Almost one century ago, in 1917, the Austrian neurologist Julius Wagner von Jauregg was able to obtain improvement in patients with late stage symptomatic neurosyphilis, by infecting them with the malaria parasite. This approach might appear strange to physicians in the contemporary era of antimicrobial treatment. However, at that time it was by far the most effective option and it earned its discoverer the Nobel Prize for Medicine in 1927. Thus, even an infection with obligatory pathogens may result in harm reduction under certain conditions.

GB virus C is a flavivirus that is closely related to hepatitis C virus. The name GB virus stems from early experiments on the transmission of acute hepatitis from humans to marmoset monkeys. One of the first source patients had the initials "G.B." and was a 34-year old colleague of the author of the experiment (Deinhardt 1967). Later on, two hepatotropic viruses, GB virus A (GBV-A) and GB virus B (GBV-B), were isolated from these monkeys. Two independent research groups simultaneously discovered the related GB virus C (GBV-C) in humans with hepatitis in the middle of the 1990s. Subsequently, the GB virus C has promoted the discussion as to whether the natural course of HIV infection might be modulated in a favorable way by this particular coinfection. In addition, because GBV-C was first found in humans with hepatitis, and due to its close relationship to the hepatitic GBV-A and GBV-B viruses, GBV-C was also called "hepatitis G virus (HGV)" by one research group. This name should no longer be used, because it has since been shown that GBV-C neither causes hepatitis nor worsens preexisting hepatitis (Berenguer 1996, Tillmann 1998, Rambusch 1998, Stark 1999). In fact, GBV-C is not a hepatotropic but a lymphotropic virus. Despite intensive research, GBV-C has not been shown to cause any other known disease.

The virus is frequently found in humans: approximately 10 to 30 % of blood donors have specific antibodies against GBV-C and up to 5 % of them show GBV-C virus replication. Assuming that the virus is apathogenic, affected individuals are not excluded from the donation of blood and consequently, serological diagnostics on GBV-C are not routinely performed. Two serological markers for GBV-C infection exist; GBV-C viremia is determined using a PCR method; and antibodies to the envelope region E2 (anti-E2) are detected by ELISA. As they are mutually exclusive, either GBV-C viremia or the presence of anti-E2 is detectable in GBV-C infected individuals. In most cases, GBV-C viremia is transient and ends with seroconversion to anti-E2, resulting in immunity to new infections. However, this does not seem to be a lifelong immunity (Table 1). Transmission of GBV-C occurs parenterally and mucosally, thus similar to HIV, HBV and HCV infections.

Is GBV-C a friendly virus?

The first report of decreased HIV disease progression and mortality in GBV-C coinfected patients was from a German monocentric study, published in 1998. Initially, these results did not draw much attention, although they were confirmed by Australian and American working groups (Toyoda 1998, Heringlake 1998). In 2001, two
larger studies with a longer follow-up again showed a favorable prognosis for HIV-infected individuals with GBV-C viremia (Tillmann 2001, Xiang 2001). These results encountered considerable resonance in the international press – and articles in some newspapers reported in a vociferous manner a "miracle virus, which stops AIDS". As a consequence, some patients requested sources of supply for GB virus C from their physicians and wanted to infect themselves with it. In summary, the GBV-C story became involuntarily discredited by a couple of simplified and unscientific reports in the secondary literature. Concomitantly, a controversial discussion of the data started within the scientific community. In recent years, however, several studies have focused on the influence of GBV-C status on surrogate markers and clinical progression in HIV infection.

<table>
<thead>
<tr>
<th>Marker</th>
<th>GBV-C-Viremia (RNA)</th>
<th>Anti-E2-Antibodies</th>
</tr>
</thead>
<tbody>
<tr>
<td>GBV-C negative</td>
<td>negative</td>
<td>negative</td>
</tr>
<tr>
<td>Replicative GBV-C Infection</td>
<td>positive</td>
<td>negative</td>
</tr>
<tr>
<td>Past GBV-C Infection</td>
<td>negative</td>
<td>positive</td>
</tr>
</tbody>
</table>

The heterogeneity of the HIV/GBV-C coinfected cohorts is a major methodical problem in an attempt to compare the results from the different studies published recently. Some studies did not follow up the status of the GBV-C viremia longitudinally. The serological status of GBV-C, however, can change over time, and the distinction between the three possible stages of GBV-C serostatus is crucial for the interpretation of the studies (see table 1). Overall, it is agreed that there is no difference between the clinical course of HIV-infected individuals without contact to the GB virus C (GBV-C negative) and those with cleared GBV-C infection (anti-E2-positive). But GBV-C viremia (GBV-C RNA positive) is prolonged in HIV infection and persistent GBV-C RNA positive patients differ from the non-viremic subgroups in the majority of studies: in four studies from the pre-HAART era, GBV-C RNA positive patients revealed less rapid progression of clinical disease, lower death rates, smaller reduction in CD4 T cells, reduced increase in HIV plasma viremia, and improved quality of life – in comparison with HIV-infected individuals without GBV-C viremia (Toyoda 1998, Heringlake 1998, Yeo 2000, Xiang 2001). These observations were confirmed in several studies from the HAART era (Tillmann 2001, Nunnari 2003, Williams 2004, Tillmann 2004). The effects were more pronounced in studies with longer follow-up periods.

However, some studies – partially with considerable follow-up time – could not find an effect of GBV-C viremia on HIV infection (Sabin 1998, Birk 2002, Bjorkman 2004, Kaye 2005, Williams 2005). One of these studies summarized GBV-C viremic and anti-E2-positive patients as GBV-C positive group (Sabin 1998), but exclusively the GBV-C RNA positive HIV-coinfected subgroup differed in clinical outcome in the other studies. Two studies (Kaye 2005, Williams 2005) were performed in women, so that a possible gender specific modulating effect of GBV-C on HIV could not be ruled out. In contrast to that hypothesis is one study investigating the GBV-C status in HIV-infected pregnant women (Handelsman 2006). The authors found a lower HIV viral load in GBV-C viremic women and less vertical
transmission of HIV from mother to child in the HAART era but not in the pre-HAART era.

Another conflicting result came from a recently published study (van der Bij 2005), which showed a more unfavorable course of HIV infection, using clinical and surrogate markers, for patients that were GBV-C viremic at the time of inclusion in the study. However, during follow up, this study also found a reduced mortality for those patients with a persisting GBV-C RNA (over years). Thus, this investigation again agrees with results from studies, which demonstrated a more favorable course for GBV-C RNA positive HIV-coinfected patients: in some of these studies the GBV-C seroconverters, who switched during the follow-up from GBV-C RNA positive status to anti-E2 positivity had a particularly worse prognosis (Williams 2004, Bjorkman 2004).

Several studies have described more pronounced antiretroviral and immunological effects of antiretroviral therapy in HAART-treated GBV-C RNA positive patients. However, other studies did not find these differences. But no study to date describes a negative influence of GBV-C viremia on the effect of HAART.

Therefore, to summarize the various cohort studies it could be cautiously concluded that a favorable clinical course of HIV infection in GBV-C RNA positive patients may be restricted to males and to those patients with ongoing GBV-C replication. However, it should be taken into account that, until now, most studies were retrospective and performed in only a few centers. Therefore, at present, it cannot be completely excluded that the association between GBV-C viremia and ameliorated HIV infection is at least in part biased by other factors.

The fundamental chicken-egg dilemma still remains unsolved: whether GBV-C viremia is an epiphenomenon or a cause for the different outcomes of HIV infection is not yet clear.

Some authors favor the explanation that GBV-C viremia is an epiphenomenon of higher CD4+ T-cell counts. GBV-C replicates predominantly in CD4 T-lymphocytes and therefore it could be expected that the level of GBV-C viremia decreases if the helper T-cell counts drop (van the Bij 2005). This hypothesis, however, does not explain why HIV-infected patients should not be able to induce the CD4+ T-cell dependent specific humoral immune response against the E2 envelope protein of GBV-C with high CD4+ T-cell levels and how they are later able to do so with an impaired immunity. Initial evidence for a causal role of GBV-C came from in vitro experiments on GBV-C and HIV coinfected cell cultures (Xiang 2001). HIV replication in the cultured cells was decreased when the cells had been infected with GBV-C prior to HIV, but HIV replication remained on the same level when the cells were infected with GBV-C afterwards.

**Does the knowledge about GBV-C have any practical use?**

The microbial zoo of pathogens of infectious diseases is crawling with lots of horrifying micro monsters, which can cause dreadful illnesses. In this frightening environment, the description of the little viral Tamagochi named GBV-C, which does not hurt its host and perhaps is able to protect him and to reduce harm caused by
another infection, would be a nice fable. But beyond the tales of a potentially healthy infection at least four questions are still open:

1. Does chronic GBV-C replication itself cause the reduced progression of HIV infection, or is the continuous GBV-C replication a secondary epiphenomenon, which is particularly frequent when HIV infection has a favorable clinical course for other reasons?

2. If GBV-C should play a causal role, on which pathophysiological mechanisms is this based?

3. If we were able to define the pathways of GBV-C-associated modulation of HIV disease, how could we translate them into new therapeutic approaches?

And last, but not least whilst this issue remains unsolved:

4. If persisting GBV-C viremia slows down the progression of an HIV coinfection, how can we maintain a durable replication of GBV-C in these patients?

We know that most humans develop anti-E2 antibodies soon after an infection with GBV-C and, at this time, GBV-C replication ends irreversibly. We also experienced that this E2 seroconversion, in the case of an HIV coinfection, is associated with a more rapid progression of HIV disease (Williams 2004, Bjorkman 2004). Until now, little has been known about the factors relevant for maintenance or termination of GBV-C replication. But, GBV-C replication can be durably terminated by interferon therapy, e.g. treatment of chronic hepatitis C. Although the question remains unsettled as to whether the clearance of GBV-C viremia induced by interferon therapy will have the same impact on the course of HIV infection as the observed cases of spontaneous clearance, this issue is of potential impact for counseling in HIV, HCV, and GBV-C coinfection. Therefore, there is at least a need for screening for GBV-C serostatus, individual counseling and a prospective follow-up during interferon therapy in controlled studies.

Proposed pathomechanisms

A couple of immunomodulatory or antiviral mechanisms can be induced by GBV-C and may play an interacting role with HIV coinfection: in GBV-C-infected peripheral blood cells decreased expression of chemokine receptors (CCR5 and CXCR4) has been found on the surface of CD4+ and CD8+ T-cells. A potential pathomechanism for this down-regulation of chemokine receptors is the E2-protein-induced release of RANTES from T lymphocytes by its binding to the CD81 receptor (Tillmann 2002, Nattermann 2003, Xiang 2004). Chemokine receptors are targets for HIV. Therefore, a result of decreased chemokine receptor expression is a decrease in HIV replication. Surprisingly, anti-E2 antibodies were also able to inhibit HIV replication in vitro (Xiang 2006b), which is in contrast to the observation that anti-E2 seroconversion accelerates the clinical HIV progression. Another study showed that a peptide consisting of a 69-amino acid subunit from NS5A (which is a viral protein from GBV-C) was able to induce RANTES in vitro and therefore down-regulates HIV replication (Xiang 2006a). Complex disturbances of the cytokine profile have been described in HIV-infected individuals in vivo, but are less prevalent in individuals with GBV-C/HIV coinfection (Nunnari 2003). Focusing on the innate immunity, normalized levels of CD69 (Fas-ligand) could be demonstrated on NK cells and were less pronounced on lymphocytes in GBV-C viremic HIV-
infected individuals, resulting in down-regulation of apoptosis (Mönkemeyer 2006). In addition, further direct and indirect mechanisms of GBV-C or its components on HIV replication have been described. Contradictory extents of some effects of GBV-C on HIV in different cohorts could be due to different levels of lymphotropism of different GBV-C genotypes or to host-related factors.

The history of GBV-C, as well as that of HIV, is still young. The near future will bring further insight into possible mechanisms of HIV and GBV-C interaction and the roles that individual-specific host factors play. At present, GBV-C gives us the opportunity to obtain insight into clinically relevant regulation pathways of HIV. This could help us in the development of new therapeutic concepts prior to, or in addition to, HAART. Presumably, these concepts could be promising with respect to their clinical and therapeutic impact, because, in several studies, a benefit of GBV-C replication remained evident under HAART.

References


