



## **Hepatitis D Virus: An Overview for Dentists**

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### **Authors' contributions**

*This work was carried out in collaboration among all authors. Authors NM and SMA designed the study. Literature search was performed by author NM. Authors NM and SMA wrote the first draft of the manuscript. Authors SRP and MR revised the paper. All authors read and approved the final manuscript.*

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## **ABSTRACT**

Hepatitis D is considered to be the most severe form of viral hepatitis. This virus requires hepatitis B for its life cycle and it is estimated that at least 5% of hepatitis B virus infected patients are also infected with hepatitis D, counting for 15 million infections worldwide most optimistically. Hepatitis D has a similar transmission pattern to hepatitis B and hepatitis C viruses. However, there is less information about the virus of hepatitis D than about the other agents of viral hepatitis. In particular, there is total lack of information on hepatitis D in the setting of dental diseases and management. To our knowledge, there are only few reports on hepatitis D of dental health care workers (DHCW), the association of hepatitis D with oral conditions and on the role of oral fluid in transmission of hepatitis D. The present report reviews current knowledge of hepatitis D for dentists and dental personnel. Therefore, epidemiology, transmission modes, sign and symptoms, diagnostic methods and treatment options of hepatitis D are discussed under relevant subheadings.

**Keywords:** *Hepatitis D; dentistry; infection control; transmission; epidemiology; Hepatitis B; review article.*

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## 1. INTRODUCTION

Hepatitis D virus (HDV) also known as hepatitis delta, firstly discovered by Rezzetto et al. is a unique single-stranded RNA virus that needs HBV for its life cycle [1-2]. With a circular single-stranded RNA genome of approximately 1.7 kb in length HDV is the smallest known virus infecting human [3-4]. Infection with HDV can occur only with an associated HBV infection. This can happen as co-infection (infection with both viruses at the same time) or super-infection (where an already HBV-infected individual can be infected with HDV). Individuals co-infected or super-infected can transmit both viruses [5].

Hepatitis D is considered to be the most severe form of viral hepatitis. HDV infection often leads to the rapid development of liver cirrhosis and is linked with a higher risk for the development of hepatocellular carcinoma (HCC). The risk of HCC development in patients infected with HDV is three-fold greater compared to the risk in those infected by HBV alone [3, 6-9].

The information on HDV is less than that on HBV, HCV and HAV. In particular, there is total lack of information on HDV in the setting of dental diseases and management. To our knowledge, there are only few reports on HDV of dental health care workers (DHCWs), the association of HDV with oral conditions and on the role of oral fluid in transmission of HDV. The present report reviews current knowledge and the implications of HDV infection to oral health care.

## 2. EPIDEMIOLOGY

Viral hepatitis is a major health problem worldwide. HBV remains a major public health problem with two billion people exposed and 350-400 chronically infected [10-12]. It is estimated that at least 5% of HBV patients

worldwide are also infected with HDV, counting for 15 million infections most optimistically [13,14]. Previous reports indicate that infection with HBV in dentists and oral surgeons is 3-6 times more frequent than in the general population [10]. This finding implies that infection with HDV might also be important. However, there is no report on HDV infection prevalence in the dental setting.

HDV affects all age groups and is endemic worldwide [15]. However, the prevalence of infection varies in different geographical areas [16]. Historically, the disease was endemic (defined as more than 5% of HBV infected patients being infected with HDV) in the Mediterranean basin, the Middle East, and parts of Africa [13]. With the introduction of HBV vaccination, systematic screening of blood and blood products and of pregnant women, socio-economic improvements, and the increased awareness of the general public on sexually transmissible agents, the prevalence of HDV has been reduced dramatically in some parts of the World such as Italy, Spain, Taiwan and Turkey. Thus, some authorities predict that HDV might be cleared from the Globe [13, 15, 17]. However, HDV remains present across the globe [18, 19] with new infection in some continents increasing as a consequence of migration of infected individuals [13, 20]. The reported prevalence rates of HDV infection in different countries and patient groups is detailed in Table 1.

Three genotypes of HDV (I-III) have been identified predominantly with a different geographic distribution: Genotype I is found worldwide with predominance in North America, Europe, Africa, the Middle East and East Asia; genotype II has been isolated only in East Asia (Taiwan and Japan) and Russia while genotype III has been restricted to Northern South America (Peru and Colombia) [4, 6, 11, 35, 36].

**Table 1. Prevalence rates of HDV infection in different countries and patient groups in recent years**

| Country | Year | Study population   | Evaluation method                                     | N studied (% infected) | Reference |
|---------|------|--|---|------------------------|-----------|
| Nigeria | 2012 | Patients positive for HBsAg more than 6 months and had not received any antiviral therapy. | IgG HDV antibodies were assayed using an Elisa method | 245 (2)                | [21]      |
| China   | 2012 | HBsAg positive blood samples collected from various areas of China                         | anti-HDV  | 1486 (1.2)             | [22]      |

| Country  | Year | Study population  | Evaluation method   | N studied (% infected) | Reference |
|--|------|---|---|------------------------|-----------|
| Italy  | 2012 | HBsAg positive subjects   | anti-HDV  | 488 (4.9)              | [23]      |
| Pakistan                                       | 2011 | HBV DNA positive samples using PCR in the Province of Sindh                           | RT-PCR  | 190 (28)               | [24]      |
| 93 centers across Europe, Israel and Argentina | 2011 | HBsAg-positive carriers in HIV infected patients enrolled in EuroSIDA*                | IgG HDV antibodies was assessed using EIA   | 422 (14.5)             | [25]      |
| Switzerland                                    | 2011 | gastroenterologists, hepatologists and infectious diseases specialists in Switzerland | Questionnaire received from specialists acknowledging the number and characteristics of patients likely to be infected with HBV and HDV | 1699 (5.9)             | [26]      |
| Pakistan                                       | 2011 | HBsAg-positive carriers admitted with liver diseases                                  | Anti-HDV using commercially available ELISA kits  | 774 (23.6)             | [27]      |
| Iran   | 2011 | HBsAg-positive patients with chronic HBV infection                                    | IgG HDV antibodies  | 81 (17.3)              | [28]      |
| Cameroon                                       | 2011 | HBsAg-positive patients   | RT-PCR HDV RNA  | 233 (17.6)             | [29]      |
| Turkey   | 2011 | patients chronically infected with HBV  | qualitative RT PCR HDV RNA  | 282 (23.4)             | [30]      |
| Pakistan                                       | 2011 | patients with HBsAg positive and a detectable HBV DNA                                 | anti-HDV by EIA assay and HDV RNA PCR qualitative assay**   | 480 (35.2)             | [31]      |
| Pakistan                                       | 2010 | HBsAg ELISA positive samples in Punjab  | nested PCR  | 96 (30)                | [14]      |
| Tajikistan                                     | 2008 | HBsAg positive patients with chronic liver disease                                    | Anti HDV  | 51 (23.5)              | [32]      |
| England  | 2008 | HBV infected adult patients referred to King's College Hospital                       | HDV Ab and IgM HDV antibodies Ab detected by EIA  | 962 (8.5)              | [13]      |
| Iran   | 2008 | HBsAg-positive individuals in the northeast part of Iran                              | anti-HDV using ELISA  | 139 (5.8)              | [33]      |
| Lebanon  | 2007 | HBsAg-positive patients   | anti-HDV  | 258 (1.2)              | [6]       |
| Mongolia                                       | 2005 | HBsAg-positive apparently healthy individuals   | Anti-HDV  | 249 (16.9)             | [34]      |

\*EuroSIDA is a prospective study of 16 597 HIV-1- infected patients enrolled at 93 centers across Europe, Israel and Argentina; \*\*HDV RNA PCR qualitative assay could only be undertaken in 49 patients with HDV co-infection as this assay was not available in early part of this investigation

### 3. TRANSMISSION

Percutaneous exposure (infected blood transfusion, contaminated syringes, injecting, tattoo and skin piercing with infected instruments) [37-38] is the cause of most infections. In non-endemic areas such as in northern Europe and in the United States, intravenous drug use is the most common route of acquisition of HDV. In the past, recipients of blood-derived factors or individuals who had received many blood transfusions were at increased risk of acquiring HDV infection, but, as mentioned before, this has largely ceased as a consequence of universal HBV vaccination and blood screening for HBsAg. Sexual contact with an HDV carrier is also an important route of HDV transmission [39-42].

In HDV endemic areas, the unapparent parenteral route of transmission accounts for most cases of HDV transmission, with a trend to form clusters among family members. In southern Italy, cohabitation with an HDV carrier has been identified as a major risk for HDV transmission [43-45].

There are also reports from endemic areas indicating intrafamilial spread of HDV known as inapparent parenteral transmission with an unknown mechanism [46,47]. Rarely, vertical (mother to infant) spread may also occur [37]. To our knowledge, there is no report showing the risk of HDV transmission following a needle stick injury.

Since HCV, HBV and HDV are transmitted via similar routes, infection with multiple hepatitis viruses can occur simultaneously. When there is such co-infection with these blood-borne viruses in the same patient the term "triple infection" is often applied as a descriptor [38].

To decrease the burden of hepatitis in DHCWs, it is recommended that the dental professionals receive immunization against hepatitis virus and use individual protective equipments such as gloves, masks and shields. It is highly recommended that each dental health care facility develop a comprehensive written program for preventing and managing occupational exposures [48].

### 4. SIGNS AND SYMPTOMS

The clinical features of HDV infection essentially mimic those of HBV infection, although the risk of

severe acute disease and complicated chronic hepatitis is increased when compared with infection solely by HBV. Unlike HCV infection, extrahepatic manifestations such as autoimmune phenomena are not a feature of HDV infection [38].

The clinical expression of acute HDV acquired by coinfection with HBV may range from mild to severe, fulminant hepatitis. In most cases, it resembles a typical acute self-limited hepatitis that is clinically and histologically indistinguishable from the ordinary HBV infection. Generally, the outcome is a complete recovery, as typically observed in acute HBV. In only 2% of cases it may progress to chronic condition. Diagnosis is made by the concomitant appearance of markers of primary infection with HBV and HDV [42,49,50].

In the superinfection pattern, the preexisting HBV viremia provides the biological background for the full expression of the virulence of HDV. Clinically, this results in a severe acute hepatitis that may run a fulminant course. It may present as an exacerbation of a preexisting HBV disease or as a new hepatitis in a previously asymptomatic HBsAg carrier. If the HBsAg state is unknown, it may be misdiagnosed as classical acute HBV infection [15,51,52]. The correct diagnosis is suggested by a negative result for IgM anti-HBc and yet the presence of serological markers of HDV. Since the HBsAg carrier permits the continuous replication of HDV, the vast majority of HDV superinfected carriers develop a progressive hepatitis (over 90% of the cases) [53].

However, it must be kept in mind that a large number of patients affected by hepatitis may not develop clinical signs and symptoms conducive to suspect their condition. Thus it is necessary to enforce biochemical controls in at risk patients to detect hepatitis infections in early stages, which can be treated easier and can decrease the burden of the disease as well. However, cost-analysis studies should be performed in this regard to show the real importance of such a screening.

### 5. DIAGNOSIS

The detection of HDV RNA by polymerase chain reaction (PCR) is presently the most reliable diagnostic method [54,55]. Its role is crucial not only in the early phase of infection, before antibody seroconversion, but also to investigate the molecular events during both acute and

chronic hepatitis. PCR has also offered a sensitive tool for monitoring the efficacy of antiviral agents, since it can detect 10–100 copies of the viral genome in serum [54,56]. Because of the genetic heterogeneity of HDV, primers from the most conserved region, the C-terminal half of the HDAg gene, are most useful in clinical practice [57]. The HDV genotype may be determined by restriction fragment length polymorphism analysis of PCR amplification products, by sequencing and, on liver biopsies, by immunohistochemical staining using genotype-specific anti-HD antibodies. The diagnosis of HDV infection may also be indirect, based on the detection in serum of antibodies against HDAg (anti-HD) of the IgG and IgM classes [58]. Testing for IgM anti-HD is crucial not only as a marker of primary HDV infection but also for its clinical relevance in the natural history of the disease [53]. As a rule, chronic hepatitis D is associated with high titers of both IgM and IgG anti-HDV antibodies, although the IgM are monomeric (7S) and not pentameric (19S) as in primary infection [59]. The decrease and disappearance of IgM anti-HD predicts impending resolution of chronic HDV disease, either spontaneous or induced by interferon (IFN) [53,60].

## 6. TREATMENT

Therapy for HDV is difficult; the minute viral genome does not code for specific enzymatic functions that can be targeted by antivirals [61]. Previous reports showed no particular effect of famciclovir, lamivudine and adefovir on HDV treatment. Also, ribavirin alone or in combination with interferon did not lead to increased rates of HDV RNA clearance [55,62,63]. To date, with an effective rate of only 20%, interferon remains as the most addressed treatment choice for HDV infected individuals followed by liver transplantation. More studies are required to find an effective treatment option for HDV infected patients [39]. Hopefully, attention of DHCWs to HDV as a viral hepatitis agent will prevent transmission of hepatitis D in particular in the HBsAg carriers undergoing dental cures, who are the major victims of HDV infection. In this setting, HDV can be transmitted up to  $10^{-11}$  serum dilutions, thus by minimal traces of mouth biological fluids residual in dental instruments [15,47].

## 7. CONCLUSION

Viral hepatitis is a major public health threat in almost all parts of the globe. However, little

attention is paid to educate dental personnel on HDV. The aim of the current review article was to basically inform DHCWs about the virus.

Screening of blood and blood products for HDV is rarely performed in the HBsAg positive subjects [43]. More seriously, despite routine HBV screening programs of individuals at high risk of blood borne pathogens (such as patients receiving hemodialysis therapy); no program is applied for HDV screening.

To date, there is no report showing transmission of HDV in dental setting. However, since at least 5% of HBV infected individuals are also infected with HDV, it is possible that there is an undetermined rate of HDV transmission by dental procedures. Most reports showing HBV transmission in the dental setting come from 1975-1989, when HDV serologic tests were not routinely available and were not performed in many areas.

Dentists should be aware of blood borne agents in order to provide safe practice for themselves and for their patients. Since HDV requires HBV for replication and has the same sources and modes of spread as HBV, prevention of HDV infection is similar to prevention for HBV and relies strongly on HBV vaccination.

## CLINICAL SIGNIFICANCE

Hepatitis D is considered to be the most severe form of viral hepatitis. However, there is less information on hepatitis D virus (HDV) than that on hepatitis B virus (HBV), hepatitis C virus (HCV) and even hepatitis A virus (HAV). In particular, there is total lack of information on HDV in the setting of dental diseases and management. The present report reviews current knowledge and the implications of HDV infection to oral health care.

## CONSENT

It is not applicable.

## ETHICAL APPROVAL

It is not applicable.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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