HEPATITIS D: A REVIEW
Bader Faiyaz Zuberi

ABSTRACT
Hepatitis D has been shown to be reducing in frequency in the Western countries commensurate with HBV decline while recent reports from Pakistan are indicating a rising frequency. This review describes the management and prevention of this often overlooked cause of hepatitis.

KEY WORDS: Hepatitis D, epidemiology, Pakistan.

INTRODUCTION
Chronic viral hepatitis is a major health problem worldwide. Recent figures have given the prevalence of hepatitis B (HBV) at about 2.0 billion and hepatitis C (HCV) at 170 million with 3-4 million new cases every year. Annual mortality is more than one million due to its complications. Cirrhosis mortality rates increased steeply in Britain during the 1990’s. Between the periods 1987-1991, and 1997-2001, cirrhosis mortality in men in Scotland exceeded more than double (104% increase) and in England and Wales rose by over two-thirds (69%). Mortality in women increased by almost half (46% in Scotland and 44% in England and Wales). Vaccination against HBV was the major factor to reduce the HBV incidence. Consequently it also reduced the incidence of hepatocellular carcinoma (HCC) and hepatitis D (HDV). Universal infant vaccination was introduced in the United States in 1991; vaccination coverage among children aged 19-35 months increased from 16% in 1992 to 90% in 2000. From 1990 to 2002, the incidence of acute hepatitis B decreased by 67% across all age groups, while in children under 20 years, incidence decreased by 89%.

Recent reports have documented about 16-27% prevalence of HDV among HBV patients in Pakistan while the rest of the world is witnessing the decrease in HDV prevalence; are we having an epidemic of HDV?

STRUCTURE & REPLICATION
HDV was first described in Italy in 1977 and it is a small 1.7 Kb single-stranded circular RNA virus. It employs a unique self-cleaving catalytic RNA motif, the HDV ribozyme, during double-rolling circle replication that is peculiar to it. The HDV self-cleaving motif folds into a double-pseudoknot model secondary structure composed of one stem (P1 stem), two pseudoknots (P1.1 and P2 stems), two stem-loops (P3-L3 and P4-L4) and three single-stranded junctions (J1/2, J1/4 and J4/2). The catalytic core takes the form of two coaxial helices formed by the stacking of the P1-P1.1-P4 stems and of the P2-P3 stems. The use of X-ray diffraction and nuclear magnetic resonance has provided high-resolution definition of the tertiary structure of this catalytic RNA, and both approaches have contributed to the elucidation of the network of interactions that take place within the catalytic center.

GENOTYPES
HDV was initially classified into three genotypes. Recent molecular phylogenetic analysis of HDV suggests at least seven major classes. The genotype I HDV is widely spread, genotype II is found in East Asia and genotype III HDV is prevalent in South America. Genotype II HDV infection is relatively less frequently associated with fulminant hepatitis at the acute stage and less unfavorable outcomes (cirrhosis or hepatocellular carcinoma (HCC)) at the chronic stage as compared to genotype I. It appears that the clinical manifestations and outcomes of patients with genotype IV (Iib) HDV infection are more like those of patients with genotype II HDV infection. Persistent replication of HBV or HDV was associated with higher adverse outcomes (cirrhosis, HCC or mortality) compared to those who cleared both viruses from the sera. HBV of the genotype C is also a significant factor associated with adverse outcomes (cirrhosis, HCC or mortality) in patients with chronic hepatitis D in addition to genotype I HDV and age. However, most patients with chronic HDV infection have low or undetectable hepatitis B virus DNA levels. During longitudinal follow-up, genotype I HDV is the most important determinant associated with survival.
**REPLICATION**

Cell-to-cell spread of these HDV genomes does not occur. The HDV replication is dependent upon an integrated cDNA source of fully functional, unchanging Ag-S'.

Thus the cells maintain about 1,000 copies of HDV genomic RNA per cell. As each cell divides, another 1,000 copies need to be transcribed, processed, and accumulated. If a fraction of the original 1,000 copies had been compromised it becomes less replication competent, then most of the new 1,000 copies would be made from the non-compromised genomes. This purging effect would occur with every cell division. For many RNA viruses, there has been some controversy in terms of the concept of quasi-species, about which heterogeneous populations of viral genomes can provide mutual support to achieve a level of replication. This concept might not be applicable to HDV replication. This is because none of the genomes that are replicating can make a functional Ag-S'. All of the genomes are dependent upon a separate source of this Ag-S. If some of the viral genomes were providing a source of functional Ag-S', they would be able to support the replication of other genomes that were unable to make any Ag or that made a Ag-S that was not fully functional. If the supported genomes were making a significant amount of a form of Ag-S that interfered with HDV replication (like Ag-L), then they may compromise the co-replication. Some aspects of the quasi-species models demand that the replicating genomes can undergo significant levels of intermolecular recombination. For HDV, this has been claimed, but the issue is still controversial.

**NATURAL COURSE**

The natural course of HDV is still under evaluation. It has been shown that people infected at a younger age with HDV develop cirrhosis one or two decade earlier than those with HBV and HCV as the disease runs a rapidly progressive course leading to early cirrhosis, decompensation and HCC and a shorter 5 year survival. In a recent study, it was documented that patients infected with genotype I HDV had a lower remission rate (15.2% vs. 40.2%, p = .007) and more adverse outcomes (cirrhosis, hepatocellular carcinoma, or mortality) (52.2% vs. 28.1%, p = .005) than those with genotype II HDV. The course of the disease also depends upon the HBV genotype. Patients infected with genotype C HBV had a lower remission rate (0 vs 32.1%, p = .005) and more adverse outcomes (70.0% vs. 33.9%, p = .005) than those with genotype B HBV. The presence of HBV or HDV viremia was associated with lower remission rates compared with those negative for both (26.4% and 24.3% vs. 69.2%, p < .001).

**TREATMENT OF ACUTE HDV**

Acute hepatitis with HDV requires the monitoring of the clinical and biochemical parameters of liver function to allow the early detection of progression to fulminant hepatitis. If fulminant hepatitis occurs, orthotopic liver transplantation is the only treatment. Although there is a report of successful treatment of three patients with Trisodium phosphonoformate (foscarnet) with fulminant HBV-HDV hepatitis with full recovery, it was subsequently found that foscarnet actually increases the HDV replication. Thus the recovery was a chance occurrence rather than the effect of drug, which has not been used subsequently. Similarly the use of interferon alpha 2c has also been found to be effective in fulminant HDV.

**TREATMENT OF CHRONIC HDV**

Deoxynucleotide analogues

Although HBV is not involved in the replicative cycle of HDV, the HBsAg represents the envelope of HDV without which HDV cannot be secreted out of the hepatocyte. The dependence of HDV on HBV could suggest that successful treatment of HDV infection would follow successful treatment of the supporting HBV infection. Unfortunately, this does not always appear to be the case. Although treatment of chronic HBV carriers with lamivudine leads to decreased levels of HBV in serum, and improved liver histology in patients with chronic delta hepatitis prolonged lamivudine therapy neither lowers HDV RNA levels nor ameliorates disease activity, even though HBV viremia is reduced. Similarly, treatment with famciclovir was not effective against HDV infection. The most likely explanation for the failure of these treatments to affect HDV is that HDV requires the HBsAg function of HBV, and lamivudine treatment does not typically reduce HBsAg levels. In a recent case report, HDV RNA was not cleared using adefovir for 20 months while HBV DNA was cleared.

Interferon

Regarding the hypothesis that prolonged treatment with interferon (IFN) might induce a therapeutic effect, several clinical trials based on the long-term administration of IFN were undertaken in the late 1980s and early 1990s. The response, assessed on the normalization of serum alanine aminotransferase (ALT) levels and the clearance of serum HDV RNA, varied widely. The rate of response
was proportional to the dose of IFN; patients treated with 9 million units (MU) responded better. Viral and biochemical evidence of relapse was common when IFN was stopped and sustained responses were unusual. ALT often remained normal despite viral recrudescence. Combination of IFN with acyclovir was also unsuccessful resulting in reactivation during the follow-up in almost all patients. Use of pegylated interferon has shown some promise for the future. The analysis of the pretreatment characteristics of patients has not identified differences between responders and nonresponders to IFN with regard to demographic, clinical, serological, biochemical and histological findings. In view of the poor prognosis of patients with active replication of both HBV and HDV, therapeutic inhibition of HBV should be considered a significant therapeutic target.

Prenylation inhibitors
Prenylation process has an essential role in HDV assembly. This suggests a basis for a novel anti-HDV strategy of using prenylation inhibitors. Mice were treated with prenylation inhibitors FTI-277 and FTI-2153; both agents were effective at clearing HDV viraemia dependent on the duration of treatment.

FUTURE PERSPECTIVES
In recent years, interest in the therapy of chronic hepatitis D by pharmaceutical companies has been much reduced. Reduction in prevalence of HDV in western countries accounts for the absence of interest on treatment of chronic HDV hepatitis with new agents such as pegylated interferon. Because of its weekly administration PEG-IFN could nevertheless represent a reasonable therapeutic option for the long-term treatment required for chronic hepatitis D. New treatment perspectives shall probably rely on the knowledge of HDV structure, life-cycle and interaction with HBV. The autocleavage activity of the genomic HDV ribozyme is strongly inhibited in vitro, in the presence of different aminoglycosides. Although none of the aminoglycosides effective in vitro exerted suppressive effects in vivo in cell lines. These observations suggest a potential strategy for anti-HDV therapy.

REFERENCES
Hepatitis D: a review


