As a result of the quest for yet unidentified viruses that cause human hepatitis, two novel flaviviruses were identified in the 1990s by two independent groups of researchers. GB virus C (GBV-C) was first identified in the sera from a West African population during an attempt to retrospectively track down the causative agent of an incident of acute hepatitis in a surgeon (whose initials were GB). This new virus was however subsequently found to be unrelated to the episode of hepatitis experienced by the surgeon. Almost concurrently, hepatitis G virus (HGV) was independently cloned from the plasma of a patient with chronic hepatitis. Sequence comparisons of both viruses showed nucleotide and amino acid homologies of 86 and 95 per cent respectively, suggesting that they were isolates of one and the same virus.

GBV-C/HGV infection is relatively common and has a worldwide distribution. GBV-C/HGV viraemia which is the presence of viral RNA in serum or plasma, reflects current infection. Clearance of viraemia is associated with antibody to the GBV-C/HGV envelope protein (E2). Viraemia detection rates vary globally from 1 to 12.2 per cent in healthy blood donors. In this issue Kumar et al report a 6 per cent viraemia rate among healthy blood donors, similar to an earlier report from this country. Exposure to GBV-C/HGV in a given population is the sum of the RNA and E2 antibody detection rates.

Transmission of GBV-C/HGV is clearly through the blood borne route. High prevalence rates have been reported in patients with high parenteral risk such as those with exposure to blood and blood products, those on maintenance haemodialysis and intravenous drug abusers. Additionally, sexual and vertical routes of transmission have been clearly documented. Analysis of the gene sequences further points to intra-familial transmission between spouses and via the horizontal route. GBV-C/HGV infection may persist for years and in one instance 16 years of viraemia has been documented. Based on comparison of genome organization and sequence homology, the human pathogen to which GBV-C/HGV is most closely related to, is the hepatitis C virus (HCV), also a member of the Flaviviridae family. However, despite genetic similarities between both viruses, significant differences exist. The envelope proteins of HCV are heavily glycosylated and the E2 has a hypervariable region. The E2 protein of HGV-C/HGV on the other hand has limited glycosylation and lacks a hypervariable region probably accounting for the higher rate of viral clearance as compared to HCV. However, not surprisingly, both viruses often co-exist in patients with high parenteral risk.

Phylogenetic analysis of different GBV-C/HGV strains groups them into five different genotypes which follow a geographic distribution. The sub-genomic regions of the 5'non-coding region (5' NCR), E1, and non-structural regions (NS3 and NS5) have been widely studied. Genotype 2 has been reported from North and South America, Europe, East Africa, and the Indian subcontinent. There is evidence of divergent GBV-C/HGV strains among individuals with high parental risk. Kumar et al studied the NS3 region of the HGV isolates from cases of acute viral hepatitis and fulminant hepatitis. These isolates were found to bear closest homology to Chinese strains which probably belong to genotype 3. Generally, 5'NCR region of the viral genome is the best studied sub-genomic region for genetic variation but larger and whole genome sequences are preferred for phylogenetic analysis. Though GBV-C/HGV genotypes are not as divergent and linked to disease outcome as HCV, such information certainly sheds light on GBV-C/HGV epidemiology and phylogenetic origins of the virus.
To determine if GBV-C/HGV was associated with hepatitis or other human diseases, several studies of blood recipients, hepatitis patients, transplant recipients and individuals with a variety of clinical diseases were undertaken soon after its discovery. Some reports clearly attributed a role in the causation of acute and fulminant non A-E viral hepatitis, while others stated that such an association of GBV-C/HGV with acute, fulminant, non-fulminant hepatitis and chronic hepatitis was due to known or hitherto unknown co-existing viruses. In the Indian population, Kumar et al. have shown that GBV-C/HGV is clinically insignificant and has no pathogenic role in fulminant and acute viral hepatitis. Studies have also demonstrated that GBV-C/HGV does not replicate in the liver but replicates in fact in the spleen and bone marrow.

Thus, the virus was clearly shown to have a worldwide distribution but lacked disease association especially in comparison to the well recognized hepatitis causing viruses. In fact, researchers prefer to refer to this agent merely as GBV-C and not hepatitis G virus. Not surprisingly, the virus acquired the label of “human orphan flavivirus”, “accidental tourist virus”, and “innocent bystander virus”. The US Food and Drug Administration therefore decided not to screen the blood supply for this virus.

What has intrigued the scientific community is the more recently discovered relationship of GBV-C with HIV infection. Several groups have shown that patients with GBV-C viraemia had significantly higher CD4 cell counts in HIV positive patients as compared to those without GBV-C viraemia. In GBV-C RNA negative HIV positive individuals, even the presence of E2 antibody conferred improved survival rates as compared to E2 antibody negative HIV infected individuals. Controlling for gender, age, baseline CD4 cell counts and HIV viral load, GBV-C viraemia is associated with longer survival and slower disease progression as defined by the CDC clinical criteria. This effect is still seen following introduction of highly active antiretroviral therapy (HAART).

GBV-C replicates in CD4+ T lymphocytes and other peripheral blood mononuclear cells, inhibiting HIV replication by inducing chemokines, downregulating HIV co-receptors and modulating cytokine profiles. GBV-C may have yet undefined effects on host lymphocytes. GBV-C however, does not seem to decrease the vertical transmission of HIV. A few research groups have failed to demonstrate the beneficial effect of GBV-C infection on progression of HIV disease. These contradictions may be in part contributed by differences in the study population, HCV co-infection, introduction of HAART and the infecting GBV-C genotype or subtype. Clearly, a lot more has to be learnt about the interaction between GBV-C and HIV which may lead to newer therapeutic strategies that can halt or slow the progression of HIV/AIDS. Such novel strategies can impact on the current issues related to anti-retroviral drug resistance and toxicity.

In summary, this commonly occurring flavivirus GBV-C has taken an unusual journey in recorded scientific literature from a candidate hepatitis virus to an innocent bystander to, possibly, a beneficial virus!

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References
