

INFECTION WITH GB VIRUS C AND REDUCED MORTALITY
AMONG HIV-INFECTED PATIENTS

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ABSTRACT

Background The flavivirus GB virus C (GBV-C, also designated hepatitis G virus) was identified in a search for hepatitis viruses, but no disease is currently known to be associated with it. We investigated the relation between coinfection with GBV-C and the long-term outcome in patients infected with the human immunodeficiency virus (HIV).

Methods A total of 197 HIV-positive patients were followed prospectively beginning in 1993 or 1994. Of these patients, 33 (16.8 percent) tested positive for GBV-C RNA, 112 (56.9 percent) had detectable antibodies against the GBV-C envelope protein E2, and 52 (26.4 percent) had no marker of GBV-C infection and were considered unexposed. We assessed the relation between GBV-C infection and the progression of HIV disease. We also tested 169 GBV-C-positive plasma samples with a quantitative branched-chain DNA (bDNA) assay in order to investigate possible correlations between GBV-C viral load and both the CD4+ cell count and the HIV load.

Results Among the patients who tested positive for GBV-C RNA, survival was significantly longer, and there was a slower progression to the acquired immunodeficiency syndrome (AIDS) ($P < 0.001$ for both comparisons). Survival after the development of AIDS was also better among the GBV-C-positive patients. The association of GBV-C viremia with reduced mortality remained significant in analyses stratified according to age and CD4+ cell count. In an analysis restricted to the years after highly active antiretroviral therapy became available, the presence of GBV-C RNA remained predictive of longer survival ($P = 0.02$). The HIV load was lower in the GBV-C-positive patients than in the GBV-C-negative patients. The GBV-C load correlated inversely with the HIV load ($r = -0.33$, $P < 0.001$) but did not correlate with the CD4+ cell count.

Conclusions Coinfection with GBV-C is associated with a reduced mortality rate in HIV-infected patients. GBV-C is not known to cause any disease, but it is possible that its presence leads to an inhibition of HIV replication. However, GBV-C infection could also be a marker for the presence of other factors that lead to a favorable HIV response. (N Engl J Med 2001;345:715-24.)

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PATIENTS infected with the human immunodeficiency virus (HIV) are often coinfecting with other viruses, especially hepatitis viruses.¹ Coinfection with the hepatitis B virus (HBV) or hepatitis C virus (HCV) appears to increase the mortality rate among HIV-infected patients.^{2,3} The course of HCV infection is accelerated in patients who are coinfecting with HIV, as compared with the course in immunocompetent patients.^{4,9}

In 1995, a new virus was identified that is related to the hepatitis C virus and was thought to be another hepatitis virus.^{10,11} It has been called both GB virus C (GBV-C)¹⁰ and hepatitis G virus (HGV).¹¹ GBV-C and HGV are closely related isolates of the same virus, with more than 95 percent sequence homology.¹² We use the name GBV-C, since it currently appears that the virus is not a cause of hepatitis.¹²⁻¹⁴ Whereas the presence of GBV-C RNA in serum or plasma indicates ongoing GBV-C infection, the presence of antibodies against the envelope protein E2 (anti-E2) indicates viral clearance.¹⁵

GBV-C is not known to cause any disease. We have studied the relation between GBV-C infection and the course of HIV infection. In a preliminary study of patients recruited in 1993 and 1994 and followed for up to three years, we found evidence of a beneficial effect of GBV-C on the course of HIV infection.¹⁶ This effect was subsequently confirmed by others.¹⁷⁻¹⁹

In the present study, we examined whether GBV-C viremia is beneficial (or is a marker for other beneficial factors) in HIV-infected patients and whether this beneficial effect, if any, continues to be important after the introduction of highly active antiretroviral therapy, which has led to declining morbidity and mortality associated with HIV infection.^{20,21} We also examine the correlation between the GBV-C load and the HIV load.

METHODS**Patients**

We prospectively enrolled 197 HIV-infected patients who attended our outpatient clinic between January 1993 and Decem-

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TABLE 1. CHARACTERISTICS OF THE PATIENTS AT ENROLLMENT, ACCORDING TO GBV-C STATUS.*

CHARACTERISTIC	UNEXPOSED TO GBV-C (N=52)	ANTI-E2-POSITIVE (N=112)	GBV-C-POSITIVE (N=33)	P VALUE†
Age (yr)	37.6±9.8	40.0±10.3	34.0±8.8	0.008
Sex (no.)				
Female	10	21	13	0.03
Male	42	91	20	0.06
Mode of transmission of HIV (no.)				
Injection-drug use	12	31	17	0.01
Blood transfusion (hemophilia)	1	4	2	0.60
Heterosexual contact	7	18	1	0.15
Homosexual contact	32	59	13	0.14
CD4+ cell count (per mm ³)	187.4±209.5	250.7±260.5	346.0±201.3	0.01‡
CD8+ cell count (per mm ³)	784.1±518.9	930.8±629.4	1325.4±733.4	0.003
Leukocyte count (×10 ⁻³ /mm ³)	4.0±1.5	4.9±2.0	5.5±1.8	0.001
Lymphocyte count (×10 ⁻³ /mm ³)	1.3±0.9	1.7±1.0	2.6±2.9	0.001
Duration of follow-up (yr)§	3.7±3.2	4.0±3.3	4.6±3.7	0.50

*Plus-minus values are means ±SD.

†Comparisons among the three groups were made with use of the Kruskal-Wallis test.

‡P=0.04 for the comparison between the anti-E2-positive group and the unexposed group.

§Data are for follow-up from the time of the first documented positive HIV test until blood was drawn for the determination of GBV-C status.

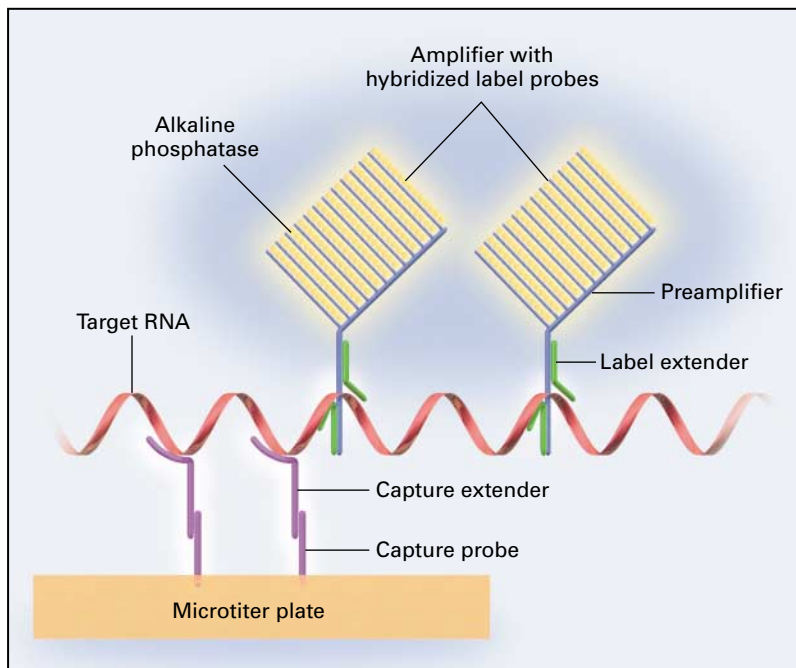


Figure 1. A GBV-C Branched-Chain DNA Prototype Assay.

The GBV-C target RNA is captured by a set of target-specific oligonucleotide probes (capture extenders) on the surface of a microtiter plate. A second set of target-specific probes (label extenders) are designed to hybridize the target to a specialized series of oligonucleotide probes (preamplifier, amplifier, and alkaline phosphatase-labeled) for signal amplification. An enzyme-triggerable substrate is added, resulting in a chemiluminescent signal that is proportional to the amount of GBV-C target added.

ber 1994. A preliminary analysis of these patients and their GBV-C status was reported previously.¹⁶ The stage of disease was classified in accordance with the European modification of the staging system of the Centers for Disease Control and Prevention (CDC). The characteristics of the patients according to their GBV-C status at enrollment are summarized in Table 1. The last follow-up was defined as the last contact with the patient. The study was approved by the institutional review board of the Medizinische Hochschule Hannover, in Hannover, Germany.

Cumulative survival and survival without progression to the acquired immunodeficiency syndrome (AIDS) were calculated from five different starting points to the date of the last follow-up: from the date of the first documented positive HIV test; from the date when a blood sample was drawn for GBV-C testing; from January 1, 1996 (when highly active antiretroviral therapy became available); from the day highly active antiretroviral therapy was initiated; and from the day AIDS was diagnosed.

The patients were divided into three groups: those who tested positive for GBV-C RNA, those who tested positive for anti-E2 antibodies (a GBV-C surface marker), and those without evidence of exposure to GBV-C.¹⁴ The physicians who examined the patients in the outpatient clinic were unaware of their GBV-C status until these data had been analyzed. Thus, decisions about antiretroviral therapy, including highly active antiretroviral therapy, were made without knowledge of GBV-C status. Highly active antiretroviral therapy became available for all patients in 1996.

Laboratory Analysis

For the evaluation of the relations between the GBV-C load and the HIV load and between the GBV-C load and the CD4+ cell count, an additional 208 patients (resulting in a total of 405 patients) with known HIV infection were screened for the presence of GBV-C RNA by nested polymerase chain reaction (PCR). RNA was transcribed with 20 pmol of the antisense primer GBV-C1 (ATGCCACCCGCCCTCACCCGAA) and amplified with GBV-C1 and the sense primer GBV-C2 (AAAGGTGGTGGATGGGTGATG) with the use of the Titan One Tube RT [reverse-transcriptase] PCR System (Roche Diagnostics, Mannheim, Germany); it was then tested by nested PCR with a second set of primers (antisense primer GBV-C3 [CCCCACTGGTCYTTGYCAACTC] and sense primer GBV-C4 [AATCCCGGTCAAYTGGTAGC-CACT]). A total of 104 of the 405 patients screened were determined to be positive for GBV-C RNA. At least one plasma sample that had been obtained after enrollment (between 1996 and 1999) and stored at -80°C was available for quantification of GBV-C from 72 of the 104 GBV-C-positive patients. A total of 169 samples from these 72 patients were quantitatively analyzed by branched-chain DNA (bDNA) assay (Fig. 1), and the results were compared with the CD4+ cell counts and the HIV loads (calculated at the same time) to determine whether a higher GBV-C load correlated with either a higher CD4+ cell count or a lower HIV load.

The GBV-C load was determined with the use of a prototype GBV-C bDNA assay at the Bayer Reference Testing Laboratory in Mijdrecht, the Netherlands. The format is similar to that of the Bayer HCV bDNA 3.0 assay. The target-specific probes used to facilitate the capture and labeling of the GBV-C RNA are located in the relatively conserved sequences of the 5' untranslated region of the GBV-C genome.¹¹ Through a series of hybridization events, mul-

tiples bDNA and alkaline phosphatase-labeled oligonucleotide molecules are bound to the target molecule of GBV-C RNA. The addition of an enzyme-triggerable substrate results in a signal that is proportional to the amount of target RNA added. The result of the quantification of a specimen is determined by interpolation from a standard curve, and the results are reported in copies per milliliter. The lower limit of detection for this prototype bDNA assay is 67,000 copies per milliliter.

CD4+ and CD8+ lymphocytes were measured by fluorescence-activated cell sorting (FACScalibur, Becton Dickinson, Heidelberg, Germany), and the HIV load was determined semiquantitatively by a commercial PCR assay (Amplicor HIV-1 Monitor, Roche Diagnostics, Basel, Switzerland).

Statistical Analysis

A chi-square or Fisher's exact test was used to analyze categorical variables. The group means were compared by Student's t-test or by the Mann-Whitney U test, Wilcoxon rank-sum test, or Kruskal-Wallis test, if appropriate. Cumulative survival and AIDS-free survival were assessed by Kaplan-Meier analysis. Equality of survival distributions was evaluated by the log-rank test. A Cox proportional-hazards regression model was used for the analysis of continuous variables such as age, CD4+ cell count, and HIV load, as well as for the estimation of hazard ratios by means of a multivariate model including categories of sex, age, CD4+ cell count, CD8+ cell count, known duration of HIV infection, HIV load, and GBV-C status (RNA-positive, anti-E2-positive, or without a marker of exposure to GBV-C). Patients who were lost to follow-up were included in the analyses, but the data were censored at the time of the last visit. P values lower than 0.05 were considered to indicate statistical significance, and all reported P values are two-sided. All statistical analyses were performed with the use of SPSS software (version 9.0, SPSS, Chicago). All the data were held at the Medizinische Hochschule Hannover.

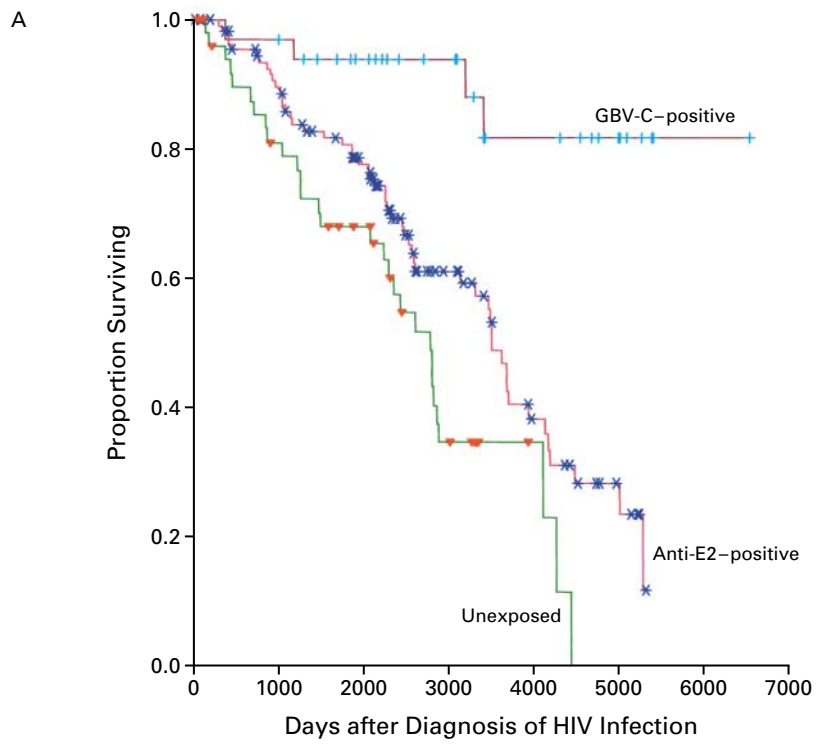
RESULTS

Survival and AIDS-free Survival

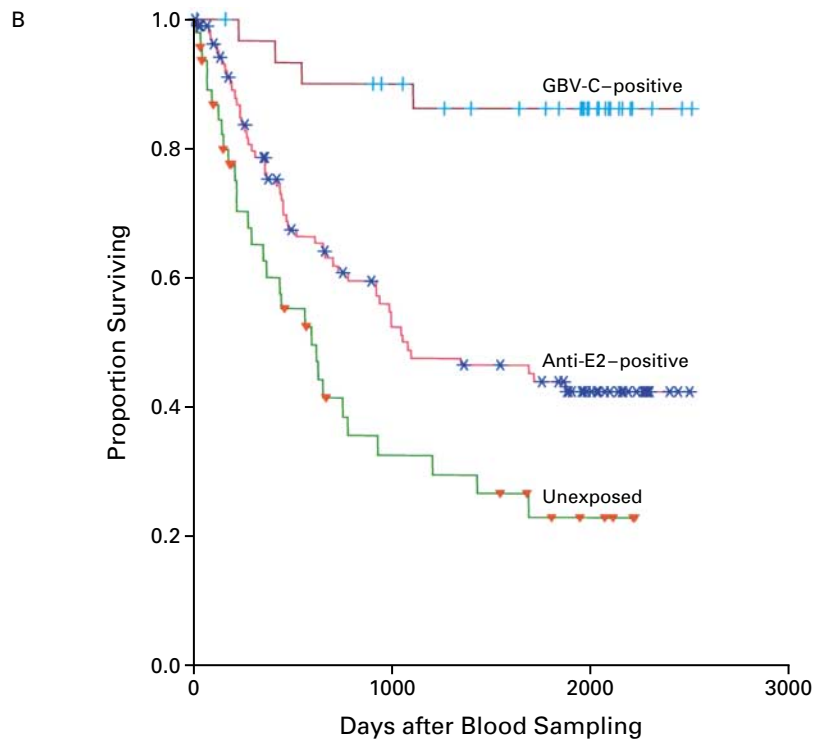
On the date on which the serum used to determine GBV-C status was obtained, the overall mean (\pm SD) duration of HIV infection was 4.0 ± 3.3 years. The mean duration of HIV infection was 4.6 ± 3.7 years among the 33 patients who tested positive for GBV-C RNA, 4.0 ± 3.3 years among the 112 patients who tested positive for anti-E2, and 3.7 ± 3.2 years among the 52 patients without a marker of GBV-C infection (the presumably unexposed group). The mean duration of follow-up after the determination of GBV-C status was 4.2 ± 2.1 years in the GBV-C-positive group, 2.7 ± 2.3 years in the anti-E2-positive group, and 1.6 ± 1.9 years in the unexposed group. A total of 59 patients were lost to follow-up. Among those lost to follow-up, the mean interval between the date of the determination of the GBV-C status and

Figure 2 (next page). 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.



No. AT RISK	0	1000	2000	3000	4000	5000	6000	7000
GBV-C-positive	33	31	25	19	11	6	1	0
Anti-E2-positive	112	101	72	35	16	6	0	0
Unexposed	52	37	27	12	3	0	0	0



No. AT RISK	0	1000	2000	3000
GBV-C-positive	33	28	25	21
Anti-E2-positive	112	65	44	38
Unexposed	52	21	11	9

the last follow-up was 2.9 ± 1.9 years for the 12 patients in the GBV-C–positive group, 1.6 ± 1.9 years for the 30 patients in the anti-E2–positive group, and 1.6 ± 1.9 years for the 17 patients in the unexposed group.

The duration of survival from the date of the first positive HIV test (Fig. 2A) and from the date of testing for GBV-C (Fig. 2B) was significantly longer among those with GBV-C viremia ($P < 0.001$ for both comparisons with the unexposed group and with the anti-E2–positive group). Survival in both analyses was also significantly longer in the anti-E2–positive group than in the unexposed group ($P = 0.02$ for the comparison of the duration of survival from the date of the first positive HIV test, and $P = 0.01$ for the comparison of the duration of survival from the date of testing for GBV-C). The longer overall survival was due in part to a significantly longer survival without progression to AIDS both from the date of the first positive HIV test ($P < 0.001$) (Fig. 3A) and from the date of testing for GBV-C ($P = 0.002$) (Fig. 3B). Even after the development of AIDS, the patients who tested positive for GBV-C RNA had a better prognosis than those who did not ($P = 0.007$ for the comparison with patients who were negative for GBV-C RNA) (Fig. 4A).

The introduction of highly active antiretroviral therapy has improved the prognosis of HIV-infected patients dramatically.^{20,21} Since highly active antiretroviral therapy became available in 1996 there has been a slower progression to death in HIV-infected patients, but the patients coinfecting with GBV-C still have a significantly better survival rate ($P = 0.02$ for the comparison with patients who were negative for GBV-C RNA) (Fig. 4B).

In 1996, 98 of the 197 patients were still alive and undergoing follow-up. Of these patients, 24 (24.5 percent) had died by March 2000. A higher risk of death was significantly associated with the absence of GBV-C RNA, since only 1 of 27 GBV-C–positive patients (3.7 percent) died, as compared with 17 of 56 anti-E2–positive patients (30.4 percent) and 6 of 15 unexposed patients (40.0 percent) ($P = 0.01$ by the chi-square test).

Cox proportional-hazards regression analysis revealed significant associations between survival and age ($P = 0.01$), CD4+ cell count and CD8+ cell count ($P < 0.001$ for the comparison with CD4+ and CD8+ cell counts as one variable), leukocyte count

($P < 0.001$), lymphocyte count ($P < 0.001$), and GBV-C–RNA status ($P < 0.001$). The multivariate Cox regression analysis, however, revealed only three significant variables: CD4+ cell count ($P < 0.001$), number of leukocytes ($P = 0.001$), and GBV-C–RNA status ($P = 0.02$). To control for the effects of age, we matched the GBV-C–positive patients with a subgroup of younger anti-E2–positive patients. Multiple regression analysis revealed only two significant variables: CD4+ cell count ($P = 0.002$) and GBV-C–RNA status ($P = 0.01$). With the inclusion in the model of the presumed duration of infection, *P* values were less than 0.001 for both the CD4+ cell count and the GBV-C–RNA status. In the Kaplan–Meier analysis of these age-matched patients, those with GBV-C RNA had a significantly better survival rate ($P < 0.001$). We then matched each GBV-C–positive patient with an anti-E2–positive patient in the next higher category of CD4+ cell count, and the survival rate remained better in the GBV-C–positive group ($P = 0.04$). The association between GBV-C and survival was further strengthened by Cox regression analyses both including and excluding the GBV-C status.

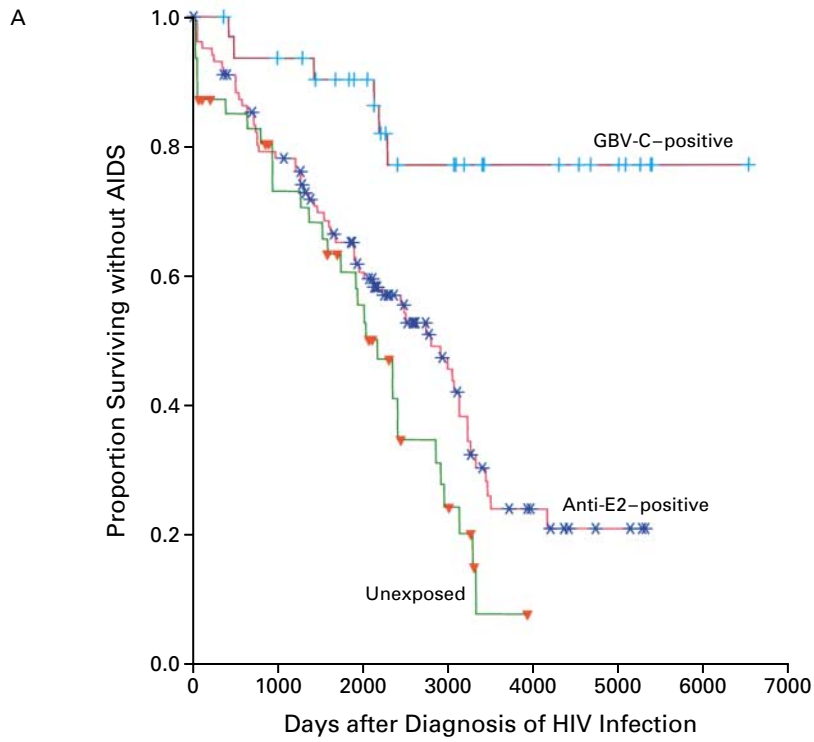
To analyze survival after highly active antiretroviral therapy became available, we performed a multivariate Cox regression analysis that included the CD4+ and CD8+ cell counts and the HIV load measured in 1996, as well as age, sex, and GBV-C status. Only the CD8+ cell count was still significantly associated with survival in this analysis ($P < 0.001$), although a univariate Cox regression analysis had revealed significant associations between survival and GBV-C–RNA status ($P = 0.01$), CD4+ cell count ($P = 0.03$), CD8+ cell count ($P = 0.01$), and HIV load ($P = 0.01$).

Viral Load in Relation to GBV-C Status

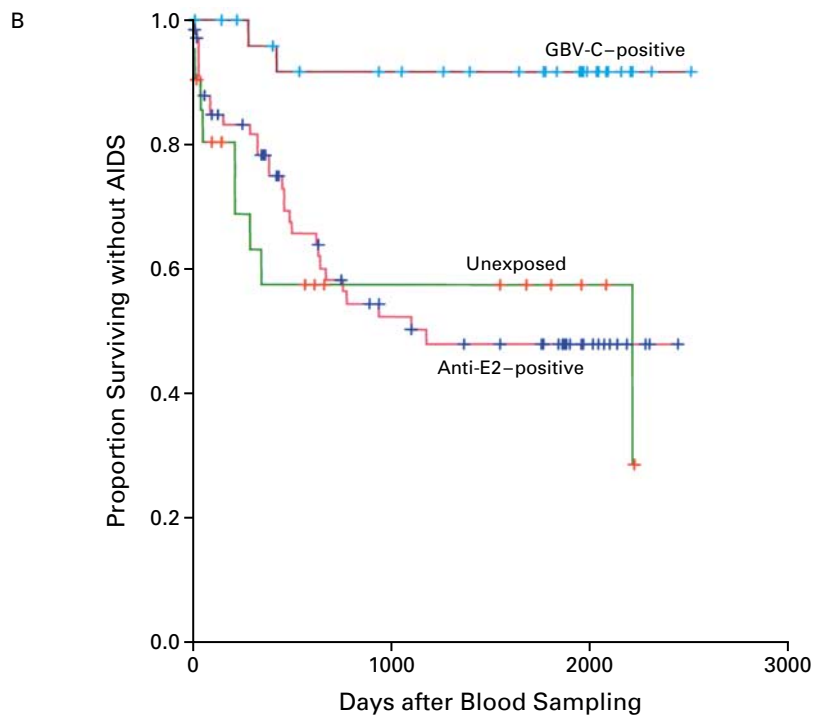
The presence of GBV-C viremia was not only associated with higher CD4+ cell counts, as described previously,¹⁶ but also with a lower mean HIV load: 3.89 ± 0.9 log copies per milliliter, as compared with 4.27 ± 0.97 log copies per milliliter for anti-E2–positive patients and 4.59 ± 0.7 log copies per milliliter for unexposed patients ($P = 0.03$). When we analyzed the relations between the HIV viral load in 1996 and both the presence of GBV-C RNA and the number of antiretroviral drugs administered (one, two, or three) with the use of a partial correlation model, we found a stronger association between a low HIV load

Figure 3 (next page). 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.



NO. AT RISK							
GBV-C-positive	33	29	23	15	9	6	1
Anti-E2-positive	103	77	52	25	8	3	0
Unexposed	47	30	21	7	1	0	0



NO. AT RISK						
GBV-C-positive	29	22	20	17	9	1
Anti-E2-positive	72	37	25	21	11	0
Unexposed	24	10	7	7	3	0

and the presence of GBV-C viremia ($r=0.22$, $P=0.03$) than between a low HIV load and the use of more antiretroviral drugs ($r=0.14$, $P=0.1$), a result that is evidence of a relation between GBV-C and HIV load.

Persistence of GBV-C Status

A total of 82 patients were retested for GBV-C RNA by PCR in 1998. According to these tests, none of the 45 previously anti-E2-positive patients who were retested had had a reactivation of, or superinfection with, GBV-C; 3 of the 13 previously unexposed patients who were retested had acquired GBV-C viremia. Two of the 24 previously GBV-C-positive patients no longer had GBV-C viremia; both these patients had received interferon because of coinfection with HCV.

GBV-C Load in Relation to HIV Load and CD4+ Cell Count

To analyze the relation between GBV-C and both the HIV load and the CD4+ cell count further, we analyzed a total of 169 plasma samples from 72 patients to determine the GBV-C load and to evaluate its correlation with the CD4+ cell count and the HIV load. All but 7 of the 169 plasma samples (162 samples or 95.9 percent) tested positive for GBV-C RNA by the bDNA assay. The GBV-C load ranged from 67,000 copies per milliliter of plasma to 143 million copies per milliliter, with a mean load of 45 million \pm 36 million copies per milliliter (7.28 ± 0.8 log copies per milliliter) for the 162 plasma samples with measurable GBV-C RNA.

A bivariate analysis found a significant inverse correlation between the GBV-C load and the HIV load ($r=-0.33$ [Pearson correlation], $P<0.001$) (Fig. 5) but no correlation between the GBV-C load and the CD4+ cell count ($r=0.1$, $P=0.22$). When we performed this analysis as a partial correlation, controlling for the receipt of highly active antiretroviral therapy and either the CD4+ cell count or the HIV load, we still found a significant correlation between the GBV-C load and the HIV load ($r=-0.22$, $P=0.005$) but no correlation between the GBV-C load and the CD4+ cell count ($r=0.009$, $P=0.91$).

An investigation of the GBV-C load and the HIV load in patients who had started highly active antiretroviral therapy showed an increase in the GBV-C load but a decrease in the HIV load in all patients (data not shown). In contrast, the GBV-C load de-

creased and the HIV load increased in a patient who discontinued highly active antiretroviral therapy (data not shown).

DISCUSSION

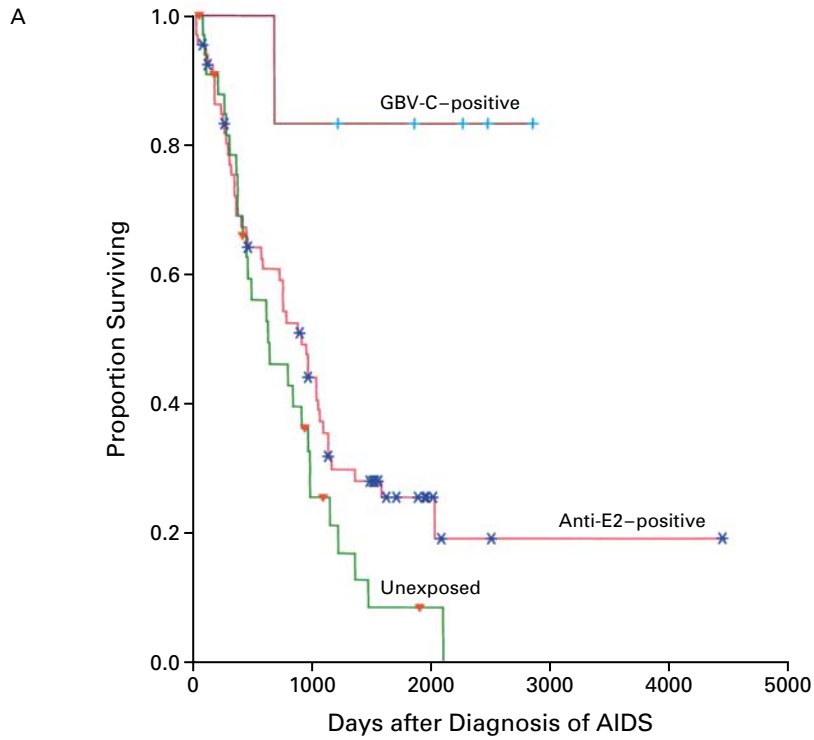
There is considerable debate about the importance of viral coinfection in patients with HIV.²² We attempted to analyze whether the presence of GBV-C infection influences the progression to AIDS or death in HIV-infected patients. In contrast to coinfections with HBV,^{2,3} HCV,^{23,24} or human T-cell lymphotropic virus type I,²⁵ which have an adverse effect on the survival of HIV-infected patients, we found significantly improved survival in association with GBV-C viremia. GBV-C RNA was associated with better survival and slower progression to AIDS in the Kaplan-Meier analysis. Even after highly active antiretroviral therapy had become available in 1996, the presence of GBV-C viremia was associated with better survival. By contrast, coinfection with HCV is associated with poorer survival in patients receiving highly active antiretroviral therapy.²⁵ Similarly, we observed better survival among GBV-C-positive patients even after the development of AIDS, whereas HCV coinfection increases the risk of death among patients in whom AIDS has developed.²

Although the effect of GBV-C infection is still widely debated,^{26,27} most studies of GBV-C in HIV-infected patients have revealed higher CD4+ cell counts in GBV-C-positive patients than in GBV-C-negative patients.²⁸ Furthermore, most studies analyzing the survival of HIV-infected patients in relation to the presence or absence of GBV-C viremia showed longer overall and AIDS-free survival for GBV-C-positive patients^{16-19,29}; the exception was one study that combined patients who tested positive for GBV-C RNA and those who tested positive for anti-E2 into one group.³⁰

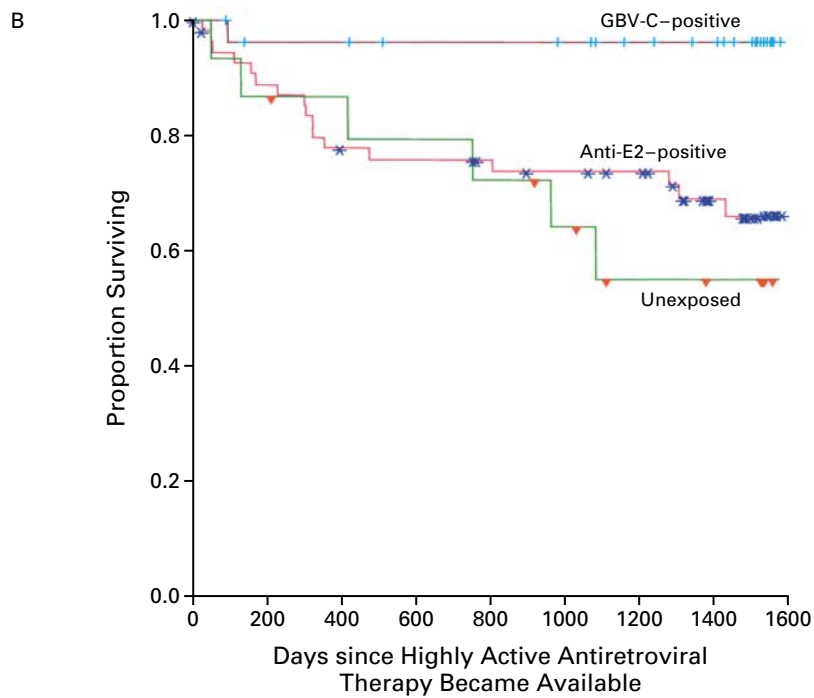
In our study, we found that GBV-C viremia was strongly correlated with longer survival even when known prognostic factors such as age, sex, CD4+ cell count, and CD8+ cell count were included in a multiple regression analysis. We hypothesized that if GBV-C has a beneficial effect on HIV infection, then the GBV-C load should correlate with either higher CD4+ cell counts, because of a mechanism such as the normalization of the half-life of CD4+ cells, or a lower HIV load, because of an inhibition of HIV replication. We found an inverse correlation between

Figure 4 (next page). Survival after the Diagnosis of AIDS and after Highly Active Antiretroviral Therapy 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.



No. AT RISK	0	500	1000	1500	2000	2500	3000	3500	4000	4500
GBV-C-positive	6	6	5	4	3	1	0	0	0	0
Anti-E2-positive	69	38	24	14	5	1	1	1	1	1
Unexposed	36	17	7	2	1	0	0	0	0	0



No. AT RISK	0	400	800	1200	1600
GBV-C-positive	27	22	20	8	
Anti-E2-positive	54	40	36	15	
Unexposed	15	11	8	4	

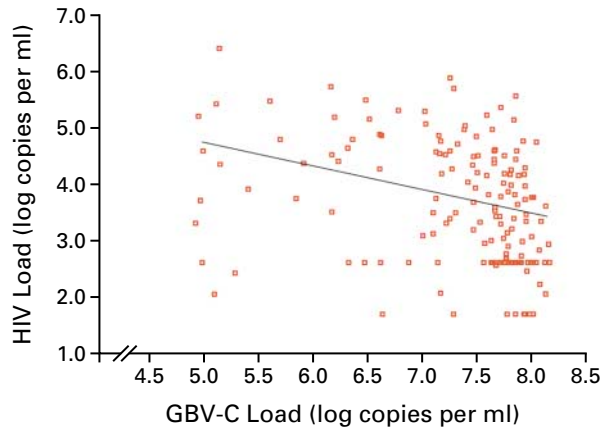


Figure 5. Correlation between the GBV-C Load and the HIV Load.

Analysis of the relation between the HIV load and the GBV-C load revealed a significant inverse correlation between the two variables ($r = -0.33$, $P < 0.001$).

the GBV-C load and the HIV load but no correlation between the GBV-C load and the number of CD4+ cells. This finding suggests that GBV-C may impair HIV replication without causing any disease itself. Interestingly, the GBV-C load increased in all patients who started highly active antiretroviral therapy.

The survival advantage of the anti-E2-positive patients as compared with the unexposed patients might be explained by the previous GBV-C viremia. Thus, patients who have cleared GBV-C probably still benefit from the previous GBV-C infection, which is further reflected by the higher CD4+ cell count in the anti-E2-positive patients than in the unexposed patients.

In addition to the clinical data suggesting an inhibitory effect of GBV-C on HIV replication, Xiang et al., in a study reported elsewhere in this issue of the *Journal*, found reduced HIV replication in cultured peripheral-blood mononuclear cells that were coinfecting with GBV-C.²⁹ Similarly, the inhibition of HIV replication in vitro was recently observed in a study of coinfection with human T-cell lymphotropic virus type II (HTLV-II), in which the coculture of HIV-infected CD4+ cells with HTLV-II-infected CD8+ cells led to a down-regulation of HIV replication.³¹

A dramatic reduction in the HIV load was also observed in patients with acute, symptomatic scrub typhus infection,³² which in itself, however, leads to disease. Nevertheless, these data illustrate that coinfections can down-regulate HIV replication and, especially when the agent is an apparently harmless virus such as GBV-C, may thereby improve the outcome of HIV infection. In view of the benign course of GBV-C infection and its effect on HIV in-

fection, our findings can lead to interesting speculations regarding potential therapeutic consequences.

In conclusion, GBV-C viremia is associated with a decrease in the mortality rate among HIV-infected patients, slower progression to AIDS, and longer survival once AIDS has developed. It is possible that GBV-C infection is a marker for the presence of other factors that result in the slower progression of HIV infection, but we think this effect probably results from an inhibition of HIV replication by GBV-C. The identification of mechanisms by which GBV-C inhibits HIV replication might lead to the development of new therapeutic approaches for HIV infection.

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