GB Virus Type C: A Virus in Search of a Disease or a Role in HIV Therapy?

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(See the article by Sathar et al. on pages 405–9)

GB virus type C, first isolated in 1995, is a single-stranded RNA flavivirus that is genetically similar to hepatitis C virus (HCV) [1]. GBV-C is a relatively common infection worldwide, with up to 2% of blood donors and up to 40% of injection drug users (IDUs) in the United States demonstrating presence of GBV-C RNA in their plasma [1]. Up to 16% of healthy US blood donors and up to 70% of US IDUs have antibody to the E2 envelope protein (anti-E2), which is evidence of a prior infection with GBV-C [1]. Among infected individuals, there is a large range of levels of GBV-C viremia. Although, the level of viremia remains relatively constant in an individual and can persist for up to 16 years. Viremia eventually resolves in the majority of individuals, with the development of anti-E2 antibody which persists for life in most individuals [1, 2]. Current data suggest that the routes of transmission of HIV-1 and GBV-C are similar. In addition to the very high rate of transmission among IDUs, GBV-C transmission by blood product transfusion and organ transplantation have been well documented. GBV-C is also more efficiently transmitted through sexual exposure than is HCV. GBV-C transmission from infected mother to her child has also been well documented previously [3].

For the past decade, a number of studies have failed to support early suggestions that GBV-C may be associated with either chronic or acute liver disease [1, 4]. In fact, there is no convincing evidence that GBV-C infection causes any human pathology, leading Dickens [4] to suggest that it be renamed “human orphan flavivirus.” In 1998, as interest in GBV-C research was beginning to wane, initial reports suggesting that HIV-infected patients coinfected with GBV-C had slower disease progression were published [4]. Subsequently, a number of other studies have demonstrated an association between GBV-C infection and a higher CD4 count, lower HIV plasma virus load, slower HIV disease progression, and an improved response to HAART [1, 5, 6]. The proposed mechanisms for this interaction include GBV-C–mediated reduction of CCR5 expression, induction of anti-HIV chemokines, improved recognition of HIV-infected cells by cross-reactive anti–GBV-C cytolytic T lymphocytes, and alteration in cytokine response that results in a preservation of a TH1 immune response to HIV-1 infection [1, 7]. Like HIV-1, GBV-C replicates in CD4+ T lymphocytes. This has led some to suggest that GBV-C viremia is simply a marker for higher CD4+ T lymphocyte count or other undetermined factors associated with a more favorable host immune response to HIV-1 infection.

A previous study by Chakraborty et al. [8] of Kenyan children provided the first data on the prevalence of GBV-C coinfection (5%) in any HIV-infected population in Africa. The study by Sathar et al. [9] provides the first data on GBV-C RNA coinfection in HIV-infected African adults, reporting that 27 (36%) of 75 HIV-infected pregnant women in South Africa had detectable levels of GBV-C RNA in plasma. Although reported rates of GBV-C viremia among HIV-uninfected adults in Africa are higher than those in the United States, these data from KwaZulu Natal are similar to data on the levels of GBV-C viremia in HIV-infected adults (39%) in the United States [1]. In their analyses of infants born to a subset of 20 of the HIV-infected South African mothers, Sathar et al. [9] detected the presence of GBV-C RNA in 4 infants 12–36 weeks postpartum. The sample size was too small to provide an estimate of the vertical transmission rate of GBV-C from coinfected mothers to their infants. However, it is interestingly to note that 2 of these 4 GBV-
C infected infants were born to mothers that were GBV-C RNA negative. In addition, of the 2 other GBV-C–infected infants born to GBV-C–infected mothers, only 1 infant was breast-fed. In both cases, nucleotide sequencing confirmed homology between the strains isolated from the mother and from the infant.

Although the data from this study are limited, they suggest that exposure to GBV-C in utero or through breast-feeding are not the primary risk factors for infant GBV-C infection in South Africa. This conclusion is consistent with a prior study from Italy that demonstrated that vertical transmission of GBV-C in HCV-infected mothers did not correlate with infant feeding practice [3]. These data support the preliminary hypothesis that exposure to a household contact, including a mother, with a GBV-C infection could be a key risk factor for infant GBV-C infection in South Africa.

The study among HIV-infected mothers from South Africa also provides preliminary data suggesting that mothers coinfected with GBV-C have a somewhat higher percentage of circulating \( \gamma \delta \) T cells than HIV-infected mothers without GBV-C infection. \( \gamma \delta \) T cells are a subset of natural T lymphocytes that participate in innate immunity and recognize infected cells without the major histocompatibility complex restriction required by CD4+ and CD8+ T lymphocytes. The findings of Sathar et al. [9] are intriguing, because \( \gamma \delta \) T cells have also been shown to lyse HIV-infected cells and release antiviral cytokines capable of down-regulating HIV replication. Although the data from this South African study were unable to demonstrate a clear association between GBV-C coinfection and slower HIV disease progression, their findings suggest a possible explanation for the association between GBV-C viremia and lower HIV load found in previous studies. One limitation of this study was the lack of quantitative measurements of GBV-C viremia. Future studies that investigate the association between circulating \( \gamma \delta \) T cell frequencies and GBV-C load may shed light on whether the increase in \( \gamma \delta \) T cells is directly related to GBV-C replication. In addition, it might be important to determine the impact of prior GBV-C infection, as indicated by the presence of anti-E2 antibody, on the levels of \( \gamma \delta \) T cells. Finally, it would be important for future studies to determine whether other coinfections, such as with the genetically similar HCV, that have been shown to increase or stimulate \( \gamma \delta \) T cells are also present in individuals coinfected with GBV-C and HIV [10].

As Sathar et al. [9] indicate, additional studies of the interaction of GBV-C and HIV are warranted, particularly in Africa, where both infections are more prevalent than in the West. However, we should be cautious before expecting a significant impact of natural GBV-C infection on the course of HIV, because in the absence of HAART, long-term nonprogression of HIV infection are very rare. In addition, HIV disease progression appears to be more rapid in Africa, despite a higher prevalence of GBV-C coinfection than in the West. Although a much greater understanding of the interaction between GBV-C and HIV is indicated before consideration of the therapeutic potential of GBV-C infection for HIV-infected individuals, investigations are already well under way that may lead to novel therapies that exploit the antimicrobial and anti-malignancy potential of \( \gamma \delta \) T cells [11–13]. Subsequent studies expanding on the findings of Sathar et al. may provide additional insights that facilitate the development of novel therapies for HIV infection.

**References**