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Diseases
Narrative review

Delta Hepatitis

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Abstract

Hepatitis delta virus (HDV) is a defective RNA virus that requires HBsAg for replication and transmission. It can cause acute or chronic hepatitis. Chronic infection with HDV is one of the most severe and difficult to treat forms of viral hepatitis. It has been estimated that there is a total of 15-20 million HDV carriers in the world. This review focuses on two fundamental aspects of HDV infection. On the one hand, epidemiological data are summarized, which are essential to understand the real burden of this disease. After the HBV vaccination programs in many countries all over the world, HDV infection has decreased since 1980's but this decline has not continued further in the last decade. Therefore, HDV infection is still an important public health problem in the world. On the other hand, therapeutic options are described. Currently, interferons are the only option for the treatment of chronic hepatitis delta infection, and pegylated-interferons have shown better results than conventional interferons (IFNs). Monotherapy of nucleos(t)ide analogs have been found ineffective against the HDV infection, but adefovir and pegylated-IFN combination therapy have had some advantages for reduction of HBsAg levels. Trials with more potent nucleoside analogs and pegylated-IFN could be effective in the treatment of chronic HDV infection. New agents like prenylation inhibitors, that can affect the interactions between the large HDV antigen and HBsAg in the HDV virion, will be a hope in treatment of HDV infection.

Keywords

Delta hepatitis; Epidemiology; Treatment; Delta virus

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Introduction

Hepatitis delta virus (HDV) is a defective RNA virus which needs hepatitis B virus (HBV) for replication and transmission. Chronic infection with HDV is known as the worst form of viral hepatitis in humans [1-3]. It can also cause acute infection as coinfection with HBV or superinfection in HBV carriers.

Delta antigen was first described by Mario Rizzetto and colleagues in the nucleus of hepatocytes derived from patients infected with HBV. They detected this antigen particularly during the severe course of HBV infection. The disease was associated with a particle consisting of an RNA genome which was encapsidated by HBV envelope proteins. This particle, named "delta agent" or "HDV", was identified as the infectious agent causing hepatitis in the presence of HBV infection [4].

Virology

The HDV virion is approximately 36 nm in diameter. It has an outer coat containing the three HBV envelope proteins termed large, medium and small hepatitis B surface antigen (HBsAg) and host lipids. The HDV virion has an inner nucleocapsid consisting of a single stranded, circular RNA of 1679 nucleotides and about 200 molecules of hepatitis D antigen (HDAg) per genome [5]. HDAg is the only protein that is encoded by the HDV genome. HDAg has major isoforms termed small and large. Small HDAg (24 kDa) with 195 amino acids accelerates HDV-RNA synthesis, whereas large HDAg (27 kDa) with 214 amino acids inhibits HDV-RNA synthesis but is necessary for virion structure [3,5].

The virion attaches to the hepatocyte membrane receptor with large HBsAg. The virion is uncoated after entering the hepatocyte. The nucleocapsid is translocated to the nucleus. The HDAg has no RNA polymerase activity to replicate the genome, therefore the genomic strand is replicated by the host RNA polymerase [5-7].

Epidemiology

HBV infection is a serious health problem: there are over 350 million people with chronic hepatitis B around the world. It has been estimated that approximately 5% of all HBsAg carriers are also coinfected with HDV, leading to a total 15-20 million HDV carriers in the world [2,3,6,7]. The virus is highly endemic in Mediterranean countries, the Middle East, Central Africa and northern parts of South America [3]. Generally, HBV and HDV infections don't exist in parallel: the rate of HDV infection is not a simple reflection of HBV infection, and other factors, such as age during HBV infection, could determine the occurring of HDV infection. In Southern Europe, before HBV vaccination programs the prevalence of HDV infection was more than 20% in the 1980's. This prevalence has significantly decreased to 5-10% after 1980. After 1995, HDV positivity rates in chronic HBV infection were 4.8%, 12.1%, 23.5%, 27.1% for Western, Middle, East and Southeastern regions in Turkey, respectively [8]. In Mongolia, the etiology of one third of chronic hepatitis infections is HDV infection [9].

HDV is transmitted in the same way as HBV, mainly parenteral route, whereas vertical transmission from mother to newborn is rare. There is a high prevalence of HDV infection in parenteral drug addicts in Western countries. Household transmission is also possible [10,11]. High-risk groups include HBsAg-positive parenteral drug users, female prostitutes and brothel-goers. In recent decades, male prostitutes and immigrant prostitutes have also entered high-risk population groups and may become reservoir for disease transmission in HBV endemic areas [12].

There are many reports about the prevalence of HDV infection, but they are difficult to interpret. In most reports, the local HDV prevalence is restricted to patients with chronic hepatitis B or cirrhosis, not including asymptomatic HBsAg carriers, or to special populations, as intravenous drug addicts, homosexuals, and prostitutes [8-10,12-15]. Therefore reports have not been representative of the whole population of HBsAg carriers in terms of HDV infection [16].

Epidemiologic studies will be discussed according to different geographic areas below.

The prevalence rate of HDV infection in asymptomatic HBV carriers was reported as 2%, 31%, and 3.3% in Jordan, Kuwait, and Saudi Arabia, respectively [17-19]. In chronic liver diseases, it was reported as 23.5%, 23%, 2%, and 10% in Egypt, Jordan, Yemen, and Iran respectively [15,17,20-22]. The prevalence of HDV infection was low (0.5% to 13.3%) in Japan except in some islands of Okinawa, Russia except in Yakutia (18-20%), Korea, Indonesia (< 0.05%), Malaysia, Thailand (0.7%), Philippines and Vietnam (1.3%), and Lebanon (1.2%) [22]. In Japan, the prevalence of antibodies against HDV (anti-HDV) ranges from 21.3% to 63.3% in Okinawa: these high figures are due to older HBV carriers, and reflect previous acquirement of HDV infection in that cohort [23]. Taiwan was endemic for hepatitis B before vaccination [22]. From June 1983 to May 1995, similarly to the decline in HBV infection, the HDV prevalence in HBsAg carriers decreased considerably to 4.4% [24]. But, in 2003, the HDV prevalence in HBsAg carriers was detected as 15.3% in Southern Taiwan [25]. In Pakistan, prevalence of HDV in HBsAg-positive patients is very high (up to 69%) [26].

In China, although the prevalence of HBV infection is high, HDV infection is not very prevalent. There are some differences across the regions of China. In Shijiazhuang, HDV prevalence rate was 12.9%, whereas in Hong Kong it was 0.15% in HBV carriers [27,28].

In Saudi Arabia, HDV prevalence in HBsAg carriers was 8% and 3.3% in 1986 and 2004, respectively [29,30]. Similarly to many other countries, HDV infection is expected to decrease in Saudi Arabia due to global vaccination program for HBV [30].

In our country, HDV infection is still an important health problem, particularly southeast and east part of Turkey. Degertekin et al. evaluated the 62 studies about the HDV infection from different centers in several regions of Turkey for epidemiology of HDV infection [31]. Anti-HDV positivity was detected in 20% of 5961 patients with chronic HBV infection and in 32% of 1264 patients with HBV cirrhosis, respectively. The positivity rate was significantly lower in Istanbul and Izmir (west part of Turkey) compared to Diyarbakır and Van (Southeast and East of Turkey). This difference could be related to multimembered family structure with close contact, unavailability of HBV vaccine, use of non-disposable injectors in the past, poor circumstantion and shortage of health services and sanitation in the East and Southeast of Turkey in the past [31]. This meta-analysis of 30 studies, which included large study groups for the epidemiology of HDV, showed that HDV infection in chronic HBV infection had decreased from 29% to 12% in central Anatolia and from 37% to 27% in Southeast of Turkey after 1995. It is probably related to the universal vaccination program in 1998, the preventive public health issues, and the improved socioeconomic status but it is still a really hard problem in our country. We hope this decline in HDV infection will continue.

The rate of anti-HDV seropositivity was found equal to 2.7% among subjects positive for HBsAg in a recent epidemiologic population-based study in 5471 subjects representing the Turkish population [32].

In Europe, HDV infection has predominated in the Mediterranean basin, in the Balkan Peninsula, ex Soviet Union. Highest European rates in terms of anti-HDV positivity were 95% and 80% in Romania and ex Soviet Union, respectively, in the 1980's [33,34]. Countries such as Denmark, Sweden, Norway in Northern Europe have low rates of HBV infection, but relatively high HDV prevalence could be detected in special high-risk groups. Since 1990's, HDV infection has decreased significantly in Europe [35,36]. In sequential surveys in Italy, rate of anti-HDV seropositivity was found equal to 24.6% in 1983 [37], 14% in 1992 [38], and 8.3 in 1997 [39]. A similar decreasing rate in HDV seropositivity was also seen in Spain [40]. Unfortunately this decline has not continued in the last decade [41]. The prevalence

of HDV detected in 21 Italian centers in 2006 was 8.1% (95 of 1179 patients); this rate was similar to the prevalence in 1997 [42]. Gaeta et al. thought that besides vaccination programs against HBV infection, the huge mortality for human immunodeficiency virus (HIV) infection before 1996 had caused the rapid reduction of patients with HBV and HDV infection. After active antiretroviral therapy in 1996, the mortality due to HIV infection had decreased but morbidity and mortality due to liver disease had increased [39]. The picture is similar in Northern Europe, HDV prevalence was about 8.5% from 2000 to 2006 in London [43] and 8-10% in Germany since 1997 [3,44]. In both countries, the majority of HDV patients were immigrants from highly endemic areas. The patients (258) with HDV infection in Hannover have presented in a high frequency with an advanced stage of liver disease and the course of disease did not differ between Turkish-born, Eastern European-born and German born patients [45]. In France, HDV is not vanishing, maybe due to immigrants from Africa [46]. The course of HDV infections may reveal a wide clinical spectrum ranging from asymptomatic carriage of the virus to very severe disease in Greece [47].

There is limited epidemiology data on hepatitis D in the United States. Prevalence of HDV in US was reported up to 30% in patients with HBV infection [48], 2% in homosexual men [49] in 1989 and in around 20% in hemophiliacs [50] in 1993. HDV infection is now a vanishing disease in the US and Canada and in many American countries and the problem of HDV infection is almost restricted to intravenous drug users. On the other hand, hepatitis D is prevalent in HBsAg-positive patients in Amazonia. Very high frequencies of HDV infection and high morbidities and mortalities are described in the Amazonian region of Western Brazil [51,52].

HDV is divided into eight major genotypes differing as much as 40% in nucleotide sequence [53,54]. Genotype I is the most frequent genotype worldwide and has broad spectrum of pathogenicity [6,35]. We can see genotype I of HDV in Europe, Middle East, North America and North Africa [3]. Genotype I HDV and genotype C HBV infections were associated with more severe outcomes such as the development of cirrhosis, hepatocellular carcinoma (HCC) or mortality due to hepatic failure than genotype II in Taiwan [55]. Genotype I has two subtypes; IA is predominant in Asia and IB in the US and both are common in the Mediterranean area[6]. Genotype II and IV are seen in East Asia usually with mild disease [56]. Genotype IIB subtype from patients in Miyako Island and Okinawa have caused more severe disease than genotype IIB subtype from Taiwan [57]. HDV genotype III is seen exclusively in the Northern part of South America (Columbia, Venezuela, Peru) [3,6]. Genotype III has been associated with outbreaks of severe and fulminant hepatitis and coexisting genotype F of HBV [6,35]. HDV genotype V and VII can be seen in Africa [3]. Le Gal et al. identified an eighth HDV clade (HDV-VIII) from 3 complete sequences obtained from strains isolated from patients of African origin in France in 2006 [54]. While the genotypes of HBV don't seem to affect the interaction between HBV and HDV, the genotypes of HDV may influence the efficiency of assembly with the HBsAg into virions. Therefore, further studies are necessary to clarify wether clinical differences among the genotypes exist for replication, infectivity and pathogenity [6,35].

Pathogenesis

The mechanisms occurring during the course of HDV infection remain unclear. Hepatitis D is mostly an immune-mediated disease, but there are some evidence that HDV infection is a cytopathic disease [3]. During the acute phase of HDV infection, HDV viremia is associated with an increased level of transaminases and low HBV-DNA level, whereas chronic phase is characterized by decreased HDV, reactivation of HBV and mild or moderate transaminitis. The late phase consists of remission with clearance of these viruses or with the development of cirrhosis or hepatocellular carcinoma due to replication of HBV or HDV [1,2,5].

Innate and adaptive immune responses of host have important roles for the viral clearance and the liver disease, but the precise mechanisms for the pathogenesis are not fully understood.

Clinical Features

Presentation of acute HDV infection could be coinfection with HBV or superinfection in a patient with established HBV infection. Acute HBV and HDV coinfection can range from mild hepatitis to usually severe acute liver failure and results in complete viral clearance in more than 90% of patients. The rate of chronicity after coinfection with HBV and HDV is less or similar to that of HBV infection alone (less than 10%). HDV superinfection results in chronic HDV infection in 70-90% of HBV carriers. At initial histological evaluation, liver biopsies usually have shown severe hepatitis with advanced fibrosis. These patients have the risk of rapid progression to cirrhosis and hepatic decompensation causing death [3,5,58]. Persistent HDV replication leads to cirrhosis and hepatocellular carcinoma at annual rates equal to 4% and 2.8%, respectively, therefore antiviral therapy is indicated in these patients with high viral load [59]. Niro et al. revealed that lack of antiviral therapy, cirrhosis at presentation and male gender were correlated with poor prognosis in patients from Italy with chronic HDV infection for a mean of 9.6 ± 7.7 years of follow-up [60].

Diagnosis

Every patient who is $HBsAg^+$ must be tested for anti-HDV IgG antibodies. The occurrence of anti-HDV antibodies is universal in patients with HDV. Anti-HDV antibodies can either disappear after recovery from infection or persist even after the patient has cleared HDV or after liver transplantation. Active HDV infection is confirmed by the detection of serum HDV-RNA with sensitive real-time PCR. Assays of HDV-RNA might return false negative results due to the variability of the genome sequence. In these cases testing of anti-HDV IgM could be useful for the diagnosis of active HDV infection [1,3,5]. Therefore international standardization of the HDV-RNA is necessary to have correct results. Quantification of HDV-RNA is not correlated with any clinical parameter or the stage of the liver disease, but is useful to evaluate the antiviral therapy [3,5,61,62]. After the identification of HDV-RNA, liver biopsy must be performed to evaluate staging and grading of liver disease. As coinfection with HCV and HIV is very common, the presence of anti-HCV and anti-HIV antibodies must be checked. In addition, HBV-DNA quantification, HBeAg and anti-HBe antibody determination must be performed to evaluate the chronic HBV infection in chronic HDV infection.

HDV genotyping is usually available in some of the research laboratories. Genotyping could give some prediction about the disease progress. As previously noted, genotype I is the most frequent genotype worldwide and the patients with this genotype have a higher risk of developing end stage liver disease [3,5,35].

Treatment

Current therapies

Patients with chronic HDV infection have a much higher risk of developing end-stage liver disease than those with HBV alone. Delta virus-related hepatitis is a difficult-to-treat disease. Acute HDV infection may present coinfection with HBV infection or in a patient with established HBV infection (su-

perinfection). Clinical manifestations of HBV and HDV coinfection could range from mild to severe fulminant hepatitis. If fulminant hepatitis occurs during the acute hepatitis D, liver transplantation is the only treatment option [3,5,6,63].

At present, **interferon** is the only option for the treatment of chronic hepatitis D. Since most patients have advanced disease and cirrhosis, the response rate to interferon (IFN) therapy is not high (less than 10% with 1-year IFN therapy [63-65]). Therapeutic efficacy increases when higher dose of interferon alpha is administered for prolonged periods (12-24 months) [63-66]. As described in an interesting case report a 12-year high-dose IFN treatment resulted in the complete resolution of HDV infection with remission of liver fibrosis and disappearance of HBV and HDV from serum [67]. We also investigated the 2-year IFN therapy with or without ribavirin in 31 patients with chronic HDV infection [68]. In our study, virological response was achieved at a median of 12 months (range = 10-20 months) in the IFN monotherapy group. Virologic response was 20% at the end of follow-up period in the IFN monotherapy group. In the IFN and ribavirin combination group, 8 out of 16 end-of-therapy responders cleared the virus after 1 year of therapy. We had emphasized that 1 year of IFN therapy had not been sufficient in nearly 50% of patients with chronic HDV infection. However, high doses of IFN alpha and prolonged treatment are tolerated only by a minority of patients, probably due to advanced liver disease in HDV infection.

After the development of **pegylated-IFN** (peg-IFN) with improved pharmacokinetics, better outcomes have been reported with peg-IFN both in naïve and in previous nonresponders to IFN standard treatments [61,62,69]. Castelnau et al. studied peg-IFN alpha-2b (1.5 μg/kg per week) therapy for 12 months in 14 patients with chronic delta hepatitis. They found sustained virological response in 43% of patients. Negativity of HDV-RNA at 6 months of therapy was suggested as a predictor for sustained response. Authors emphasized the importance of measurement of HDV-RNA by real-time quantitative PCR assay during follow-up [61]. In Edhardt's study with peg-IFN alpha-2b, sustained response was achieved in 2 out of 12 patients (17%) with HDV infection and researchers identified nonresponders as those having less than 3 log decrease of HDV-RNA at 6 months of treatment [62]. With more knowledge on the basis of HDV-RNA kinetics, we can decide the duration of therapy more properly. Another study with peg-IFN for 72 weeks detected the sustained response rate in 21% out of 38 patients in chronic HDV infection [69]. This response rate is lower than the study by Castelnaue et al., probably due to the high prevalence of cirrhosis (28/38, 73%) in this study [61].

Several nucleos(t)ide analogs effectively used for HBV infection were found ineffective in the treatment of HDV infection [3,65,70].

Lamivudine and **famciclovir** had no significant antiviral activity against HDV infection [70-72].

Ribavirin was shown to be able to inhibit HDV replication in primary woodchuck hepatocyte cultures infected with HDV [73], but ribavirin had no effect on the viral clearance rate with standard IFN or peg-IFN in patients with chronic delta hepatitis [61,68,69,74]. Clevudine, another nucleoside analog, had significantly decreased HDV-RNA in woodchucks infected with HDV [75].

Clevudine was tried in six patients with HDV infection in a pilot study. Only five of these patients could have used clevudine for 9-12 months and clevudine had no effect in terms of HBsAg, ALT and HDV-RNA levels [76]. In addition, clevudine could cause severe myopathy by depletion of mitochondrial DNA as side effect [77].

A multicenter randomized study (HIDIT I) compared the efficacy of **peg-IFN alpha-2a plus adefovir** versus peg-IFN alpha-2a plus placebo versus adefovir in chronic HDV infection [78]. 72-week results of this study showed that peg-IFN alpha-2a had a significant antiviral effect for HDV in more than 40% of patients, HDV-RNA relapse had occurred in only 1 patient, and 8 additional patients receiving peg-IFN had become negative after stopping therapy. Adefovir had not affected HDV replication but combination therapy of peg-IFN and adefovir had some advantages in terms of reduction of HBsAg

levels [78]. An international study group had found positive correlation between the HBsAg levels and HDV viremia in chronic HDV infection [79].

Therefore combination therapies with peg-IFN and nucleos(t)ide analogs, which are more potent than adefovir, could have advantages in the therapy of HDV infection.

There is a case report with resolution of HDV infection with 1-year **combination therapy of peg-IFN, tenofovir and emtricitabine** [80].

A trial with **tenofovir and peg-IFN** combination therapy is still ongoing and will provide informations to take more precise decisions about the combination therapies. Some of the most relevant trials about the therapy of chronic HDV infection are summarized in Table I.

Liver transplantation is the best treatment option for end-stage liver disease in HDV infection as in other causes of chronic liver diseases [3,63]. Post-transplant course of chronic HDV infection is good,

Reference	Number of patients (total)	Treatment		Duration of treatment (w)	Outcomes
		Patients treated	Regimen		
Farci et al, 1994 [64]	42	14	IFN alpha-2a 3 MIU TIW	48	EOT: HDV-RNA- 36% and 71% of pts Relapses in all pts
		14	IFN alpha-2a 9 MIU TIW		
		13	Control: no treatment		
Gaudin et al, 1995 [65]	22	11	IFN alpha-2a 5 MIU/m² for 4 months, then 3 MIU/m² control	48	EOT: HDV-RNA- 66% of pts, EOF: HDV-RNA- 9% of pts
		11	Control		
Madejon et al, 1994 [66]	26	12	IFN alpha-2a TIW 18 MIU for 6 months, 9 MIU and 6 MIU for 1 month 3 MIU for 4 months	48	EOT: HDV-RNA- 50% and 19% of pts EOF: relapses in all pts
		14	3 MIU for 12 months		
Gunsar et al, 2005 [68]	31	10	9 MIU IFN alpha-2a TIW	96	EOT: HDV-RNA- 52% of pts EOF: HDV-RNA- 24% of pts Ribavirin has no beneficial effect
		21	IFN + ribavirin (1000-1200 mg/day)		
Niro et al, 2006 [69]	38	16	Peg-IFN alpha-2b 1.5µg/kg	72	EOT: HDV-RNA- 13% of pts EOF: HDV-RNA- 21% of pts Ribavirin has no beneficial effect
		22	Monotherapy with ribavirin 48 weeks		
Yurdaydın et al, 2008 [70]	39	17	9 MIU IFN alpha-2a TIW	48	EOF: HDV-RNA- • Lam group: 12% • Lam + IFN: 36% • IFN: 50% Lam has no beneficial effect
		14	Lam 100 mg/d		
		8	Lam 100 mg/d+ 9 MIU IFN alpha-2a TIW		
Wedemeyer et al, 2011 [78]	90	29	Peg-IFN alpha-2a 180 µg/w	48	EOF: HDV-RNA- • Peg-IFN group: 31% • Peg-IFN + ADV: 26% of pts • ADV: 0% Combination therapy was found better in terms of decreasing the HBsAg levels
		31	Peg-IFN alpha-2a 180 µg/w + ADV		
		30	ADV 10mg/day		

Table I. Review of treatment of chronic delta hepatitis

ADV = adefovir; d = day; EOF = end of follow-up; EOT = end of treatment; IFN = interferon; Lam = lamivudin; MIU = million units; Peg-IFN = pegylated interferon; pts = patients; TIW = three times in a week; w = week

the risk of re-infection is significantly lower for HDV than for HBV and/or HCV. Five-year survival rates are significantly higher in patients with HDV cirrhosis than in patients undergoing transplantation for the other causes of liver cirrhosis [63,81].

- Treatment of chronic delta hepatitis is really one of the most difficult issues in hepatology. Treatment failures might result from the interference of HDV with IFN alpha intracellular signaling and the severe histology [35,82]. The problem in HDV therapy is that there is no specific enzymatic function to target, such as the polymerases and proteases of HBV and HCV. HDV activity, in fact, depends on the HBsAg and not on HBV replication or on the level of HBV-DNA [35]. The new agents preventing the association of the HDV ribonucleoprotein with the HBsAg might form the basis of a new therapeutic area in chronic hepatitis D. The large antigen contains at its carboxyl terminus a cystein with four amino acid motifs. These motifs serve as substrate for prenyl transferases, which add a prenyl group to the large antigen. It has been shown that prenylation of large antigen is necessary for HDV replication [83]. Prenylation inhibitors have been used for treatment of malignancies and have been found to be safe in this setting [3,35]. Therefore, prenylation inhibitors have been investigated in chronic HDV infection. Bordier et al. provided the first preclinical data supporting the *in vivo* efficacy of prenylation inhibition as a novel antiviral therapy with potential application to HDV [84]. Using glucosidase inhibitors in HDV infection could prevent the secretion of virions from the hepatocytes, but these molecules may stimulate oncogenic pathways in terms of hepatocellular carcinoma [85,86]. New agents that can affect the interactions between the large HDV antigen and HBsAg in the HDV virion will be a hope in treatment of HDV infection [35]. Nowadays, peg-IFN is the only agent used as first-line therapy in chronic HDV infection in naïve patients or nonresponders to standard IFN therapy. Measuring the kinetics of HDV-RNA during therapy will give some advantages to identify who needs extended therapy or who is nonresponder.

Questions for further research

Duration, dosage of pegylated interferon and termination rules according to HDV-RNA kinetics are not defined clearly. The results of studies about HDV-RNA kinetics which can be used as road map during therapy are needed.
The studies about the therapy preventing the association of the HDV ribonucleoprotein with the HBsAg will be hope for the new agents for this difficult disease.

The review in brief	
Clinical question	Delta hepatitis is a health problem in the world, being the virus highly endemic in Mediterranean countries, the Middle East, Central Africa and Northern parts of South America. After the HBV vaccination programs in many countries all over the world, HDV infection has decreased since 1980's, but this decline has not continued further in the last decade, particularly in Europe. Immigrants from endemic areas, parenteral drug users and the patients who could not respond to therapy for HDV are still reservoir for disease transmission. HDV infection is too difficult to treat. This paper about delta hepatitis is a narrative review
Type of review	Narrative
Search of the literature	Search on PubMed for all the most recent articles on delta hepatitis, with keywords: delta hepatitis, epidemiology, treatment, and delta virus
Conclusions	Nowadays, pegylated IFNs are only options for the treatment. The new agents preventing the association of the HDV ribonucleoprotein with the HBsAg might form the basis of a new therapeutic area in chronic hepatitis D. Therefore prenylation inhibitors and combination therapy with pegylated interferon and tenofovir have been investigated in the treatment of chronic HDV infection
Limitations	

After the HBV vaccination programs in many countries all over the world, HDV infection has decreased since 1980's, but this decline has not continued further in the last decade, particularly in Europe, probably due to migration from the endemic regions [87]. Parenteral drug users and the patients who could not respond to therapy for HDV are still reservoir for disease transmission. As HDV infection is too difficult to treat, there are many patients expecting the new therapies. Therefore HDV infection is still an important public health problem in the world. We need much more studies to understand the molecular mechanisms of HDV to manage the disease and acquire better therapy responses in HDV infection.

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