HIV and hepatitis G virus/GB virus C co-infection: beneficial or not?

The independently discovered human viruses GB virus C (GBVC)[1] and hepatitis G virus (HGV)[2] are two isolates of the same single-stranded RNA virus. The viral genome is approximately 9·4 kb long and is of positive polarity. The two isolates have high similarity, sharing 85% of nucleotides and having 95% aminoacid sequence identity.[3] The RNA is translated into a single polyprotein of about 3000 aminoacid residues. HGV shows characteristics of a flavivirus-like genome, closely related to hepatitis C virus (HCV).

HGV is widely spread as a result of blood transfusions and sexual transmission. The virus infects lymphocytes, but not hepatocytes. There is no conclusive evidence for a causal link between HGV and either acute or chronic liver disease—HGV remains an "orphan virus looking for a disease".

Recent publications[4–12] have stimulated a vigorous debate about the role of HGV co-infection—natural or intentional—in HIV-infected people, with some reports finding that co-infection prolonged survival of patients and served as a potentially effective treatment.[4–8] However, other authors see these claims as being premature[9] and contest the findings.[10–12]

The Multicenter AIDS Cohort Study (MACS),[10] which involved a large cohort of homosexual men with established dates of HIV-1 seroconversion, concluded that HGV RNA persistence did not affect the end points tested. Nevertheless, an association between HGV RNA loss and faster HIV-1 disease progression was consistently found. The authors hypothesised that HGV RNA persistence was dependent on the presence of sufficient numbers of CD4+ cells and the decrease of these cells associated with HIV-1 disease progression was a cause, not a consequence, of HGV RNA loss.

HGV is thought to replicate in CD4+ lymphocytes, which may be the sole cell type bearing the receptor targets for anchoring HGV RNA to permit replication.[11] We suggest that as HIV-1 infection progresses and CD4+ cell numbers fall, the sites for anchoring HGV RNA, when gradually diminished, are insufficient for maintaining replication. Another study[12] concluded that the presence of HGV RNA at diagnosis of HIV-1 infection cannot be used as a predictor of favourable disease course in patients not receiving combination antiretroviral therapy.

Authors claiming that co-infection with HGV is beneficial interpret the MACS data differently, claiming that (1) the participants who were HGV RNA-positive at the late visit were 2·78 times more likely to survive than those who were HGV RNA-negative,[7] and (2) the MACS data confirmed that prolonged HGV viraemia was highly predictive of prolonged survival among HIV-positive individuals.[7] However, the authors give no direct quantitative molecular evidence that HGV is causally related to improved survival.

Curiously, no benefit from co-infection with HGV was found in a cohort of African women with HIV-1 or HIV-2, although sex-based differences in T-lymphocyte responses in HIV-1-seropositive individuals may generally exist.[13] A small study on HGV infection in children with perinatal HIV infection showed that there was no evidence of improved HIV disease outcome in co-infected patients, but the number of HIV/HGV co-infected children was small.[14]

Perhaps HGV infection is not the reason that HIV-positive people live longer but, rather, it is a marker of another factor related to HIV disease progression. An inverse correlation between the titres of HGV RNA and HIV-1 RNA has been reported.[5] Based on a co-infection model, HGV may influence HIV disease by inhibiting HIV by inducing chemokines, down-regulating HIV co-receptor(s), influencing cytokine profiles, and other as yet undefined effects on the host lymphocytes.[4,8] In this context, it is noteworthy that—unlike the related HCV—HGV viraemia persists in only a minority of individuals exposed, and there is a strong tendency towards viral clearance over time. Once cleared, HGV RNA never reappears, and no new HGV infections were observed in 61 injection drug users who were positive for HGV antibodies followed for 382 person-years, even though all had ongoing drug abuse.[15] Might this finding imply that HGV infection does not persist long enough to modulate HIV infection?

The lessons learnt from the therapy of patients with acute and chronic viral hepatitis co-infected with the infectious bursal disease virus (IBDV)[16] may be helpful in

reconciling the conflicting views. The safety and efficacy of IBDV co-infection therapy were reported in 42 patients with acute hepatitis B virus (HBV) or HCV infection in a phase II clinical trial. The encouraging evidence was that progression to chronic infection was marginally better in IBDV-treated patients than in the controls. More importantly, the IBDV therapy was also effective in four decompensated chronic hepatitis patients (two with HBV, and two with HCV), who went into long-lasting remission or were stabilised with striking clinical improvement.[16–18] It also emerged that it was necessary to administer continuous large doses of the viral preparation over a long period to ensure maintenance of "artificial viraemia" by IBDV, which is not known to infect human beings naturally.

Establishing whether co-infection with HGV in HIV-infected individuals is beneficial[4–8] or not[10–13] requires exactly similar methods and analyses. We urge great caution about drawing rash conclusions and without considering (1) why no benefit of HGV co-infection in African women with HIV-1 or HIV-2 was observed, and (2) sex, age, and ethnicity in responses to viruses, drugs, or pharmacological agents.[16]

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Traditional African medicine in the treatment of HIV

In Africa, traditional medicines and natural health products are often used as primary HIV treatment and as therapy for HIV-related symptoms including dermatological disorders, nausea, depression, insomnia, and weakness.[1–3] This practice is intrinsically linked with the central role of traditional healers as health-care providers in many regions of Africa. The interactions between western medicine, traditional healers, governments, and those living with HIV are complex, since they pertain to the use, legislation, and research of traditional herbal remedies in Africa. Notwithstanding these concerns, the use of traditional medicines by Africans living with HIV is believed to be widespread.[3–5]

Those practising western medicine may view alternative forms of medical therapy with scepticism. Still, it is not unreasonable to suggest that some herbal products possess therapeutic benefits. Indeed, effective antimalarials, cancer treatments, and some of the earliest protease inhibitors were derived from natural products.[6] However, herbal and traditional medicines are