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A closer look at hepatitis C clearance in HIV controllers: a response

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Seaberg and Thio [1] refer to evidence that suggests that route of infection may play a role in hepatitis C virus (HCV) spontaneous clearance. We did not examine the role of the route of infection on HCV clearance in HIV controllers in our study. HCV clearance differs by HIV status, but little prospective data are available to assess clearance by transmission route. One retrospective analysis showed that presumed sexually acquired HCV had higher rates of spontaneous clearance than parenterally acquired HCV [2]. Other studies have not shown this [3,4]. In prospective studies of HCV monoinfected patients, there is no evidence that clearance differs by transmission route [5,6]. Less examined is how genetic variations and mode of transmission impact divergent HCV outcomes. Seaberg *et al.* [7] found a higher magnitude of association between *IL28B* CC and HCV clearance in men MSM with reported injected drug use (IDU) than in those without, but this analysis includes MSM with and without HIV. We examined these factors in HIV controllers, the study population examined in our study ‘Human Leukocyte Antigen (HLA) B*57 Does Not Fully Explain Hepatitis C Clearance in HIV Controllers’ [8].

People with the *IL28B* CC (vs. CT or TT) allele are significantly more likely to spontaneously clear HCV infection [9,10]. In our study, the presumed mode of HCV acquisition did not modify the association between *IL28B* genotype and HCV clearance: there was no difference in the effect of *IL28B* CC (vs. CT/TT) on HCV clearance between those with a history of IDU [prevalence ratio 2.98; 95% confidence interval (CI) 1.57–5.64] and those without reported IDU history (prevalence ratio 2.51; 95% CI 1.52–4.16; test for heterogeneity $P=0.93$). Unlike the study by Seaberg *et al.* [7], we found no evidence that the impact of *IL28B* CC (vs. CT/TT) on HCV clearance was modified by IDU history among

MSM (prevalence ratio in non-IDU MSM 2.13; 95% CI 1.25–3.65; prevalence ratio in IDU and MSM 1.57; 95% CI 0.36–6.86).

HLA B*57 has been shown to be highly enriched in people who innately control their HIV infection [11,12], prompting questions about whether this may hold true for other viral infections, including HCV. We found no evidence that HLA B*57 is associated with clearance in HIV-infected patients (adjusted prevalence ratio 1.36; 95% CI 0.71–2.60, $P=0.35$) [8]. Although power was limited, we also found no evidence for a protective role of HLA B*57 in any subgroup of interest. For example, patients with HLA B*57 had similar prevalence of HCV clearance to those without HLA B*57 among both HIV controllers (31 vs. 34%, $P=0.83$) and noncontrollers (29 vs. 27%, $P=0.79$). HLA B*57 does not explain the increase in HCV clearance in controllers in our cohort. We also found no association between HLA B*57 and HCV clearance in those with and without an IDU history (prevalence ratio 1.18; 95% CI 0.56–2.51 vs. prevalence ratio 1.19; 95% CI 0.62–2.28) and in MSM vs. non-MSM exposure groups (prevalence ratio 0.98; 95% CI 0.49–1.99 vs. prevalence ratio 1.36; 95% CI 0.68–2.70).

The table presenting the multivariate analysis in the original article was mis-printed and omitted the significance of *IL28B* CC on clearance. An erratum will correct this. Seaberg and Thio [1] state that we did not discuss the finding that HIV controllers were more likely to clear HCV when negative for HLA B*57. The original publication states that HLA B*57 cannot explain the increased prevalence of HCV clearance in HIV controllers in our cohort. We agree with our colleagues that this is perhaps the most important novel finding from our study. It suggests that other unmeasured factors associated with HIV control must also contribute to HCV clearance in this setting. Future host genetic studies of HIV/HCV-coinfected controllers and noncontrollers may help shed light on these factors, potentially identifying novel genetic factors that contribute to the clearance and/or control of multiple viral pathogens. Nevertheless, as pointed out, HLA B*57 has been associated with HCV clearance in other studies [13,14]. Our study does not discount those studies, as a larger sample size might have revealed a more significant effect of HLA B*57. However, our study does suggest that there are factors other than HLA B*57 that contribute to HCV clearance in HIV controllers.

The evidence of differential outcome of HCV in association with route of exposure is inconclusive; further research is necessary to improve our understanding of this potential effect and putative mechanisms involved. We agree that further research is needed to understand why HIV controllers are more likely to clear HCV, as this cannot be entirely explained by enrichment for HLA B*57.

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