

Advocating the Concept of GB Virus C Biotherapy Against AIDS

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(See the Major Article by Vahidnia et al, on pages 1012–9.)

In medical research of epidemiological importance, controversies come and go, but the GB virus (GBV)/human immunodeficiency virus (HIV) confusion is persisting longer than what is reasonable. Taking sides becomes important whenever saving lives is of concern. This is one reason for continued research on the non-pathogenic, “normal flora virus” initially tagged by the misnomer of hepatitis G virus (HGV), but now commonly known as GBV-C. GBV-C infects 1%–5% of the general population in developed nations, and up to 20% of persons in developing countries; it is transmitted via parenteral, vertical, and sexual routes. In the United States alone, 750–1000 individuals are exposed daily to GBV-C through blood transfusion. Based on extensive clinical data, the virus is so common, yet so innocuous, that the Food and Drug Administration has not required blood product screening. This is the only agent

knowingly transmitted through iatrogenic interventions in humans, and that fact alone is quite interesting.

The interest was amplified in 2001, when 2 independent reports in the *New England Journal of Medicine* documented positive and dramatic impact of GBV-C coinfection on death rates in AIDS patients. However, some investigators concluded that the GBV-C effect on AIDS progression might be an artifact, resulting from loss of viremia and/or anti-GBV-C antibodies in the late stages of immune suppression. A full-blown controversy arose, which persists today despite results of a 1294-subject meta-analysis, which found highly significant protective effects of persistent GBV-C coinfection among HIV-infected persons. Many investigators remain skeptical concerning the possibility that GBV-C coinfection might be life-saving in persons with AIDS. Furthermore, the introduction and tremendous success of highly active antiretroviral therapy (HAART) has made the sticky issue of lower priority to researchers because control of AIDS mortality has drastically improved, at least in developed nations. Nonetheless, understanding mechanisms behind this phenomenon of viral interference has tremendous implications for antiviral and vaccine strategic development; therefore, resolving the controversy regarding GBV-C and HIV disease association remains highly important.

Pursuit of in vitro models of GBV/HIV interaction has been highly fertile. GBV-C is lymphotropic, infecting both CD4⁺ and CD8⁺ T cells. Although inefficient, peripheral blood mononuclear cell cultures are infected by GBV-C in vitro. CD4⁺ T-cell infection by GBV-C in vitro represses interleukin 2 (IL-2) responsiveness, as well as the ability of HIV to cause infection and cell death. This phenomenon is referred to as viral interference and is not uncommon. At least 2 GBV-C gene products can independently alter CD4⁺ T cells to make them less permissive for HIV. The envelope gene E2 encodes a product that interferes with HIV entry and fusion, potentially via interaction with HIV gp41 and an unidentified host membrane component. The E2 protein also blocks the proliferative effect of IL-2 on CD4⁺ T cells, which is detrimental to HIV because the latter virus replicates optimally in activated cells. The GBV-C NS5A gene product downregulates the HIV coreceptor CXCR4, and GBV-C is also a potent inducer of at least 3 host-cell molecules that are inhibitory to HIV via coreceptor ligand interactions. Thus, molecular evidence for a strong, negative effect of GBV-C on HIV success is readily evident from in vitro models. It is therefore not surprising that an inverse relationship between GBV-C and HIV load has been observed in several studies.

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The recent study by Vahidnia and colleagues [1] has added a precious piece to the puzzle. A retrospective analysis of GBV/HIV coinfection and its effect on death rates in AIDS patients was performed. The study addressed a sentinel knowledge gap: what is the impact of GBV-C incident infection on HAART-naive patients with preexisting HIV? The study included longitudinal sampling before and after iatrogenic blood transfusion in 489 subjects from the Viral Activation Transfusion Study (VATS) cohort. Thirty-nine subjects acquired GBV-C infection (viremia), and this superinfection was highly protective in this cohort, reducing AIDS mortality by 78% after multivariate analysis and control for time-updated covariates such as HAART introduction. Case closed. GBV-C viremia is associated with protective effects in persons with HIV, and

the idea of a therapeutic GBV-C biovaccine in persons with HIV is an important one to consider, especially in resource-poor countries where AIDS death rates remain high. Additional provocative data were obtained from maternal-fetal HIV transmission studies, where fetal GBV-C acquisition at birth was associated with an 87% reduction in HIV transmission. Sex partner transmission studies, presently underway, are also of high interest from the potential intervention perspective. Finally, other data suggest that the presence of GBV-C coinfection in persons with HIV improves therapeutic response to HAART.

To summarize this perspective, GBV-C appears to be safe in humans, and is a natural bio-antagonist of HIV. It is difficult to estimate how many years of human life GBV-C has already saved. Still, today, the death rate from HIV

remains enormous, especially in resource-poor countries, and we have yet to see a trial of GBV-C biovaccination in HIV-infected populations with high death risk. Similar to the days of smallpox, it's time for an interventional GBV biotherapy study in persons with life-threatening HIV infections.

Note

Potential conflicts of interest. Author certifies no potential conflicts of interest.

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Reference

1. Vahidnia F, Petersen M, Stapleton JT, Rutherford GW, Busch M, Custer B. Acquisition of GB virus type C (HGV) and lower mortality in patients with advanced HIV disease. *Clin Infect Dis* 2012; 55:1012-9.