

# When Two Infections Are Better Than One: The Exceptional Role of GB Virus-C (GBV-C) in HIV Disease

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WHEN IT COMES TO HIV AND HEPATITIS VIRUS COINFECTIONS, THE PAGES of *The PRN Notebook* have been filled with numerous reports highlighting the distressing prevalence and negative consequences of both hepatitis B virus (HBV) and hepatitis C virus (HCV) in HIV-infected individuals. However, it does not appear that all coinfections are harmful. In fact, some may be associated with a significant survival advantage—a theory that has many HIV experts both perplexed and excited.

GB virus-c (GBV-C) infection is one such example. Originally identified as potential hepatitis virus, there is no evidence to suggest that it is responsible for chronic liver disease in either HIV-negative or HIV-positive individuals. As explained by Dr. Hans Tillmann, an expert in the field of GBV-C research, it is an “orphan virus” still seeking its disease. In the process of attempting to better understand the clinical consequences of GBV-C infection, Dr. Tillmann and several of his peers have come to an intriguing conclusion: that not only does GBV-C not aggravate the course of HIV infection, it actually confers a survival advantage to those who remain chronically infected with GBV-C.

## GBV-C: A Primer

THE DISCOVERY OF GBV-C DATES BACK TO 1967, WHEN A TEAM OF GERMAN investigators induced self-limiting hepatitis in tamarin monkeys that had been inoculated with serum from a surgeon with the initials G.B. who had developed acute hepatitis in 1964 (Deinhardt, 1967). During the 1970s, testing determined that neither the hepatitis A virus (HAV) nor the hepatitis B virus (HBV) were present in the GB agent. And in the 1980s, with the availability of newer assays, studies concluded that the hepatitis C virus (HCV) and the hepatitis E virus (HEV) were also free of any wrongdoing. It wasn't until 1995, when a team of researchers at Abbott Laboratories used a PCR method—representational difference analysis—to clone specific nucleotide sequences present in the plasma of a tamarin that had been inoculated with the GB agent (Simon, 1995, 1995a).

Two viruses were isolated by the Abbott team, which went on to be called GBV-A and GBV-B. The group then developed antibody assays based on GBV-A and GBV-B and found some samples from West Africa to be highly reactive. However, when the investigators trained their PCR probes on the samples to find GBV-A and GBV-B, they instead stumbled upon another closely related virus, which they named GBV-C. Additional studies concluded that GBV-A and GBV-B were only detectable in nonhuman primates and that GBV-C was the GB virus responsible for hepatitis in humans.

At about the same time, researchers at Genelabs Technologies made their own discovery in chimpanzees infected with sera from a patient in-

fectured with HCV (Linnen, 1996). A second virus was isolated in this patient, which the Genelabs team called the hepatitis G virus (HGV).

With the discovery of both viruses, researchers set out to determine the full genomic sequences of the isolates. It turned out that GBV-C and HGV are closely related isolates of the same virus, with more than 95% sequence homology (Alter, 1996). It was also determined that the genomic organization of these viruses is similar to that of HCV and all are considered to be members of the Flaviviridae family.

With the viruses isolated and analyzed, it was then time to determine their role in various diseases, most notably hepatitis. By Dr. Tillmann's estimates, more than 700 papers have been published thus far on the subject. However, the studies that have been completed have not been able to conclusively demonstrate that the virus—even with such close ties to HCV—has any negative clinical effects on the liver. In one meta-analysis, a team of Hannover investigators, which included Dr. Tillmann, analyzed the medical histories of 3,183 patients participating in one of 37 HCV cohort studies (Rambusch, 1998). Roughly 20% of the patients were coinfecting with GBV-C. Three of the 37 studies indicated a more severe course of HCV disease in coinfecting patients; two of the 37 studies indicated more severe changes in liver histology among the coinfecting patients; and one study indicated higher transaminase levels in GBV-C-viremic patients. Based on these limited findings—six out of 37 studies demonstrating any discernible effects of GBV-C infection—it was concluded that GBV-C did not appear to have had any negative influence on the course of HCV-related chronic liver disease or the development of chronicity of acute HCV infection.

Further evidence of the limited role of GBV-C in liver disease can be found in studies evaluating responses to interferon therapy. In the meta-analysis reviewed above, the Hannover group was unable to demonstrate that patients coinfecting with GBV-C and HCV had a lower response to interferon therapy than HCV-monoinfecting patients (Rambusch, 1998).

Based on these and other findings, many experts no longer think it fair to categorize the new virus as a hepatitis virus. As a result, the name GBV-C is now preferred over HGV. While it is possible that GBV-C infection does result in acute hepatitis-related symptoms and possibly fulminant hepatic failure, it has not yet been shown to play a role in chronic liver disease.

Dr. Tillmann did point out that, while GBV-C does not appear to be directly associated with any cause of liver disease, the virus does induce a humoral immune response against the GBV-C envelope 2 (E2) protein, which may promote some degree of liver damage and/or protection against GBV-C infection. To take a closer look at the potential role of GBV-

c and E2 antibodies (anti-E2), Dr. Tillmann and his colleagues conducted a study evaluating 182 patients undergoing orthotopic liver transplantation (OLT), 117 of whom were evaluated for GBV-C recurrence or *de novo* infection (Tillmann, 1998). Before OLT, GBV-C RNA was detected in 4.0% to 10.0% of patients, depending on the form of chronic liver disease, and anti-E2 was detected in 28.6% to 68.8% of patients, again depending on the form of liver disease. GBV-C reinfection after OLT was documented in 85.7%. Of the patients without evidence of exposure to GBV-C before OLT, 30/65 (46.2%) became GBV-C RNA positive after OLT. None of the 38 patients who were anti-E2 positive before OLT became GBV-C RNA positive after OLT, indicating a protective role associated with anti-E2. Neither patient nor graft survival was significantly affected by the presence of either GBV-C RNA or anti-E2 antibody before OLT.

GBV-C, which is believed to be transmitted sexually and parenterally, can be detected in human serum by RT-PCR and bDNA. Past GBV-C infection can be determined by detecting E2 antibodies, although commercially available assays are not yet readily available.

### GBV-C and HIV

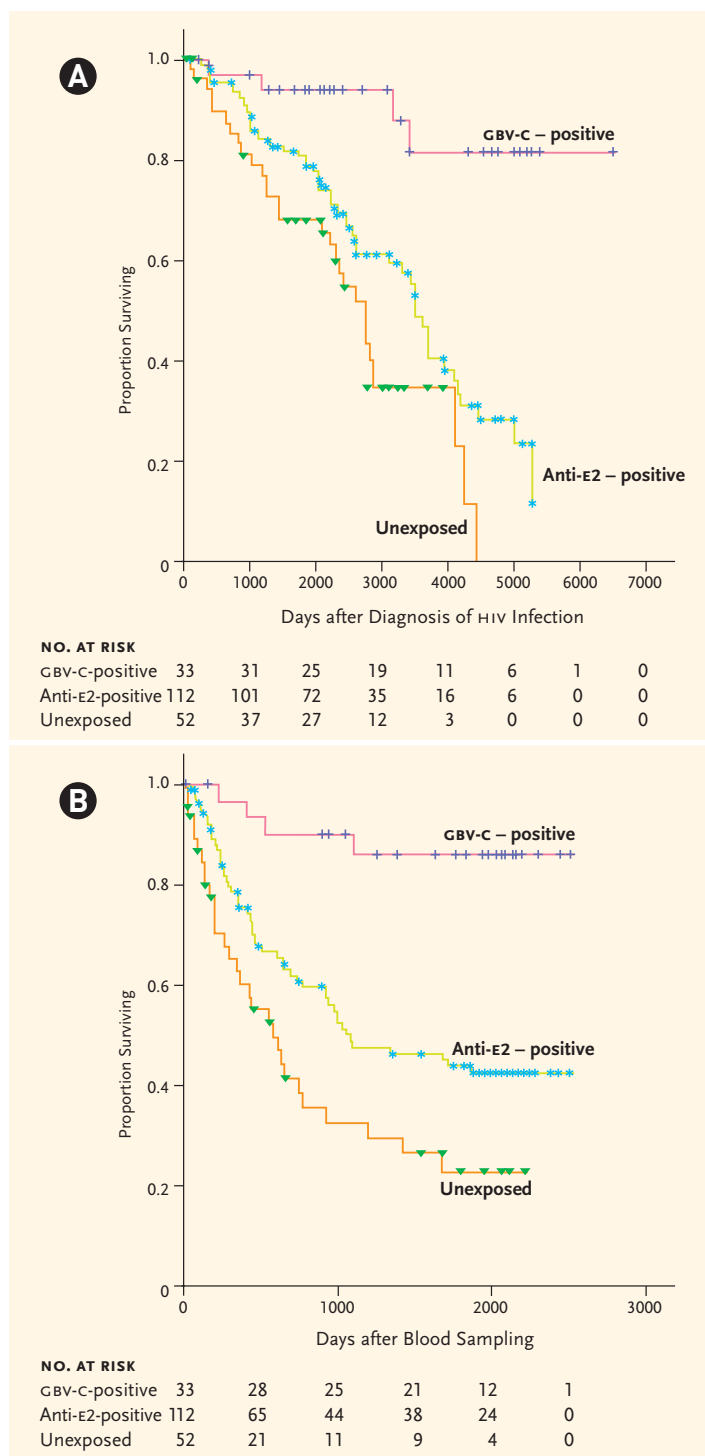
WHEN IT WAS BELIEVED THAT GBV-C WAS A HEPATITIS VIRUS, VARIOUS RESEARCH TEAMS became interested in studying the prevalence and clinical history of GBV-C infection in HIV-positive individuals. Given the high rates of chronic HBV and HCV infection in HIV, compounded by the fact that both infections are associated with increased morbidity and mortality in this patient population, many investigators eyed HIV-positive individuals as an ideal coinfection host. What they found, however, was most surprising.

Several groups have attempted to determine the prevalence of GBV-C coinfection among HIV-positive individuals. GBV-C RNA prevalence in HIV-infected individuals appears to be higher than in those not coinfecting with HIV, with rates ranging from as low as 14%, to 37% in a study focusing almost exclusively on men who have sex with men, and as high as 45% in a group of 56 intravenous drug users (Puig-Basagoiti, 2000; Lau, 1999; Rey, 1999). Turning to the prevalence of anti-E2 in HIV-infected individuals, a group of researchers that included Dr. Tillmann found a threefold increased prevalence of anti-E2 (56.8%) compared to GBV-C RNA (16.8%) in HIV-positive patients (Heringlake, 1998). These data, Dr. Tillmann pointed out, are in agreement with prevalence data reported in the OLT study discussed above. To be balanced, Dr. Tillmann pointed out that a handful of other studies have found lower rates of anti-E2, in relation to rates of GBV-C RNA positivity, in HIV-infected patients. In the general (non-HIV-infected) population, the prevalence of anti-E2 tends to be three to five times higher than the prevalence of GBV-C RNA. In other words, it's possible that HIV-positive individuals are less likely to seroconvert to anti-E2 and to remain chronically infected with GBV-C.

Considering the relatively high rates of GBV-C infection among HIV-positive individuals, along with the data suggesting that GBV-C is not a pathogenic virus, Dr. Tillmann and his colleagues—along with several other groups—have studied the clinical consequences of GBV-C/HIV coinfection.

Virtually all of the studies completed to date have shown that GBV-C coinfection in HIV-positive individuals does not increase the risk of liver disease or impair survival. In fact, numerous studies have demonstrated that active GBV-C coinfection is associated with higher CD4+ cell counts and prolonged survival in HIV-positive individuals.

In a review article published in *Antiviral Research*, Dr. Tillmann and his colleagues neatly summarized the results of seven studies examining the effects of active GBV-C infection on CD4+ cell counts in HIV-



**Figure 1. Survival According to GBV-C Status.**

Survival from the time of diagnosis of HIV infection (Panel A) and survival from the time the blood sample was drawn to determine the GBV-C status (Panel B) are shown in relation to the GBV-C status. For both measures, the patients who tested positive for GBV-C RNA had significantly better survival ( $P < 0.001$  for the comparison with the unexposed group and with the anti-E2-positive group; in Panel A,  $P = 0.02$  for the comparison between the anti-E2-positive group and the unexposed group; in Panel B,  $P = 0.01$  for the comparison between the anti-E2-positive group and the unexposed group). The tick marks on the curves indicate the last follow-up visits.

Source: Reprinted with permission of the Massachusetts Medical Society and the *New England Journal of Medicine*. Tillmann HL, Heiken H, Knapik-Botor A, et al. **Infection with GB virus C and reduced mortality among HIV-infected patients.** *N Engl J Med* 345(10):718, 2001.

positive individuals (Tillmann, 2001). Three studies did not show a significant association between GBV-c infection and CD4+ cell counts in HIV infection. Three studies did show a significant positive association between GBV-c infection and CD4+ cell counts in HIV infection (i.e., a beneficial effect). Conversely, one study demonstrated a negative association between GBV-c infection and CD4+ cell counts in HIV-positive individuals (i.e., a harmful effect).

As for the effect of GBV-c infection on HIV viral load, an initial study conducted by a team of Japanese researchers found that the mean HIV-RNA titer was lower (3.52 log copies/mL) in 11 patients with GBV-c/HIV coinfection than in 30 HIV-positive patients without coinfection (5.76 log copies/mL), with no significant difference in the length of HIV infection between the two groups (Toyoda, 1998).

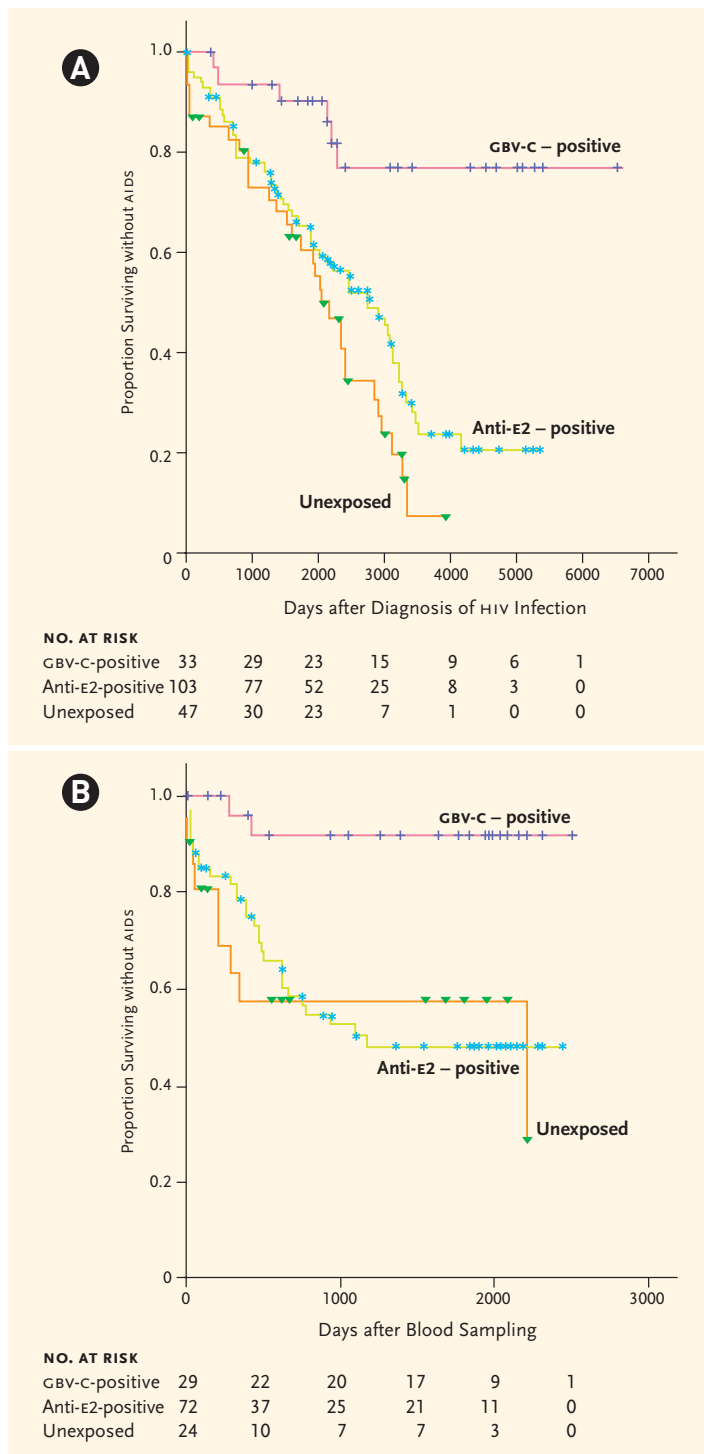
In a more recent study highlighted by Dr. Tillmann, Dr. Jinhua Xiang and his colleagues in Iowa City set out to determine whether GBV-c infection altered HIV replication *in vitro* by infecting PBMCs with HIV alone, GBV-c alone, or HIV and GBV-c together (Xiang, 2001). Mock-infected PBMCs served as the negative controls. HIV replication, demonstrated by the production of p24 antigen in the supernatant fluid of the cell cultures, was inhibited by 23% after three days in culture and by 49% after six days in culture when GBV-c and HIV were used to infect cells simultaneously.

Dr. Xiang's group also followed 362 HIV-positive individuals, 144 (39.8%) of whom had evidence of GBV-c viremia on an initial test and during a subsequent follow-up. The mean duration of follow-up for the entire cohort was 4.1 years. Forty-one (28.5%) patients with GBV-c/HIV coinfection died during the follow-up period, compared with 123/218 (56.4%) patients who tested negative for GBV-c RNA. In a Cox-regression analysis adjusted to reflect HIV treatment, baseline CD4+ cell count, age, sex, race, and mode of transmission of HIV, the mortality rate among the 218 HIV-infected patients without GBV-c coinfection was significantly higher than that among the 144 patients with GBV-c coinfection.

Dr. Tillmann also reviewed the clinical research conducted by his group and collaborators, reported in the same issue of the *New England Journal of Medicine* (NEJM) as Dr. Xiang's paper. A total of 197 HIV-positive individuals were followed prospectively beginning in 1993 or 1994 (Tillmann, 2001a). Of these patients, 33 (16.8%) tested positive for GBV-c RNA, 112 (56.9%) tested positive for anti-E2, and 52 (26.4%) had no marker of past or present GBV-c infection. First, Dr. Tillmann's group set out to assess the relationship between GBV-c infection and the progression of HIV disease. Next, his group tested 169 GBV-c-positive plasma samples with a bDNA prototype assay in order to examine the possible correlations between GBV-c viral load and both the CD4+ cell count and HIV viral load.

As shown in Figures 1 and 2, survival was significantly longer— with a slower progression to AIDS—among patients who tested positive for GBV-c RNA. The association between GBV-c viremia with reduced mortality remained significant in analyses that were stratified according to age and CD4+ cell counts. Patients with anti-E2 also had significantly slower progression of HIV disease. With respect to HIV viral load, patients with GBV-c viremia had a mean HIV viral load of 3.89 log copies/mL, compared to 3.27 log copies/mL in the anti-E2 group and 4.59 log copies/mL in the GBV-c-negative group.

While these studies clearly indicated a positive effect of GBV-c infection on CD4+ cell counts, viral load, and survival, Dr. Tillmann pointed out two studies that have not corroborated these findings. In one study conducted by investigators at the Huddinge University Hospital in Stockholm, plasma samples demonstrating GBV-c replication, collected soon after a diagnosis of HIV infection was made, were not shown to have any effect on the prognosis of HIV infection (Birk, 2002). Another study, reported



**Figure 2. AIDS-Free Survival According to GBV-c Status.** AIDS-free survival from the time of diagnosis of HIV infection (Panel A) and AIDS-free survival from the time the blood sample was drawn to determine the GBV-c status (Panel B) are shown in relation to the GBV-c status. For both measures, the patients who tested positive for GBV-c RNA had significantly better survival ( $P < 0.001$  for the analysis in Panel A and  $P = 0.002$  for the analysis in Panel B for the comparisons with the unexposed group and with the anti-E2-positive group; the differences between the anti-E2-positive group and the unexposed group were not significant). The tick marks on the curves indicate the last follow-up visits.

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three years earlier by a team of investigators in Lyon, also failed to demonstrate a significant survival advantage associated with GBV-C infection (Sabin, 1998). However, Dr. Tillmann commented that this study examined GBV-C RNA-positive and anti-E2-positive patients as one group, potentially overlooking the advantage of active GBV-C replication in coinfecting patients compared to GBV-C-unexposed HIV-positive individuals.

Dr. Tillmann explained that the discrepancies in the results from these various studies likely speak more to the limitations of cross-sectional studies than to the actual effects of GBV-C infection. Cross-sectional studies provide a “snapshot” of a particular moment in time and do not provide the necessary follow-up data. For example, a study may document GBV-C-RNA positivity in a high number of HIV-positive patients at a particular moment in time and find that this, in itself, is not associated with prolonged survival. However, some of these patients will seroconvert to anti-E2 whereas others will remain chronically infected with GBV-C for a prolonged period of time. “Active GBV-C replication is the important factor here,” Dr. Tillmann said. “If these studies continued to follow these patients and determined which ones remained chronically infected and which ones converted to anti-E2, we would likely see a survival advantage among those who remained chronically infected with the virus.”

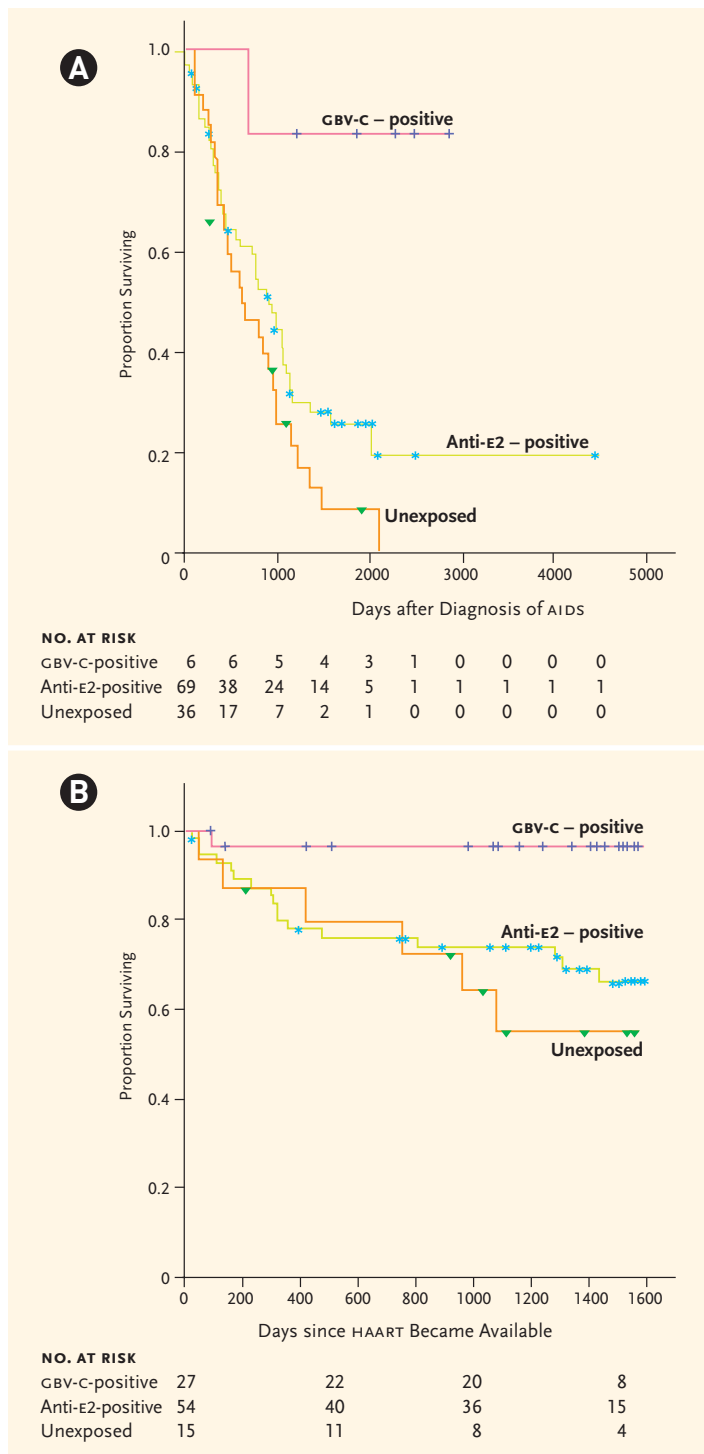
### Impact of GBV-C Infection on HAART

THE AVAILABILITY AND WIDESPREAD USE OF HIGHLY ACTIVE ANTIRETROVIRAL THERAPY (HAART) has, without doubt, had a profound effect on both mortality and morbidity rates among HIV-positive patients. Dr. Tillmann explained that a number of studies have been conducted to assess the role of GBV-C infection in HIV-positive patients receiving HAART, the results of which have been encouraging.

Turning back to the study reported by Dr. Tillmann’s group in the *NEJM*, additional analyses were conducted to assess survival after the introduction of HAART (see Figure 3). In 1996—the year HAART became widely available—98/197 (49.7%) patients originally enrolled in the study were still alive and undergoing follow-up. Of these patients, 24 (24.5%) had died by March 2000. A higher risk of death was significantly associated with the absence of GBV-C RNA, since only 1/27 (3.7%) GBV-C-positive patients died, compared to 17/56 (30.4%) anti-E2-positive patients and 6/15 (40%) GBV-C-uninfected patients. Interestingly, in a Cox-regression analysis conducted using data available in 1996, only the CD8+ cell count—not the CD4+ cell count, HIV viral load, age and sex of the patients, or GBV-C status—was found to be significantly associated with survival. However, a univariate Cox regression analysis revealed significant associations between survival and GBV-C RNA status, CD4+ cell count, CD8+ cell count, and HIV viral load.

In another study, conducted by a French team, patients infected with HIV, HCV, and GBV-C experienced a CD4+ cell count increase during four years of HAART, whereas the increase stopped after two years among patients infected only with HIV or HIV/HCV (Voinin, 2002). In a more recent study, conducted by investigators at the University Hospitals of Cleveland and Case Western Reserve University Center for AIDS Research, GBV-C-infected patients exhibited a complete virological response to HAART more often than patients without GBV-C and had a greater median increase in their CD4+ cell counts and a marginally greater median decrease in their HIV viral loads (Rodriguez, 2003). This association was found to be independent of baseline CD4+ cell counts and HIV-RNA levels, indicating that an association exists between GBV-C infection and response to HAART.

Also of interest are data reported at the 9th Conference on Retroviruses and Opportunistic Infections, held in Seattle in 2002 (Kozal,



**Figure 3. Survival after the Diagnosis of AIDS and After HAART Became Available.**

From the time the diagnosis of AIDS was established, patients who tested positive for GBV-C RNA had better survival than those without GBV-C RNA ( $P=0.007$ ) (Panel A). Even after the introduction of highly active antiretroviral therapy in 1996, survival was better among GBV-C-positive patients than among those without GBV-C RNA ( $P=0.02$ ) (Panel B). The differences between the anti-E2-positive group and the unexposed group were not significant. The tick marks on the curves indicate the last follow-up visits.

Source: Reprinted with permission of the Massachusetts Medical Society and the *New England Journal of Medicine*. Tillmann HL, Heiken H, Knapiak-Botor A, et al. **Infection with GBV-C and reduced mortality among HIV-infected patients.** *N Engl J Med* 345(10):720, 2001.

2002). This study hypothesized that because GBV-C appears to decrease HIV replication *in vitro*, fewer replication events may in turn result in a decreased probability of developing mutations conferring resistance to antiretroviral agents. The study evaluated 212 HIV-positive patients being monitored at either the Yale University School of Medicine or the University of Iowa, 57 (27%) of whom had evidence of GBV-C viremia. Among the 35 HAART-experienced patients from the Iowa cohort—94% had received monotherapy or dual NRTI treatment—HIV genotypic resistance was present in 53% of the GBV-C-infected patients and in 80% of the HIV-monoinfected patients. Likewise, among 90 HAART-experienced patients from the Yale cohort—all had a history of exposure to regimens containing at least three drugs—genotypic resistance was present in 23% of the GBV-C RNA-positive patients and 35% of the GBV-C-uninfected patients. However, the observations from these two cohorts did not reach statistical significance.

Contradictory data are available from a study conducted by investigators at the British Columbia Centre for Excellence in HIV/AIDS in Vancouver (Brumme, 2002). In this study, 461 HIV-positive patients who initiated HAART between June 1996 and August 1998 were retrospectively evaluated for GBV-C RNA and their responses to HAART. Of the 441 individuals for whom results were available, 90 (20.4%) had detectable GBV-C RNA. While GBV-C RNA was significantly associated with lower HIV-RNA levels at baseline, univariate and multivariate Cox regression models did not show that individuals differed with respect to the time to virologic or immunologic failure in relation to the presence or absence of GBV-C RNA.

## Possible Mechanism(s) of Action in HIV

THE DEFINITIVE MECHANISM BY WHICH GBV-C RNA WORKS TO THE advantage of HIV-positive people has not yet been determined. A handful of studies have been completed, yet none have provided definitive information.

In one study, GBV-C replication in PBMCs appeared to be noncytotoxic and did not inhibit the synthesis of cellular proteins (Xiang, 2001). In other words, the effect of GBV-C on HIV replication did not appear to be a consequence of cellular toxicity. The inhibitory effect of GBV-C replication on HIV growth in cell cultures was evident when HIV infection preceded GBV-C infection, and GBV-C did not alter the expression of CD4, CXCR4, or CCR5. Dr. Tillmann's group has looked at the potential role of various chemokine receptor mutations—such as those in CCR5, CCR2, and SDF-1, all of which are associated with more benign courses of HIV disease—and was not able to find any associations with GBV-C viremia (Tillman, 2002). Taken together, these two studies suggest that the mechanism of inhibition appears to operate during a stage of HIV replication, after attachment and entry have occurred.

Dr. Tillmann pointed out that GBV-C is not the only infection known to have an inhibitory effect on HIV replication. In one study he reviewed, coculture of HIV-infected CD4+ cells with HTLV-II-infected CD8+ cells led to a downregulation of HIV replication (Casoli, 2000). HIV replication also appears to be reduced in patients with acute, symptomatic scrub typhus infection (an acute, febrile, infectious illness caused by *Rickettsia tsutsugamushi*) (Watt, 2000). “What’s also interesting,” Dr. Tillmann added, “is that we tend to see better survival in liver-transplanted patients infected with both HBV and HCV or HBV and HDV [hepatitis delta virus], compared to those only infected with HBV or HCV.”

More recent studies conducted by Dr. Tillmann's group have suggested that HIV-infected lymphocytes are longer lived when exposed to GBV-C than those not exposed to the virus. “It could be that GBV-C inhibits HIV-induced apoptosis, which would be a significant advantage.”

## Conclusion

IN SUMMARIZING HIS TALK, DR. TILLMANN REITERATED THAT GBV-C continues to replicate for many years, often for as long as the patient remains untreated. “In recent years, we’ve seen a higher frequency of patients seroconverting to anti-E2,” he said. “However, it’s not clear if this is perhaps related to certain drug combinations.” And once seroconversion has taken place, a recurrence of viremia is highly unlikely.

Dr. Tillmann's research, along with that of other groups around the world, indicates that GBV-C infection—provided that it continues to replicate—correlates with better survival of HIV-infected patients. “We believe this to be related to the lowering of viral load,” he explained. “However, there are a number of questions that still need to be answered. For starters, we could be looking at geographical differences in the effects of GBV-C, which would relate to the different subtypes of the virus that we’re now looking at. More work is needed in this area, just as there is much more work needed to understand the mechanisms by which GBV-C viremia inhibits HIV replication. These are just a few of the challenges we face with GBV-C.”

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