIV controller status does not contribute to HCV clearance, and that *IL28B* CC genotype does. Identifying other factors that contribute to enhanced viral control may support the development of novel vaccine and treatment strategies for HIV and HCV, ultimately reducing the morbidity and mortality caused by these viruses.

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## Table 1

| Demographics by HIV controller status | | | | |
|---|---|---|---|---|
| | | **Non-controllers N (col %) N=231** | **HIV controllers † N (col %) N=48** | **p-value** |
| Gender | | | | 0.85 |
| | Male | 156 (68) | 31 (65) | |
| | Female | 66 (29) | 14 (29) | |
| Age | Median (IQR) | 40 (36-46) | 41 (37-48) | 0.69 |
| Race/Ethnicity | | | | 0.57 |
| | Caucasian | 97 (42) | 18 (38) | |
| | Non-Caucasian | 134 (58) | 30 (62) | |
| HIV risk: | | | | 0.16 |
| | Injection drug use | 109 (47) | 28 (58) | |
| | No history of Injection drug use | 122 (53) | 20 (42) | |
| HCV clearance | | | | 0.23 |
| | Yes | 62 (27) | 17 (35) | |
| | No | 169 (73) | 31 (65) | |
| **Demographics by HCV clearance status** | | | | |
| | | Did not clear N (col %) N=200 | Cleared N (col %) N=79 | |
| Gender | | | | 0.14 |
| | Male | 128 (64) | 59 (75) | |
| | Female | 62 (31) | 18 (23) | |
| Age | Median (IQR) | 40 (36-46) | 40 (35-47) | 0.78 |
| Race/Ethnicity | | | | 0.08 |
| | Caucasian | 76 (38) | 39 (49) | |
| | Non-Caucasian | 124 (62) | 40 (51) | |
| HIV risk: | | | | 0.20 |
| | Injection drug use | 103 (52) | 34 (43) | |
| | No history of Injection drug use | 97 (49) | 45 (57) | |
| HIV controller status | | | | 0.23 |
| | Non-controllers | 169 (85) | 62 (79) | |
| | HIV controllers | 31 (16) | 17 (22) | |

Note:

† Elite controllers + HIV viremic controllers (<2000 copies/ML without ART for at least 12 months). Proportions may not add to 100% due to rounding and missing data.

## Table 2a

### Overall (percent)

| Overall Polymorphisms column percent | | | |
|---|---|---|---|
| **Genetic polymorphisms by HIV controller status** | | | |
| | **Non-controllers N (col %) N=231** | **HIV controllers † N (col %) N=48** | **p-value** |
| HLA B*57 status | | | <0.001 |
| No | 207 (90) | 32 (67) | |
| Yes | 24 (10) | 16 (33) | |
| HLA Cw*04 | | | 0.19 |
| No | 172 (74) | 40 (83) | |
| Yes | 59 (26) | 8 (17) | |
| *IL28B* genotype§ | | | 0.49 |
| Non-CC | 137 (59) | 24 (50) | |
| CC | 89 (39) | 12 (25) | |
| Genetic polymorphisms by HCV clearance status | | | |
| | Did not clear N (col %) N=200 | Cleared N (col %) N=79 | p-value |
| HLA B*57 status | | | 0.53 |
| No | 173 (86) | 66 (84) | |
| Yes | 27 (14) | 13 (16) | |
| HLA Cw*04 | | | 0.12 |
| No | 147 (73) | 65 (82) | |
| Yes | 53 (27) | 14 (17) | |
| *IL28B* genotype§ | | | <0.001 |
| Non-CC | 133 (67) | 28 (35) | |
| CC | 54 (27) | 47 (59) | |

Note:

† Elite controllers + HIV viremic controllers (<2000 copies/ML without ART for at least 12 months). Proportions may not add to 100% due to rounding and missing data.

§ *IL28B* genotype missing for 17 participants.

## Table 2b

Stratified by gender:

| **Females:** | | | |
|---|---|---|---|
| **Genetic polymorphisms by HIV controller status** | | | |
| | **HIV Non-controllers N (col %) N=66** | **HIV controllers † N (col %) N=14** | **p-value** |
| HLA B*57 | 8 (12) | 3 (21) | 0.36 |
| HLA Cw*04 | 25 (38) | 4 (29) | 0.51 |
| *IL28B* (CC) | 25 (38) | 3 (21) | 0.932 |
| **Genetic polymorphisms by HCV clearance status** | | | |
| | Did not clear N (col %) N=62 | Cleared N (col %) N=18 | p-value |
| HLA B*57 | 8 (13) | 3 (17) | 0.68 |
| HLA Cw*04 | 27 (44) | 2 (11) | 0.012 |
| *IL28B* (CC) | 17 (27) | 11 (61) | 0.002 |

| **Male:** | | | |
|---|---|---|---|
| **Genetic polymorphisms by HIV controller status** | | | |
| | **HIV Non-controllers N (col %) N=156** | **HIV controllers † N (col %) N=31** | **p-value** |
| HLA B*57 | 16 (10) | 13 (42) | <0.001 |
| HLA Cw*04 | 33 (21) | 3 (10) | 0.14 |
| *IL28B* (CC) | 62 (40) | 8 (26) | 0.346 |
| **Genetic polymorphisms by HCV clearance status** | | | |
| | Did not clear N (col %) N=129 | Cleared N (col %) N=58 | p-value |
| HLA B*57 | 19 (15) | 10 (17) | 0.71 |
| HLA Cw*04 | 25 (19) | 11 (19) | 0.89 |
| *IL28B* (CC) | 35 (27) | 35 (60) | <0.001 |

Note:

† Elite controllers + HIV viremic controllers (<2000 copies/ML without ART for at least 12 months). Proportions may not add to 100% due to rounding and missing data.

§ IL28B genotype missing for 17 participants.

## Table 3
## Multivariable Analysis on Spontaneous HCV Clearance

| | Adjusted Prevalence Ratio* | 95% CI | P-value |
|---|---|---|---|
| HIV elite/viremic controller status | | | |
| Non-controller | ref | - | - |
| Controller | 1.78 | 1.06-3.00 | 0.030 |
| HLA B*57 | | | |
| No | ref | - | - |
| Yes | 1.36 | 0.71-2.60 | 0.349 |
| Gender | | | |
| Female | ref | - | - |
| Male | 1.57 | 0.98-2.51 | 0.062 |
| IL28B | | | |
| Non-CC | ref | - | - |
| CC | 2.76 | 1.85-4.11 | <0.001 |
| HIV elite/viremic controller with HLA B*57 | | | |
| No | ref | - | - |
| Yes | 0.52 | 0.18-1.45 | 0.210 |

* models adjusted for age and race/ethnicity