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GB virus-C infection in patients infected with the human immunodeficiency virus

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Abstract

Hepatitis virus infections are frequent in patients suffering from HIV infection due to similar transmission routes of these viruses. In addition, hepatitis virus infections lead to impaired survival in HIV positive patients. The recently discovered flavivirus GB virus C (alias Hepatitis G Virus) was initially believed to be another hepatitis virus. While there is still some minor discussion whether GB virus C (GBV-C) plays a role in fulminant hepatic failure, there is no evidence that this virus is responsible for chronic liver disease. Thus this 'orphan virus' still seeks its disease. In this review we concentrate on the published data concerning the co-infection of GBV-C and HIV. By summarizing the studies available, we show evidence for a beneficial influence of GBV-C on HIV infection. Many studies demonstrated a high prevalence of GBV-C infection in HIV positive patients due to its parenteral and sexual transmission. However, in contrast to the expectations, GBV-C does not aggravate the course of patients suffering from HIV infection. Even though not uniformly found, one often sees higher CD4 counts in patients with ongoing GBV-C viral replication. Likewise, a lower viral load appears to be accompanied by the presence of GBV-C RNA in the serum. In addition, longitudinal studies indicate that GBV-C infection slows down the progression to AIDS and eventually to death. GBV-C probably influences HIV infection associated disease by either directly inhibiting HIV replication or enhancing the immune competence to cope with HIV. Still the definitive mechanism how GBV-C could inhibit the progression to AIDS and eventually death needs to be identified. © 2001 Published by Elsevier Science B.V.

Keywords: GBV-C; HGV; HIV; Coinfection; Hepatitis; Survival

Recently, a group of new flavi-like viruses (GB viruses A, B, C and hepatitis G virus) were identified (Simons et al., 1995a,b; Linnen et al., 1996). While GBV A and B were only detected in non-human primates with hepatitis (Schlauder et al., 1995), GB virus C (GBV-C) and hepatitis G virus

Abbreviations: ALT, alanine transaminase; anti-E2, antibody against the envelope 2 protein of GBV-C/HGV; bDNA, branched chain DNA assay; HBV, hepatitis B virus; HCV, hepatitis C virus; anti-HCV, antibody against the hepatitis C virus; GBV-C, GB virus-C/hepatitis G virus (synonymous in this manuscript); HIV, human immunodeficiency virus; PBMC, peripheral blood mononuclear cells; RT-PCR, reverse transcriptase-polymerase chain reaction.

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(HGV) were identified in humans with posttransfusion hepatitis, cryptogenic or acute indeterminate hepatitis (Simons et al., 1995b; Linnen et al., 1996; Fiordalisi et al., 1996) GB virus-C and hepatitis G virus (GBV-C/HGV) are closely related isolates of the same virus with more than 95% sequence homology (Alter, 1996) and high homology with the hepatitis C virus. Still GBV-C/HGV form a distinct group within the flaviviridae family (Linnen et al., 1996), we will subsequently refer in the text to GBV-C. GBV-C is thus a novel flavivirus with a single stranded positive orientated genome of approximately 9400 nucleotides in length (Leary et al., 1996). A striking difference to HCV is the absence of a core within the coding sequence of the GBV-C/HGV genome. However, the absence of a core protein is still a matter of debate, as recent data indicated to presence of a coding sequence upstream of the E1 protein (Xiang et al., 1998).

The initial description of GBV-C led to an enormous enthusiasm to elucidate the association of GBV-C with certain diseases, resulting in over 700 publications. However, although GBV-C was originally identified in patients with documented hepatitis (Simons et al., 1995b; Linnen et al., 1996; Fiordalisi et al., 1996), subsequent studies were unable to prove any influence of GBV-C on chronic liver damage. In a meta-analysis investigating the influence of GBV-C on chronic hepatitis C, including some thousands of patients, we showed that there is no aggravation of the course of hepatitis C by GBV-C co-infection, nor any influence on the response to interferon therapy (Rambusch et al., 1998). Likewise, the course after liver transplantation is not altered by GBV-C infection (Tillmann et al., 1998; Berenguer et al., 1996)

Cases of fulminant hepatic failure have been associated with GBV-C/HGV (Yoshiba et al., 1995; Heringlake et al., 1996), but even this aspect is very much under debate, as many investigators failed to associate GBV-C with a fulminant hepatic failure. As the clinical implication of GBV-C in liver disease is very minor if evident at all (Mushahwar and Zuckerman, 1998), renaming of hepatitis G virus appears appropriate (Lefrere et al., 1999a). Thus referring to the name GB virus C appears appropriate.

An interesting disease to look at for a role of GBV-C is the infection with the human immunodeficiency virus (HIV). First, HIV infections are world wide emerging health problems with an estimated 40 million infected persons. Second, HIV infections are acquired by the parenteral or sexual route, thus co-infections with hepatitis viruses are a common complication of HIV infection (McNair et al., 1992). The prevalence of hepatitis B (up to 90%) (Scharschmidt et al., 1992; Hadler et al., 1991) and hepatitis C (4–94%) (Wright et al., 1994; Quaranta et al., 1994; Dorruci et al., 1992) have been reported to be dependent on individual transmission risk factors in HIV infected patients. Third, the impact of co-infection with hepatitis B or C virus on the outcome of AIDS patients is, although still controversial (Scharschmidt et al., 1992; Wright et al., 1994; Ockenga et al., 1997), associated with an impaired survival. Interestingly, these patients often die from liver failure instead of AIDS. Thus when GBV-C was assumed to be a hepatitis virus, one would expect similar results for the interaction of GBV-C and HIV.

The presence of GBV-C is determined by RT-PCR or a bDNA assay (Nolte, 1998) Past GBV-C infection can be determined by detection of an antibody against the envelope 2 region of GBV-C (anti-E2) (Tacke et al., 1997; Dille et al., 1997). GBV-C RNA and anti-E2 are almost exclusively present in the serum (Nubling et al., 1997)

The prevalence of GBV-C infection in patients with HIV infection has been assessed but few studies have performed a detailed analysis of the clinical influence of GBV-C on the course of HIV infection. Prevalence ranges from as low as 14% (Puig-Basagoiti et al., 2000) to 37% in a study including mainly homosexual men (Lau et al., 1999), and even 45% in a subgroup of 56 i.v. drug addicts (Rey et al., 1999). We and others have previously determined that anti-E2 protects from GBV-C infection (Tillmann et al., 1998). This usually is also true for HIV infected patients, although one case of reinfection or reactivation after loss of anti-E2 has been reported (Devereux et al., 1998). It is important to differentiate such patients with past exposure from those who have ongoing GBV-C infection. In our previous study

on the relevance of GBV-C for HIV infected patients, we find a threefold increased prevalence of anti-E2 (56.8%) compared to GBV-C RNA (16.8%) (Heringlake et al., 1998) in agreement with data in other patient groups (Tillmann et al., 1998). However, other studies in HIV infected patients found anti-E2 approximately only twice (Lefrere et al., 1999b) or a similar frequency (Tassies et al., 1999), although in the overall population GBV-C anti-E2 are approximately two to threefold as frequent as GBV-C RNA. One study even found five times higher prevalence of anti-E2 compared to GBV-C RNA (Tanaka et al., 1998).

Thus, it is evident from the prevalence of GBV-C in the patient population suffering from HIV infection, that it is important to know the consequences of the GBV-C co-infection for HIV infected patients.

Only a few studies have looked at the clinical consequences of GBV-C co-infection in HIV positives. Uniformly, they all confirm the absence of liver disease in relation to GBV-C. GBV-C neither induces nor aggravates hepatitis in these patients (Stark et al., 1999; Lau et al., 1999), similar to what has been reported in hepatitis C virus infected immunocompetent patients (Lau et al., 1999)

When we started analyzing GBV-C in HIV infected patients, we wanted to prove that GBV-C aggravates the course of hepatitis or at least impairs survival. Surprisingly, besides no evidence for hepatitis associated with GBV-C, CD4 counts turned out to be higher in GBV-C positive patients. Even more astonishing was the fact of the prolonged survival of GBV-C positive patients compared to patients with past GBV-C infection or no exposure to GBV-C infection (Heringlake et al., 1998) In agreement with our data a Japanese study demonstrated a significantly lower HIV viral load in GBV-C RNA positive patients compared to GBV-C RNA negatives, and at least a trend for improved survival (Toyoda et al., 1998). Similar data have recently been confirmed by French (Lefrere et al., 1999b), and American colleagues (Yeo et al., 2000). They demonstrated a significantly improved survival, a slower disease progression, slower increase of HIV viral load and a slower drop of CD4 cells in HIV-GBV-C co-infected patients compared to those without GBV-C RNA in their sera. This led us to re-analyze the published data on GBV-C co-infection in HIV infected patients with special attention to studies which include information on CD4 counts in addition to GBV-C RNA status.

Lau et al. (1999) retrospectively analyzed a cohort of 180 mainly male homosexuals, who participated in a trial on zidovudine and interferon in HIV infection, and showed a CD4 cell count of at least 500 cells/μl. They found no influence on liver disease or on HIV progression. However, CD4 cells at follow-up were insignificantly lower in those who lost their GBV-C co-infection compared to those who remained GBV-C RNA positive on the treatment (615 vs. 700 cells/ml; $P = 0.13$, see Table 1). Another study which gave information on CD4 counts, but failed to show significantly different CD4 counts for GBV-C RNA positive and GBV-C RNA negative patients was reported by Woolley et al. (1998) from Chicago IL. In addition, CD8 cells were significantly higher in GBV-C RNA positive patients compared to GBV-C RNA negatives. However, both these studies had selected their patients on the basis of CD4 counts of either above 500 (Lau et al., 1999) or below 200 cells/μl (Yeo et al., 2000). A third study by Goubau et al. (1999) also did not show a significant higher CD4 count in GBV-C RNA positive patients even though they had no specific inclusion criteria apart from being HIV positive.

Three studies show support for a beneficial influence of GBV-C by demonstrating significant association of GBV-C RNA presence in the serum and higher CD4 counts. A study by Hollingsworth et al. (1998) concentrating on the presence of GBV-C in seminal fluid, found GBV-C RNA in the blood of 8/21 patients. Interestingly, they found a CD4 level below 200 cells/μl in only 25% of the GBV-C positives compared to 71% in the GBV-C negative patients ($P = 0.0382$), even though the difference of the mean CD4 values just failed to be significant ($P = 0.067$). In addition, the HIV viral load tended to be lower, but without any evidence for significance. Similarly, a Spanish study by Ibáñez et al. (1998)

found that 51% (30/51) of HIV infected patients with HCV (without other co-infections) had a CD4 count below 200 compared to only 6% (1/17) of HIV infected patients with GBV-C co-infection ($P = 0.002$). Another study was reported by Bonacini et al. (1998) They investigated GBV-C in patients referred for evaluation of hepatitis. They showed that CD4 counts were higher in GBV-C RNA positive patients. This was especially pronounced in those patients without concurrent HBV or HCV infection (see Table 1).

However, there is also conflicting data by a French study, the largest of all, conducted prospectively between December 1996 and May

Table 1
Cross-sectional studies on GBV-C and HIV

N	CD4 counts		HIV load $10(^3)$ copies/ml	Reference
Studies showing no significant association of GBV-C and CD4 counts in HIV infection				
180	CD4 at entry	CD4 at follow-up		Lau et al. (1999)
	GBV-C+723 (mean)	GBV-C+700 (mean)	17.53	
	GBV-C-753 (mean)	Lost GBV-C 615 (mean)	16.3	
192	G+160 (mean)	CD8 853	117	Woolley et al. (1998)
	G-120 (mean)	CD8 682 $P = 0.03$	89	
137, 27 excluded	No GBV-C 277.1 (mean) GBV-C RNA 301.2 (mean) anti-E2 360.5 (mean)			Goubau et al. (1999)
Studies showing a significant association of GBV-C and CD4 counts in HIV infection				
54	CD4>200	Mean CD4	Not given but	Hollingsworth et al. (1998)
	G+75%	approx. 250	tented to be lower in GBV-C '+'	
	G−29% $P = 0.038$	approx. 170, $P = 0.067$		
168	CD4<200 HCV+51% 30/59 HGV+6% 1/17 $P = 0.002$			Ibáñez et al. (1998)
157	All patients	without HCV, HBV		Bonacini et al. (1998)
	GBV-C+159	GBV-C+277		
	GBV-C-87, $P = 0.03$	GBV-C-29		
Studies showing no significant association of GBV-C and CD4 counts in HIV				
		GBV-C RNA prevalence according to HIV-stage		
397, 18 excluded	CD4			
	>500 G 29.2% (40/137)	A: 48/136 (35.3%)		Rey et al. (1999)
	>200 G 45.4% (79/174)	B: 76/196 (38.8%)		
	<200 G 35.3% (24/68)	C: 19/47 (40.4%)		
	$P = 0.012$[a]	$P = 0.75$		

[a] CD>200: 119/311 (38.3%) vs. 35.3%. CD500>40/137 vs. 103/242 (42.6%).

1997 including 397 HIV positive consecutive HIV infected patients. They showed a slightly higher frequency of GBV-C in patients with AIDS compared to those without AIDS. In addition they found the lowest rate of GBV-C RNA in the group of patients with a CD4 count above 500 cells/μl (Rey et al., 1999). However, one can evaluate the given data differently. If patients with CD4 cells above 200 are compared to those with CD4 cells below 200 cells/μl the rate of GBV-C infection is slightly higher in those with a CD4 count above 200 cells/μl (CD > 200 119/311 (38.3%) vs. 24/68 (35.3%) if CD4 < 200 cells/μl. Furthermore, that study was performed between 1996 and 1997, when highly active retroviral therapy (HAART) was already introduced.

Thus interpreting the given studies indicates, as highlighted by the longitudinal studies, that GBV-C leads to an improved survival (Heringlake et al., 1998; Lefrere et al., 1999b; Toyoda et al., 1998). One study from Sabin et al. (1998), not cited above, showed no such improved survival, but they studied GBV-C RNA and anti-E2 positive patients as one group. This appears inadequate as the influence of ongoing GBV-C infection would probably be different from past infection.

Also the cross-sectional studies evaluating only CD4 values from one visit without survival analysis tend to indicate a beneficial effect of GB virus C on HIV associated disease.

One possible explanation would be a direct viral interaction between GBV-C and HIV. This aspect is supported by three findings. First, a study analyzing the HIV load in hemophiliacs showed a significantly lower HIV viral load in patients with GBV-C RNA, compared to those without GBV-C RNA presence in the blood (Toyoda et al., 1998). This is further supported by our finding of a reciprocal correlation of GBV-C viral load and HIV viral load (Tillmann et al., 2001). Second, one longitudinal study showed a slower increase of HIV viral load during the course of infection in GBV-C RNA positive patients compared to those without GBV-C RNA (Lefrere et al., 1999b). A third argument depends on a few assumptions. These would be that GBV-C really has a core protein, as recently stated (Xiang et al., 1998), and that this core protein displays similar features like the HCV core protein, which was shown to repress the HIV long terminal repeat (LTR) induced basal transcription (Ray et al., 1995; Srinivas et al., 1996) With respect to the structural homology of HCV and GBV-C, the existence of a similar molecular interaction between GBV-C and HIV has to be investigated. To understand the observed phenomena, further in vitro studies as well as further in vivo studies with analysis of sequential serum samples should be performed.

Besides the improved survival of GBV-C RNA positive patients, another argument for a beneficial effect of GBV-C for patients with HIV infection comes from the data indicating that the presence of GBV-C usually correlates with higher CD4 counts. Thus, assuming that CD4 cells counts are positively correlated with the presence of GBV-C, a possible mechanism of how GBV-C influences HIV disease might be due to an enhanced generation of CD4 cells without leading to an exhaustion of the CD4 cell pool. Similar effects have been reported in patients under highly active anti-retroviral therapy (HAART) (Hellerstein et al., 1999)

However, we shall exclude that the correlation of GBV-C and CD4 counts is just due to major replication of GBV-C in CD4 cells, as this would explain the significant depletion of GBV-C positive patients in AIDS patients. In this case we would estimate to frequently detect viral negative strand RNA as a replication intermediate in lymphocytes of GBV-C positive patients. We have investigated three available PBMC samples of GBV-C positive patients and detected genomic but not minus-stranded viral RNA in the isolated PBMCs by RT-PCR using gene-specific antisense or sense primer for cDNA synthesis (Heringlake et al., 1998) similar to other data (Seipp et al., 1996). Additionally, we were able to detect GBV-C in the serum of a patient with less than 10 CD4 cells/μl. However, presence of GBV-C minus-strand RNA was recently shown in PBMCs from immunosuppressed patients (Kobyashi et al., 1999). In addition it has been shown, that an effective infection of cultivated lymphocytes is possible, and it was even possible to detect the

minus strand for up to 30 days (Fogeda et al., 1999).

A recent study excluded down-regulation of CD4, CCR5 or CXCR4 receptor expression on the cell surface as a factor for reduced susceptibility for HIV infection (Xiang et al., 2001).

Even though the definitive mechanism remains to be elucidated, there is strong evidence for a beneficial influence of GBV-C infection on HIV infection. Still, one can currently not rule out that GBV-C is just an innocent bystander for another yet unidentified agent influencing the outcome of HIV infection.

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References

Alter, H., 1996. The cloning and clinical implications of HGV and GBV-C. N. Engl. J. Med. 334, 1536.

Berenguer, M., Terrault, N.A., Piatak, M., Yun, A., Kim, J.P., Lau, J.Y., et al., 1996. Hepatitis G virus infection in patients with hepatitis C virus infection undergoing liver transplantation. Gastroenterology 111, 1569–1575.

Bonacini, M., Qian, D., Govindarajan, S., Valinluck, B., 1998. Prevalence of hepatitis G virus RNA in the sera of patients with HIV infection. J. Acquir. Immune Defic. Syndr. Hum. Retrovirol. 19, 40–43.

Devereux, H., Sabin, C.A., Kinson, Z., Brown, D., Griffioen, A., Dusheiko, G.M., et al., 1998. Influence of HIV-1 infection on GBV-C infection in multiply infected haemophilic patients. J. Med. Virol. 56, 316–320.

Dille, B.J., Surowy, T.K., Gutierrez, R.A., Coleman, P.F., Knigge, M.F., Carrick, R.J., et al., 1997. An Elisa for detection of antibodies to the E2 protein of GB virus C. J. Infect. Dis. 175, 458–461.

Dorruci, M., Pezzotti, P., Phillips, A.N., Lepri, A.C., Rezza, G., 1992. Coinfection of hepatitis C virus with human immunodeficiency virus and progression to AIDS. J. Infect. Dis. 172, 1503–1508.

Fiordalisi, G., Zanella, I., Mantero, G., Bettinardi, A., Stellini, R., Paraninfo, G., et al., 1996. High prevalence of GB virus C infection in a group of Italian patients with hepatitis of unknown etiology. J. Infect. Dis. 174, 181–183.

Fogeda, M., Navs, S., Martin, J., Casqueiro, M., Rodriguez, E., Arocena, C., et al., 1999. In vitro infection of human peripheral blood mononuclear cells by GB virus C/hepatitis G virus. J. Virol. 73, 4052–4061.

Goubau, P., Liu, H.F., Goderniaux, E., Burtonboy, G., 1999. Influence of CD4+ lymphocyte counts on GB virus C/hepatitis G virus carriership in HIV-positive individuals. J. Med. Virol. 57, 367–369.

Hadler, S.C., Judson, F.N., O'Malley, P.M., Altman, N.L., Penley, K., Buchbinder, S., et al., 1991. Outcome of hepatitis B virus infection n homosexual men and its relation to prior human immunodeficiency virus infection. J. Infect. Dis. 163, 454–459.

Hellerstein, M., Hanley, M.B., Cesar, D., Siler, S., Papageorgopoulos, C., Wieder, E., et al., 1999. Directly measured kinetics of circulating T lymphocytes in normal and HIV-1-infected humans. Nat. Med. 5, 83–89.

Heringlake, S., Osterkamp, S., Trautwein, C., Tillmann, H.L., Boker, K., Muerhoff, S., et al., 1996. Association of a certain strain of GBV-C with fulminant hepatic failure. Lancet 348, 1626–1629.

Heringlake, S., Ockenga, J., Tillmann, H.L., Trautwein, C., Meissner, D., Stoll, M., et al., 1998. GB virus C/hepatitis G virus infection: a favorable prognostic factor in human immunodeficiency virus-infected patients? J. Infect. Dis. 177, 1723–1726.

Hollingsworth, R.C., Jameson, C.L., Minton, J.E., Crowe, M., Curran, R., Rowe, T., et al., 1998. GBV-C/HGV coinfection in HIV-1-positive men: frequent detection of viral RNA in blood plasma but absence from seminal fluid plasma. J. Med. Virol. 56, 321–326.

Ibáñez, A., Gimenez-Barcons, M., Tajahuerce, A., Tural, C., Sirera, G., Clotet, B., et al., 1998. Prevalence and genotypes of GB virus C/hepatitis G virus (GBV-C/HGV) and hepatitis C virus among patients infected with human immunodeficiency virus: evidence of GBV-C/HGV sexual transmission. J. Med. Virol. 55, 293–299.

Kobyashi, M., Tanaka, E., Makayama, J., Furuwatari, C., Katsuyama, T., Kawasaki, S., et al., 1999. Detection of GB virus C/hepatitis G virus genome in peripheral blood mononuclear cells and liver tissue. J. Med. Virol. 57, 114–121.

Lau, D.T., Miller, K.D., Detmer, J., Kolberg, J., Herpin, B., Metcalf, J.A., et al., 1999. Hepatitis G virus and human immunodeficiency virus coinfection: response to interferon-alpha therapy. J. Infect. Dis. 180, 1334–1337.

Leary, T.P., Muerhoff, A.S., Simons, J.N., Pilot-Matias, T.J., Erker, J.C., Chalmers, M.L., et al., 1996. Sequence and genomic organisation of GBV-C: a novel member of the flaviviridae associated with human non A-E hepatitis. J. Med. Virol. 48, 60–67.

Lefrere, J.J., Roudot-Thoraval, F., Morand-Joubert, L., Brossard, Y., Parnet-Mathieu, F., Mariotti, M., et al., 1999a. Prevalence of GB virus type C/hepatitis G virus RNA and of anti-E2 in individuals at high or low risk for blood-borne or sexually transmitted viruses: evidence of sexual and parenteral transmission. Transfusion 39, 83–94.

Lefrere, J.J., Roudot-Thoraval, F., Morand-Joubert, L., Petit, J.C., Lerable, J., Thauvin, M., et al., 1999b. Carriage of

GB virus C/hepatitis G virus RNA is associated with a slower immunologic, virologic, and clinical progression of human immunodeficiency virus disease in coinfected persons. J. Infect. Dis. 179, 783–789.

Linnen, J., Wages, J., Zhang-Keck, Z.Y., Krawczynski, K.Z., Alter, H., Koonin, E., et al., 1996. Molecular cloning and disease association of hepatitis G virus: a transfusion-transmissible agent. Science 271, 505–508.

McNair, A.N., Main, J., Thomas, H.C., 1992. Interactions of the human immunodeficiency virus and the hepatotropic viruses. Semin. Liver Dis. 12, 188–196.

Mushahwar, I.K., Zuckerman, J.N., 1998. Clinical implications of GB virus C. J. Med. Virol. 56, 1–3.

Nolte, F.S., 1998. Branched DNA signal amplification for direct quantitation of nucleic acid sequences in clinical specimens. Adv. Clin. Chem. 33, 201–235.

Nubling, C.M., Bialleck, H., Fursch, A.J., Scharrer, I., Schramm, W., Seifried, E., et al., 1997. Frequencies of GB virus C/hepatitis G virus genomes and of specific antibodies in German risk and non-risk populations. J. Med. Virol. 53, 218–224.

Ockenga, J., Tillmann, H.L., Trautwein, C., Stoll, M., Manns, M.P., Schmidt, R.E., 1997. Hepatitis B and C in HIV-infected patients: prevalence and prognostic value. J. Hepatol. 27, 18–24.

Puig-Basagoiti, F., Cabana, M., Guilera, M., Gimenez-Barcons, M., Sirera, G., Tural, C., et al., 2000. Prevalence and route of transmission of infection with a novel DNA virus (TTV), hepatitis C virus, and hepatitis G virus in patients infected with HIV. J. Acquir. Immune. Defic. Syndr. 23, 89–94.

Quaranta, J.F., Delaney, S.R., Alleman, S., Cassuto, J.P., Dellamonica, P., Allain, J.P., 1994. Prevelance of antibody to hepatitis C virus (HCV) in HIV-1-infected patients. J. Med. Virol. 33, 177–180.

Rambusch, E.G., Wedemeyer, H., Tillmann, H.L., Heringlake, S., Manns, M.P., 1998. Significance of coinfection with hepatitis G virus for chronic hepatitis C — a review of the literature. Z. Gastroenterol. 36, 41–53.

Ray, R.B., Lagging, L.M., Meyer, K., Steele, R., Ray, R., 1995. Transcriptional regulation of cellular and viral promoters by the hepatitis C virus core protein. Virus Res. 37, 209–220.

Rey, D., Fraize, S., Vidinic, J., Meyer, P., Fritsch, S., Labouret, N., et al., 1999. High prevalence of GB virus C/hepatitis G virus RNA in patients infected with human immunodeficiency virus. J. Med. Virol. 57, 75–79.

Sabin, C.A., Devereux, H., Kinson, Z., Griffioen, A., Brown, D., Dusheiko, G., Lee, C.A., 1998. Effect of coinfection with hepatitis G virus on HIV disease progression in hemophilic men. J. Acquir. Immune. Defic. Syndr. Hum. Retrovirol. 19, 546–548.

Scharschmidt, B.F., Held, M.J., Hollander, H.H., Read, A.E., Lavine, J.E., Veereman, G., et al., 1992. Hepatitis B in patients with HIV infection: relation to AIDS and patient survival. Ann. Intern. Med. 117, 837–838.

Schlauder, G.G., Dawson, G.J., Simons, J.N., Pilot-Matias, T.J., Gutierrez, R.A., Heynen, C.A., et al., 1995. Molecular and serologic analysis in the transmission of the GB hepatitis agents. J. Med. Virol. 46, 81–90.

Seipp, S., Wahl, R., Selzer, S., Müller, H.M., Stremmel, W., Goeser, T., et al., 1996. Prevalence of GB-C virus positive and negative strand RNA in human peripheral blood mononuclear cells of GBV-C infected and coinfected patients. Hepatology 24, 288A.

Simons, J.N., Pilot-Matias, T.J., Leary, T.P., Dawson, G.J., Desai, S.M., Schlauder, G.G., et al., 1995a. Identification of two flavivirus-like genomes in the GB hepatitis agent. Proc. Natl. Acad. Sci. USA 92, 3401–3405.

Simons, J.N., Leary, T.P., Dawson, G.J., Pilot-Matias, T.J., Muerhoff, A.S., Schlauder, G.G., et al., 1995b. Isolation of novel virus-like sequences associated with human hepatitis. Nat. Med. 1, 564–569.

Srinivas, R.V., Ray, R.B., Meyer, K., Ray, R., 1996. Hepatitis C virus core protein inhibits human immunodeficiency virus type 1 replication. Virus Res. 45, 87–92.

Stark, K., Doering, C.D., Bienzle, U., Pauli, G., Hamouda, O., Engel, A.M., et al., 1999. Risk and clearance of GB virus C/hepatitis G virus infection in homosexual men: A longitudinal study. J. Med. Virol. 59, 303–306.

Tacke, M., Kiyosawa, K., Stark, K., Schlueter, V., Ofenloch-Haehnle, B., Hess, G., et al., 1997. Detection of antibodies to a putative hepatitis G virus envelope protein. Lancet 349, 318–320.

Tanaka, E., Tacke, M., Kobayashi, M., Nakatsuji, Y., Kiyosawa, K., Schmolke, S., et al., 1998. Past and present hepatitis G virus infection in areas where hepatitis C is endemic and those where it is not endemic. J. Clin. Microbiol. 36, 110–114.

Tassies, D., Magallon, M., Quintana, M., Fernandez-Urgelles, R.P., Rodriguez-Pinto, C., Tusell, J., et al., 1999. Hepatitis G virus infection markers (RNA and anti-E2 antibodies) in a multicenter cohort of hemophiliacs. Haematologica 84, 930–936.

Tillmann, H.L., Heringlake, S., Trauwein, C., Meissner, D., Nashan, B., Schlitt, H.J., et al., 1998. Antibodies against the GB virus C envelope 2 protein before liver transplantation protect against GB virus C de novo infection. Hepatology 28, 379–384.

Tillmann, H.L., Heiken, H., Knapile-Botor, A., Heringlake, S., Ockenga, J., Wilber, J., et al., 2001. Infection with GB virus C and reduced mortality among HIV infected patients. N. Engl. J. Med. 345, 715–724.

Toyoda, H., Fukuda, Y., Hayakawa, T., Takamatsu, J., Saito, H., 1998. Effect of GB virus C/hepatitis G virus coinfection on the course of HIV infection in hemophilia patients in Japan. J. Acquir. Immune. Defic. Syndr. Hum. Retrovirol. 17, 209–213.

Woolley, I., Valdez, H., Walker, C., Landay, A., Zdunek, D., Hess, G., et al., 1998. Hepatitis G virus RNA is common among AIDS patients' plasma but is not associated with abnormal liver function tests or other clinical syndromes. J. Acquir. Immune. Defic. Syndr. Hum. Retrovirol. 19, 408–412.

Wright, T.L., Hollander, H., Pu, X, Held, M.J., Lipson, P., Quan, S., et al., 1994. Hepatitis C in HIV-infected patients with and without AIDS: prevalence and relationship to patient survival. Hepatology 20, 1152–1155.

Xiang, J., Klinzman, D., McLinden, J., Schmidt, W.N., LaBrecque, D.R., Gish, R., et al., 1998. Characterization of hepatitis G (GB-C Virus) particles: evidence for a nucleocapsid and expression of sequences upstream of the E1 protein. J. Virol. 72, 2738–2744.

Xiang, J., Wünschmann, S., Diekema, D.J., Klinzman, D., Patrick, K.D., Georg, S.L., et al., 2001. Effect of coinfection with GB virus C on survival among patients with HIV infection. N. Engl. J. Med. 345, 707–714.

Yeo, A.E.T., Matsumoto, A., Hisada, M., Shih, J.W., Alter, H.J., Goedert, J.J., 2000. Effect of hepatitis G virus infection on progression of HIV infection in patients with hemophilia. Multicenter Hemophilia Cohort Study. Ann. Intern. Med. 132, 959–963.

Yoshiba, M., Okamoto, H., Mishiro, S., 1995. Detection of the GBV-C hepatitis virus genome in serum from patients with fulminant hepatitis of unknown etiology. Lancet 346, 1131–1132.