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EDITORIAL COMMENTARY

Human Hepegivirus-1: Innocent Traveler, Helpful Symbiote, or Insidious Pathogen?

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(See the Major Article by Fama et al on pages 1221–8.)

A revolution in biomedicine has yielded a glimpse of the nonhuman multitudes within us. As we pull back the covers, we are left with questions about which of our fellow travelers are commensals, and which are more sinister. The question is more pressing when we consider the safety of the blood supply. Because of their transmissibility, viruses that circulate in the bloodstream are particularly worrisome. Many viruses of medical consequence, hepatitis C virus (HCV), hepatitis B virus, and the human immunodeficiency virus (HIV) 1 (HIV-1), spread rapidly through the population, in part because they circulate in the blood supply. On that backdrop, we have long fretted about the implications of human hepegivirus-1 (HHpgV-1), a prevalent RNA virus that infects nearly 3% of Americans, with detectable viremia in 1–2% of US blood donors [1]. The meta-analysis by Fama et al [2] in this issue of *Clinical Infectious Diseases* brings us closer to understanding the pathogenic potential of HHpgV-1.

HHpgV-1 has had several previous aliases: hepatitis G virus, GB virus C (named after the initials of a surgeon from which the virus was initially cloned), and a recent proposal to rename it Pegivirus-C [3]. Its identification in 12 individuals, of whom 4 had evidence of liver damage, led to the hypothesis that it caused hepatitis [4]. However, further studies teased out the confounding of this association, since the identification of HHpgV-1 was often in the presence of HCV [5, 6]. Several well-done epidemiologic studies reported that most people with HHpgV-1 infection do not have any evidence of liver injury [7, 8]; among people who had HHpgV-1 and signs of liver injury, there was no correlation between the magnitude of viremia and the height of transaminase elevation. Thus, the specter of HHpgV-1 as an agent of liver disease was banished. It was next recognized that HHpgV-1, which co-circulated with HIV-1, was linked with improved outcomes among people who were coinfected with both viruses compared to people with HIV-1 monoinfection [9]. Although data have been conflicting, some studies continue to find associations between HHpgV-1 viremia and improved HIV-1 outcomes [10–13]. This intriguing association is still being unpacked, as is the biology underpinning such a link.

More recently, there have been a handful of studies over 2 decades linking HHpgV-1 infection with lymphoma [14–23]. Because of the presence of HHpgV-1 RNA in lymphocytes and lymphoid tissues, it is plausible to consider that the virus may cause lymphoid pathology. Most prior studies have been small and difficult to interpret in isolation. Fama et al have attempted to lend clarity to the topic by the well-designed meta-analysis found here.

The authors performed a broad PubMed search to find observational studies that addressed HHpgV-1 exposure (or its aliases) and the development of lymphoma. Of the 38 studies that fit their inclusion criteria, they eliminated 23 studies of questionable validity. They used 2 arbiters to rate and select articles, and encountered rare discrepancies between them. Using a random-effects model, the authors found that across 15 studies there were increased odds of an association between HHpgV-1 and lymphoma. Although the authors included studies that they themselves considered of "poor" quality, a sensitivity analysis that excluded these studies still found suggestive odds of an association between HHpgV-1 and lymphomas.

To put this study into context, 6 of the 15 studies included in the meta-analysis reported no association between HHpgV-1 and lymphoma. Twelve of these studies included fewer than 30 people with HHpgV-1 viremia. It is worth discussing the findings from the exception, the largest negative study, published by Ernst et al [18] as a letter. The authors examined 617 persons with HIV in a case–cohort investigation, 33 with lymphoma and 584 without: HHpgV-1 viremia was found in 30.3% of the patients with lymphoma and in only 23.6% of patients without lymphoma, but the result was not statistically significant.

Several studies were not included in the meta-analysis that bear mention.

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Kerestzes et al [24] studied 111 persons with Hodgkin's disease in Hungary and compared the prevalence of HHpgV-1 viremia with that in the Hungarian blood bank, finding no significant association between Hodgkin's disease and HHpgV-1 viremia. In a study of 127 lymphoma cases and 133 controls, Nicolosi Guidicelli et al [21] reported no differences in the proportion of patients with HHpgV-1. However, it is difficult to judge the quality of these studies as assessments were not made sufficiently in advance of the lymphoma diagnosis to interpret the role of preceding HHpgV-1 viremia on the subsequent development of lymphoma.

Although the study by Fama et al is intriguing, there are several challenges to consider. The number of studies included in the meta-analysis belies the small number of studies (n = 3) that were considered "good" according to the Ottawa-Newcastle scale and the small number of participants in the included studies (aside from 4 that had total sample sizes of >500 participants). On the other hand, the meta-analysis included substantial data collectively, from 9741 persons, 4416 (45.3%) of whom had lymphoma and 591 of whom had viremia (6.1%). Despite these impressive numbers, the included studies were mostly from Europe and North America, regions in which predominantly genotype 2 HHpgV-1 circulates, and so the results may not be generalizable to other parts of the world.

An important strength of the study is that the authors only included studies that documented HHpgV-1 viremia, rather than just seropositivity. However, only one of the included studies sampled viremia sufficiently prior to the ascertainment of lymphoma for the reader to conclude plausible causation. More often, there was a single measurement of HHpgV-1 viremia among people who had lymphoma, and this was compared with the proportion of people without lymphoma (from the general population) who had HHpgV-1 viremia. Since persons with lymphoma are more likely than healthy individuals to have had blood transfusions, and since HHpgV-1 is so common, it is just as likely that people with lymphoma were more likely to be exposed to HHpgV-1 after their cancer diagnosis as before their cancer diagnosis.

Publication bias is also worth considering with these nascent observations. It is reassuring that, among the studies included in the meta-analysis by Fama et al, all showed supportive odds of an association, even if the confidence intervals overlapped 1. Notably, although the largest study (n = 3666) was also performed by the same authors, 7 additional studies also found an association between HHpgV-1 and lymphoma.

A critical challenge in interpreting these findings is that persons with HHpgV-1 often have viral coinfections that have also been linked to B-cell disorders, such as HIV-1 or HCV. The authors note in their discussion that because the individual studies that composed the meta-analysis did not include data on individual coinfections, it was difficult to separate the contribution of viral coinfections from that of HHpgV-1 on lymphoma. Future studies will need to address the separate contribution of HHpgV-1 on lymphomagenesis to avoid the confounding effect from other viruses.

How might HHpgV-1 cause lymphoma? HHpgV-1 has been found in B and T lymphocytes, among other cells [25, 26]. It has also been noted by several groups that persons with HHpgV-1 viremia have lesser amounts of activation of T and B cells, monocytes, and natural killer (NK) cells than persons without viremia [10, 27–32]. Ex vivo stimulation of NK cells taken from people with HHpgV-1 infection resulted in less interferon (IFN)-γ production than cells taken from healthy controls [33]. Additionally, HHpgV-1 appears to inhibit type 1 IFN responses in a manner akin to HCV [34]. Taken together, the effects of HHpgV-1 on the immune system may weaken its critical role in immune surveillance that typically prevents or checks oncogenesis.

If the risk of lymphoma is increased by HHpgV-1 viremia, then the Food and Drug Administration is likely to mandate screening for the virus and exclusion of units of blood that contain it. The impact on the blood supply would be considerable, given the prevalence of HHpgV-1. Among people who already have HHpgV-1, it needs to be understood whether the virus causes cancer, and if inhibition of viral replication can attenuate this risk.

Before such steps are taken, prospectively designed studies are required where HHpgV-1 acquisition is noted sufficiently in advance of lymphoma diagnosis to be plausibly causal. These studies should be carefully designed to tease out the role of viral coinfections on lymphomagenesis; ideally, the risk of lymphoma will be ascertained in people with HHpgV-1 monoinfection. An animal model of HHpgV-1 replication will also help to answer whether pathologic changes in lymphoid tissues are associated with oncogenesis. More broadly, when a virus is in the blood and is transmitted routinely by transfusion, the National Institutes of Health (NIH) should fund research into the potential medical consequences until they are confidently excluded. Stated differently, viruses of no known medical importance that are transmitted intentionally in medical practice should be prioritized (not excluded) from NIH funding. On the other hand, it is our opinion that, until these questions are answered, it is difficult to justify screening out HHpgV-1 from the blood supply, since it would impinge on this vital resource without clear benefit.

HHpgV-1 is prevalent and would have a major impact on the public's health if it is found to cause lymphoma. The meta-analysis published here by Fama et al strengthens the case that there is an association between the virus and lymphoma. Moving forward, more research is needed to solidify the association and to understand its underlying biology. Until then, the medical community, and the many infected patients, will have to wait for more answers.

Note

Potential conflicts of interest. The authors: No reported conflicts of interest. Both authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Handa A, Jubran RF, Dickstein B, et al. GB virus C/hepatitis G virus infection is frequent in American children and young adults. Clin Infect Dis **2000**; 30:569–71.
2. Fama et al. Clin Infect Dis 2019.
3. Smith DB, Becher P, Bukh J, et al. Proposed update to the taxonomy of the genera Hepacivirus and Pegivirus within the Flaviviridae family. J Gen Virol **2016**; 97:2894–907.
4. Simons JN, Leary TP, Dawson GJ, et al. Isolation of novel virus-like sequences associated with human hepatitis. Nat Med **1995**; 1:564–9.
5. Feucht H-H, Zollner B, Polywka S, et al. Prevalence of hepatitis G viraemia among healthy subjects, individuals with liver disease, and persons at risk for parenteral transmission. J Clin Microbiol **1997**; 35:767–8.
6. Blackard JT, Ma G, Welge JA, et al. GB virus C (GBV-C) infection in hepatitis C virus (HCV) seropositive women with or at risk for HIV infection. PLoS One **2014**; 9:e114467.
7. Thomas DL, Nakatsuji Y, Shih JW, et al. Persistence and clinical significance of hepatitis G virus infections in injecting drug users. J Infect Dis **1997**; 176:586–92.
8. Berenguer M, Terrault NA, Piatak M, et al. Hepatitis G virus infection in patients with hepatitis C virus infection undergoing liver transplantation. Gastroenterology **1996**; 111:1569–75.
9. Xiang J, Wünschmann S, Diekema DJ, et al. Effect of coinfection with GB virus C on survival among patients with HIV infection. N Engl J Med **2001**; 345:707–14.
10. Stapleton JT, Chaloner K, Martenson JA, et al. GB virus C infection is associated with altered lymphocyte subset distribution and reduced T cell activation and proliferation in HIV-infected individuals. PLoS One **2012**; 7:e50563.
11. Sahni H, Kirkwood K, Kyriakides TC, Stapleton J, Brown ST, Holodniy M; OPTIMA Study Team. GBV-C viremia and clinical events in advanced HIV infection. J Med Virol **2014**; 86:426–32.
12. Ernst D, Greer M, Akmatova R, et al. Impact of GB virus C viraemia on clinical outcome in HIV-1-infected patients: a 20-year follow-up study. HIV Med **2014**; 15:245–50.
13. de Miranda BKB, de Sá KSG, da Silva ANR, et al. GBV-C/HIV-1 coinfection is associated with low HIV-1 viral load and high CD4+ T lymphocyte count. Arch Virol **2017**; 162:3431–8.
14. Stapleton JT, Chaloner K. GB virus C infection and non-Hodgkin lymphoma: important to know but the jury is out. Int J Cancer **2010**; 126:2759–61.
15. Pavlova BG, Heinz R, Selim U, Tüchler H, Pittermann E, Eder G. Association of GB virus C (GBV-C)/hepatitis G virus (HGV) with haematological diseases of different malignant potential. J Med Virol **1999**; 57:361–6.
16. Krajden M, Yu A, Braybrook H, et al. GBV-C/hepatitis G virus infection and non-Hodgkin lymphoma: a case control study. Int J Cancer **2010**; 126:2885–92.
17. Giannoulis E, Economopoulos T, Mandraveli K, et al; Hellenic Cooperative Oncology Group Study. The prevalence of hepatitis C and hepatitis G virus infection in patients with B cell non-Hodgkin lymphomas in Greece: a Hellenic Cooperative Oncology Group Study. Acta Haematol **2004**; 112:189–93.
18. Ernst D, Pischke S, Greer M, Wedemeyer H, Stoll M. No increased incidence for GB-virus C infection in a cohort of HIV-positive lymphoma patients. Int J Cancer **2011**; 128:3013; author reply: 2.
19. De Renzo A, Persico E, de Marino F, et al. High prevalence of hepatitis G virus infection in Hodgkin's disease and B-cell lymphoproliferative disorders: absence of correlation with hepatitis C virus infection. Haematologica **2002**; 87:714–8; discussion: 8.
20. Civardi G, Tanzi E, Ferrari B, Vallisa D, Zanetti A, Cavanna L. High prevalence of anti-HGV/E2 antibodies in HCV-positive patients with non Hodgkin's lymphoma. Haematologica **1998**; 83:957–8.
21. Nicolosi Guidicelli S, Lopez-Guillermo A, Falcone U, et al. Hepatitis C virus and GBV-C virus prevalence among patients with B-cell lymphoma in different European regions: a case-control study of the International Extranodal Lymphoma Study Group. Hematol Oncol **2012**; 30:137–42.
22. Chang CM, Stapleton JT, Klinzman D, et al. GBV-C infection and risk of NHL among U.S. adults. Cancer Res **2014**; 74:5553–60.
23. Fama A, Xiang J, Link BK, et al. Human Pegivirus infection and lymphoma risk and prognosis: a North American study. Br J Haematol **2018**; 182:644–53.
24. Keresztes K, Takács M, Horányi M, Miltényi Z, Illés A. HCV and HGV infection in Hodgkin's disease. Pathol Oncol Res **2003**; 9:222–5.
25. George SL, Xiang J, Stapleton JT. Clinical isolates of GB virus type C vary in their ability to persist and replicate in peripheral blood mononuclear cell cultures. Virology **2003**; 316:191–201.
26. Chivero ET, Bhattarai N, Rydze RT, Winters MA, Holodniy M, Stapleton JT. Human pegivirus RNA is found in multiple blood mononuclear cells in vivo and serum-derived viral RNA-containing particles are infectious in vitro. J Gen Virol **2014**; 95:1307–19.
27. Stapleton JT, Xiang J, McLinden JH, et al. A novel T cell evasion mechanism in persistent RNA virus infection. Trans Am Clin Climatol Assoc **2014**; 125:14–24; discussion: 6.
28. Lanteri MC, Vahidnia F, Tan S, et al; NHLBI REDS III Study. Downregulation of cytokines and chemokines by GB virus C after transmission via blood transfusion in HIV-positive blood recipients. J Infect Dis **2015**; 211:1585–96.
29. Bhattarai N, Rydze RT, Chivero ET, Stapleton JT. GB virus C viremia is associated with higher levels of double-negative T cells and lower T-cell activation in HIV-infected individuals receiving antiretroviral therapy. J Infect Dis **2012**; 206:1469–72.
30. Bhattarai N, McLinden JH, Xiang J, Landay AL, Chivero ET, Stapleton JT. GB virus C particles inhibit T cell activation via envelope E2 protein-mediated inhibition of TCR signaling. J Immunol **2013**; 190:6351–9.
31. Baggio-Zappia GL, Barbosa Ade J, Brunialti MK, Salomão R, Granato CF. Influence of GB virus C on IFN-γ and IL-2 production and CD38 expression in T lymphocytes from chronically HIV-infected and HIV-HCV-co-infected patients. Mem Inst Oswaldo Cruz **2011**; 106:662–9.
32. Stapleton JT, Martinson JA, Klinzman D, Xiang J, Desai SN, Landay A. GB virus C infection and B-cell, natural killer cell, and monocyte activation markers in HIV-infected individuals. AIDS **2013**; 27:1829–32.
33. Chivero ET, Bhattarai N, McLinden JH, Xiang J, Stapleton JT. Human Pegivirus (HPgV; formerly known as GBV-C) inhibits IL-12 dependent natural killer cell function. Virology **2015**; 485:116–27.
34. Chowdhury AY, Tavis JE, George SL. Human pegivirus (GB virus C) NS3 protease activity inhibits induction of the type I interferon response and is not inhibited by HCV NS3 protease inhibitors. Virology **2014**; 456-457:300–9.