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Hepatitis D Virus (HDV): A Review of Epidemiological Aspects, Clinical Characteristics and Diagnosis

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Abstract

Hepatitis D in co-infection with hepatitis B is an infectious disease that particularly affects the liver. This is a defective virus, which requires the presence of HBV surface antigen to replicate and cause infection. However, VHD is associated with acute or chronic hepatitis present in the body, it can manifest itself through tiredness, fever, malaise, dizziness, nausea, vomiting, abdominal pain, yellow skin and eyes, dark urine and pale stools. The purpose of this article is to describe and highlight in the form of a review the main epidemiological data, clinical characteristics and diagnosis of the hepatitis D virus. The methodology used selected 70 relevant articles, published between 2006 and 2021, in the electronic databases: National Library of Medicine National Institutes of Health (PubMed) via MEDLINE, CAPES Journal Portal, Latest Medical News, Clinical Trials, Guidelines – Medscape, Springer, Latin American and Caribbean Literature in Health Sciences (LILACS) and Scientific Electronic Library Online (SciELO). The literary analysis of the articles observed showed high mortality indicators, several epidemiological studies revealed that the global burden of HDV is greater than previously estimated, it was also evidenced the need for more studies to better understand the HDV infection and determine the epidemiology of HDV infection among HBV patients.

Keywords: hepatitis, virus, delta, epidemiology, diagnosis and HDV.

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1. INTRODUCTION

Hepatitis Delta virus (HDV) was first described by Mario Rizzetto and his collaborators during an analysis of liver biopsies from patients chronically infected with hepatitis B virus (HBV) with more severe liver damage (RIZZETTO ET AL, 1977). VHD was identified in hepatocytic nuclei as a novel antigenic reactivity using the direct immunofluorescence technique on paraffinized liver sections from HBsAg positive patients. It belongs to the *Deltaviridae* Family and *Deltavirus* genus (RIZZETTO ET AL, 1977; RIZZETTO ET AL, 1980). HDV is a defective hepatotropic virus that depends on the hepatitis B virus (family *Hepadnaviridae*), particularly on the expression of the HBV surface antigen (HBsAg), for assembly and release of infectious particles (MENTHA, ET AL, 2019). VHD has a circular genome approximately 1.7kd, with a single strand of negative-sense ribonucleic acid (RNA), enclosed in a viral particle measuring between 36–43 nm in diameter, and has no nucleocapsid structure (TAYLOR, 2012). The VHD-RNA genome is self-complementary, it folds into an unclosed stem structure with 70% nucleotide pairing (RIZZETTO, 2015) measuring between 35nm and 37nm. This circular RNA encodes a protein, the hepatitis delta antigen (HDAg). HDAg is found in two forms, the small HDAg (S-HDAg) (p24) that acts in the viral replication process and the large HDAg (L-HDAg) (p27), which, through interaction with HBsAg, acts in the formation of RNA (TAILOR, 2015). VHD uses the same mechanism as HBV due to its shared envelope protein (BOTELHO-SOUZA, ET AL, 2017). HDV is among the smallest viruses capable of causing human disease, and the co-infection of HBV with HDV is the most severe form of viral hepatitis (HUGHES ET AL, 2011).

Due to its distinct characteristics, HDV was postulated to originate from plant viroids or circular cellular RNAs and is currently the only member of the Deltavirus genus described (MAGNIUS ET AL, 2018).

The transmission of HDV can occur parentally and sexually, being co-infection with HBV or by super-infection in chronic carriers of HBV, both types of transmission can cause acute, self-limited hepatitis of both viruses in most individuals infected simultaneously, while in the case of HDV superinfection in chronic HBV carriers, the disease has a chance of progressing to the chronic phase in almost 90% of cases (SAGNELLI ET AL, 2021).

To date, no treatment has been approved by the FDA (Food and Drug Administration), despite the great importance of HDV infection. However, pegylated alpha interferon (Peg-IFN) has been used and recommended for treatment by leading scientific societies for the study of the liver (KOH ET AL, 2019).

Since it was first identified 55 years ago (CHEN ET AL, 2019) epidemiological data on HDV infection have changed considerably in almost all countries. These changes are related to new population life habits, changes in economic levels, expansion of the use of nucleotide analogues for the treatment of HBV in chronic carriers, and the effectiveness of universal vaccination campaigns against HBV infection in most countries, which have been of fundamental importance (SAGNELLI ET AL, 2021). In this time of the coronavirus 2019 (COVID-19) pandemic, other changes are also expected, such as less possibility of screening, access to treatment and reduced effectiveness of the vaccination policy against HBV infection and the management of patients with severe chronic hepatites, causing a great impact on the quality of life of human beings. In this review, we highlight the epidemiology, clinical features, and molecular diagnostics options for VHD, focusing on resource-limited settings through an integrative review (CHEN ET AL, 2019).

2. METHODOLOGY

This is a review of the literature of national and international articles produced on epidemiological aspects, clinical characteristics and molecular diagnosis of VHD.

The electronic databases selected for the search were: National Library of Medicine National Institutes of Health (PubMed) via MEDLINE, Portal de Periódicos da CAPES, Latest Medical News, Clinical Trials, Guidelines – Medscape, Springer, Latin American and Caribbean Literature in Health Sciences (LILACS) and Scientific Electronic Library Online (SciELO). Approximately 60 articles published in the period from 2006 to 2021 were included and the most relevant articles were selected. Some articles, published before 2006, were also added to the review because they present data related to the history of VHD. The survey was designed around the question: "What is the level of scientific evidence on HDV infection?".

After defining the databases for the search and the eligibility criteria, the scientific articles published in full in English and Portuguese in the last 15 years, with free access and thematic focused on the objective of the review, were considered eligible; the keywords used in the searches were: hepatitis, virus, delta, epidemiology, diagnosis and VHD.

3. RESULTS

Epidemiology

Epidemiological studies for HDV infection have been carried out specifically to assess the prevalence of infected individuals among chronic HBV carriers (SAGNELI, 2021). Of the 350 million HBV surface antigen (HBsAg) positive

individuals worldwide, about 74 million are also co-infected with HDV (CHEN, 2021). The co-infection of HDV/HBV has a geographic variation, this fact influences the prevalence. The accuracy of the global prevalence of HDV infection is still unknown due to heterogeneous and non-standardized screening practices and the lack of accessibility to testing in many endemic areas (POLARIS, 2018).

According to the World Health Organization in 2018, among people infected with HBV, HDV infection is particularly common in Central and West Africa, Namibia and Ireland, Mongolia, Pakistan, Japan, Taiwan Province of China, the Pacific Islands (Kiribati, Nauru), Middle East, Eastern Europe (eg Turkey), South America (Amazon basin, Peru and Venezuela) and Greenland (WENDEMEYER, 2010; SILVA, 2012; ROMEO, 2014; FRANÇOIS-SOUQUIERE, 2015; SAGNELLI, 2021).

In a 2017 systematic review carried out on the African continent, it was confirmed that among people infected with HBV the prevalence of HDV antibodies (anti-HDV) ranged from 26% in Central Africa, 7% in West Africa and 0.05% in East Africa. (STOCKDALE, 2017).

High prevalence points were reported in Gabon (45%, 2015), Democratic Republic of Congo (26%, 2017), Mauritania (19%, 2009), Cameroon (14-35%, 2011) and Nigeria (5%, 2014). Among people co-infected with HIV-HBV, high prevalence points were reported in Guinea-Bissau (25%, 2011), Cameroon (12%, 2010), and Nigeria (7%, 2004) (STOCKDALE, 2017).

The chronic carrier status of HBV (HBsAg positive) is the main epidemiological factor for the spread of HDV, which occurs, for example, among the native populations of the Brazilian, Peruvian, Venezuelan Amazon and, in certain areas of Africa (WENDEMEYER, 2010; SILVA, 2012; ROMEO, 2014; FRANÇOIS-SOUQUIERE, 2015).

Rizzetto contributors conducted a study with the objective of reporting the impact of residual domestic HDV infections in Italy, for this study, 121 native Italians were considered to determine their clinical characteristics and the impact of the disease on liver transplant programs and concluded- Although VHD is disappearing in Italy, a legacy of elderly Italian patients with advanced VHD liver disease still represents an important medical issue and maintains an impact on liver transplantation (RIZZETTO ET AL, 2021).

In Uzbekistan, Asia, a study was carried out to observe the medical impact of hepatitis D virus infection determined in 6,589 patients with viral cirrhosis collected in 3 years, where it was concluded that HDV superinfection is present in more than 80 % of HBsAg-positive cirrhosis in Uzbekistan. VHD appears to be the main cause of advanced viral liver disease and juvenile cirrhosis in the country (KHODJAEVA ET AL, 2019).

Another very relevant study was carried out in Greece, showing that the prevalence of HDV is lower in native Greeks compared to immigrants, and may contribute to more than 50% of the burden of HDV infection in Greece, confirming that hepatitis D is a disease rapidly progressive, but interferon-based treatment can alter its course (MANESIS ET AL, 2013).

On the other hand, in Korea, the prevalence and clinical characteristics of HDV co-infection in patients with chronic HBV infection, where HBV infection is endemic, were observed in a study. Nine hundred and forty patients [median age, 48 (18-94) years; men, 64.5%] chronically infected with HBV were enrolled to participate in the trial. In conclusion, the prevalence of HDV infection is very low (0.32%) in Korea. All VHDs were genotype 1 and detected in inactive carriers of HBsAg. Therefore, HDV co-infection may not have a significant clinical impact in Korean patients with chronic HBV infection (KIM ET AL, 2011).

In Brazil, historical accounts dating from the mid-18th century record the deaths of members of the Royal Academy of Sciences in Paris from a disease described as acute jaundice fever, during an expedition along the Amazon River (FONSECA, 2007). In the second half of the 20th century, studies described a condition of severe jaundice, with rapid evolution and death records five days after the initial symptoms in the municipality of Lábrea, in the interior of the state of Amazonas. The condition was initially called Labrea black fever (FONSECA, 1983), but the cases were investigated and in 1987 it was confirmed that Labrea black fever was a condition of fulminant hepatitis caused by HDV infection in patients with HBV (BENSABATH, 1987; BERTOLLO ET AL, 2015)

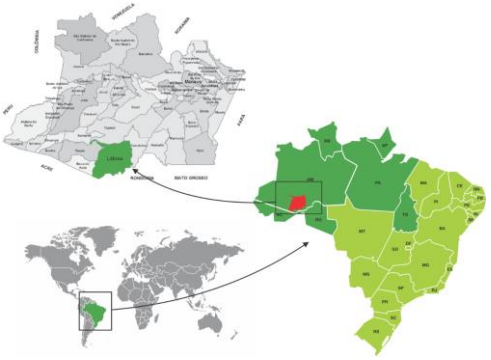

Figure 1: First HDV records in the municipality of Labrea, in the interior of the state of Amazonas (OLIVEIRA, 2022).

From 1999 to 2017, 587,821 confirmed cases of viral hepatitis were reported in SINAN (Information System on Notifiable Diseases), 37.1% of which were Hepatitis B and 0.7% of Hepatitis D. The North region accumulates 75% of

the total number of cases. cases of hepatitis D in Brazil. In 2017, 159 cases were reported in the country, 87 (54.7%) in the North region, where most cases were in males and the chronic form was the one with the highest percentage in the clinical classification of reported cases (VILLA DI FILIPPO D, ET AL, 2015; MINISTRY OF HEALTH, 2018).

Despite the low prevalence of HDV in non-endemic regions, this infection remains a major concern in the north of the country, indicating that a continuous epidemiological surveillance program should be implemented in all Brazilian regions (LAGO ET AL, 2018). According to studies, in other states of Brazil the presence of HDV is confirmed, such as in Maranhão (NUNES ET AL, 2021), Minas Gerais (SCARPONI ET AL, 2019) and Tocantins (VILLAR ET AL, 2018).

Currently, the general prevalence of HDV highlights that the disease is far from being controlled in Brazil, despite the infection being recorded throughout the Brazilian territory, 77% of cases occur in the North region, in the states of Acre, Amazonas and Roraima, mainly the Juruá, Solimões and Purus river basins, in the state of Amazonas, are considered highly endemic and highly prevalent in the indigenous population (CÍCERO, ET AL, 2012; MENTHA, ET AL 2019).

Figure 2: Serological test performed in the indigenous community (ALAVRENGA, 2015).

3.1 Vhd genetic diversit

Its origin of genetic diversity is related to a geographically isolated area, it is currently classified in eight genotypes distributed in specific geographic areas (BARROS, 2011; PRAVEEN ET AL, 2021). Genotype 1 (HDV-1), for example, is found in almost all parts of the world, it is the most common, as in Europe, the Middle East, North America and North Africa (WENDEMEYER, 2010; ABBAS, 2013); genotypes 2 and 4 (HDV-2 and HDV-4) are found in East Asia, with genotype 2 found in Japan, Taiwan and Russia and 4 found in Taiwan and Japan (FOUPOUAPOUOGNIGNI, 2011; MESHKAT, 2015). Genotype 3 (HDV-3) is found exclusively in the northern region of South America, being quite common in the Amazon Basin of Brazil, Peru, Colombia and Venezuela

(ABBAS ET AL, 2010; HUGHES, 2011; MESHKAT, 2015; DI FILIPPO VILLA ET AL, 2015; BRAGA ET AL, 2014; ALVARADO-MORA ET AL, 2011; NGUYEN ET AL, 2017) and genotypes 5 to 8 were identified in individuals from West and Central Africa, including those who migrated to the northern Europe (HUGHES, 2011; ROMEO, 2014, NGUYEN ET AL, 2017; (SAGNELLI ET AL, 2021).

Figure 3: Worldwide prevalence of HDV and distribution of its genotypes (OLIVEIRA, 2022).

3.2 Infection and transmission

HDV infection occurs with the presence of HBV, and co-infection with both 748írus748t can result in an acute infection with 748írus748tes B and D. When a person is chronically infected with HBV and subsequently infected with HDV, phenomenon of superinfection (ALVARADO, 2011). Clinically, co-infection is very similar to classic acute 748írus748tes B, this is because HBV infection is first established during acute co-infection before HDV infection begins to spread. Hepatitis D complications are more severe than a person infected with 748írus748tes B alone. Chronic HDV infection causes more serious morbidity and complications than chronic HBV infection, such as progressive fibrosis, cirrhosis, 748írus748tes748lar carcinoma, and liver decompensation (VASCONCELOS ET AL, 2020).

When there are cases of triple infection with HBV, 748írus748tes C 748írus (HCV) and HDV, HDV or HCV in most reports dominates the 748írus 748írus748t, but this depends on geographic region, host immunological factors, HDV activity and genotype. (FARCI, 2012; MENTHA, ET AL 2019; MASOOD, 2021).

The transmission of HDV occurs through parenteral exposure, considered co-infection 748íru it occurs in the primary or acute phase of HBV infection and superinfectionvírus it occurs in cases of chronic vírus vtes B. Regarding demographic data, HDV infection mainly affects male patients, a fact that results from the higher prevalence of HBV in this sex. Regarding the relationship between HDV infection and age group, a higher prevalence is observed in people under 15 years of age (WEDEMEYER, 2010).

The transmission of HDV can occur through sexual intercourse with positive individuals without using a condom, perinatally (YURDAYDIN, 2017) depending on the infectivity of HBV and whether mothers carrying HBV have serological signs of viral replication, for example, HbeAg positive or anti-Hbe+/HBV-DNA positive, and can transmit the 749írus to the child during pregnancy, childbirth or breastfeeding (FARCI, 1994; FONSECA, 1993). As well as sharing material for injecting drug use, personal hygiene utensils, sharps or making tattoos, piercings and blood transfusions of positive people (MELO, 2011; CHEN, 2021).

3.3 Prevention and treatment

The HBV vaccine is the best procedure for reducing the prevalence and incidence of HDV infection. However, the vaccine is effective only in co-infection (simultaneous HBV+HDV infection) among individuals susceptible to HBV infection. Among individuals who are chronic carriers of HBV, residing in areas that are endemic for HDV infection, or belonging to risk groups, prophylaxis of HDV superinfection continues to pose risks (TERRAULT, 2018). As HDV depends on HBV, prevention can be achieved with hepatitis B vaccination. If the host is immune to HBV, they are therefore protected against HDV. Patients who are at risk of contracting HDV infection should be encouraged to receive the hepatitis B vaccine (LEE, 2021).

Currently, options for treating acute or chronic hepatitis D are limited and there is no specific treatment. Even not approved by the Medicines Committee or the European Medicines Agency, standard treatment and pegIFNα are the most used as an anti-HDV strategy in the last three decades (GOYAL, 2018). The only treatment regimen currently recommended by international guidelines has been PegIFNα (TERRAULT, 2018; URBAN ET AL, 2021). The administration of weekly subcutaneous injections of pegIFNα for 48 weeks eliminates HDV replication in approximately 30% of patients with 24 weeks with interval therapy, however the side effects are very significant, the use of continuous IFN for more than 48 weeks can induce a lower probability of the disease progressing (URBAN ET AL, 2021).

Although the long-term virological/biochemical response when using IFN for treatment has been associated with better outcomes (YURDAYDIN, 2017), IFN is contraindicated in the elderly or in those with stigmata of autoimmune disease or with advanced or decompensated liver disease, limiting thus its use in clinical practice. It may be that the failure of IFN treatment to induce a long-term sustained virological response in HDV is due to the persistence of the virus in the liver even though HBsAg has very low levels, as it is observed that even after liver transplantation, HDV can persist in the liver. liver for many months even in the absence of liver HBV DNA/serum HBsAg and VHD RNA DNA (MEDERACKE, 2012). The use of

IFN for treatment is used to suppress VHD replication, which is demonstrated by the inability to detect VHD RNA in serum and HDAg in the liver. Endpoints of treatment include normalization of alanine aminotransferase (ALT) and inflammation on liver biopsy. When the disease progresses to cirrhosis, liver transplantation is the only viable option (MASOOD, 2021).

3.4 Diagnosis

Traditionally, the diagnosis of a viral disease is based on culture analysis methods that directly detect the intact virus or its components (proteins or nucleic acids) or serological tests that indirectly detect virus antigens or antibodies (MAURIZ, 2020). Currently, polymerase chain reaction (PCR) based methods are widely used in virus diagnosis due to their high specificity, sensitivity and ease of operation. These tests can quickly amplify certain parts of the genome necessary for virus identification (CHEN, 2021).

3.5 Serological Diagnosis

Shortly after the discovery of HDV, antibody tests were developed and marketed as serological markers of HDV infection, therefore, to diagnose it, it is necessary to undergo serological tests, however, currently the enzyme immunoassay (ELISA) is the most used to search for anti-HD IgG, anti-HD IgM and HDAg. HDAg, a marker of acute infection and anti-HD Total (anti-HD IgG, from anti-HD IgM) is the screening test for past or chronic infection (SARACENI, 2001; HUGHES, 2011; WRANKE, 2014; KOH, 2014; KOH, 2019; VLACHOGIANNAKOS, 2020).

Normally in co-infection, anti-HDV IgM appears and then converts to anti-HDV IgG. HDV RNA levels reach high levels in serum. HBV IgM anti-HBc will also be found to be positive in this acute co-infection. In superinfection, HDV antibodies appear early as IgM, followed by anti-HDV IgG, while anti-HBc is only IgG. Antibodies may increase in superinfection as the disease progresses to chronicity and may be present in high titers along with positive HDV RNA (SARACENI, 2001; OLIVEIRO, 2012; NOUREDDIN, 2014; SAGNELLI, 2021).

3.6 Molecular Diagnosis

Molecular analyzes in the study of HDV allow both manipulation of genes and qualitative and quantitative detection of viral DNA, which can be used to diagnose and monitor treatment results, especially for confirmation of viremia in chronic cases. The greatest use of the technique is the determination of viral load, during therapeutic monitoring and in the genotypic characterization of HDV (HOLANDA, 2012; TERRAULT, 2018; BEHERA, 2020).

The Polymerase Chain Reaction (PCR) technique has been recognized worldwide as one of the most important scientific advances of our generation. Like traditional PCR, real-time PCR has quickly become a major nucleic acid amplification technology in the world, as it adds greater sensitivity and specificity, allowing for an early diagnosis of infectious agents and monitoring of disease progression and the therapeutic response (CRISPIM, 2014; GIERSCH, 2014).

The qualitative test generally used to detect HDV DNA is PCR (polymerase chain reaction), this technique allows the in vitro replication of DNA, through specific primers, extremely quickly. Minimal amounts of genetic material can be detected and amplified millions of times in a few hours. A PCR is considered sensitive when it is able to detect between 10 and 100 copies of the virus per mL of serum. In order to avoid false-positive and false-negative results, it is necessary to standardize the technique before using it in routine analysis (PARASKEVIS, 2010; SILVA, 2012).

In HBV, the S and C genes are generally the most used in PCR amplifications, as they contain the most conserved regions of the viral genome and allow genotyping. Another gene that is currently being investigated is the Polymerase P gene as it allows the analysis of viral resistance to antivirals. The development of commercial HBV molecular diagnostic kits has spread the use of PCR in laboratories. Thus, a variety of qualitative and quantitative tests are commercially available and are used to determine the presence of infection or to assess the response to treatment (PAS, ET AL, 2000; RODRIGUES, 2006; PARASKEVIS, 2010). These tests are designed to target sequences that encode the conserved regions of HDAg or the ribozyme domain. The HDV genome has a robust secondary structure, which can be destroyed by adding heat shock treatment before the reverse transcription step, thus improving reverse transcription efficiency. The use of one-step RT-qPCR reduces the risk of contamination during reverse transcription and amplification (PAGONI, 2013; HOMS, 2014).

Real-time PCR technology makes it possible to develop a test that allows to quantify the VHD viral load in serum or plasma samples from infected patients with efficiency and potentially reduced costs, as there is knowledge of both the real-time PCR and PCR technique and of genetic engineering, technique used for the production of recombinant clones that will be used in the construction of the standard curves, using minimum amounts of inputs. (CRISPIM, 2014; GIERSCH, 2014; KUMAR, 2016).

Viral load is generally measured using PCR techniques, including real-time PCR, which is much more sensitive and reliable than other techniques. Quantification of viral load is a crucial component in the assessment of patients with chronic HBV infection and in the assessment of the effectiveness of antiviral treatment (TERRAULT, 2018).

In the late 1990s, a new quantitative diagnostic method, quantitative real-time PCR (qPCR), began to be used for the quantification of viruses in humans, such as hepatitis B (CANE ET AL, 1999) and HIV (LEWIN ET AL, 1999). The conceptual and practical simplicity, together with the combination of speed, sensitivity, and specificity in the same assay, made the qPCR technique a reference for the quantification of nucleic acids (BUSTIN ET AL, 2009) and a powerful tool for quantification. of gene expression (SCHMITTGEN AND LIVAK, 2008).

4. FINAL CONSIDERATIONS

The cases of quality of life hepatitis due to HDV associated HBV with health also represent a serious public health problem, generating continuous demands on the health services of several considerable patients in the lives of all those infected, also manifesting in the lives of those infected, taking the lives of the infected. Epidemiological studies disclosed that the global burden of VHD is higher than previously (OLIVEIRA, 2017).

Rapid laboratory diagnosis of HDV infection is of significant importance in identifying, monitoring and controlling the spread of the disease, the sensitivity of different methods of detection of HDV RNA varies substantially, and there is a lack of a unified international detection standard for comparable results between different laboratories. In addition, insufficient access to healthcare in low- and middle-income countries often leads to underdiagnosis of the disease, making early diagnosis and effective treatment difficult (CHEN, 2021).

However, there is still a need to develop new detection methods that not only have high sensitivity and specificity, but can also monitor a number of processes, such as RNA extraction from HDV, reverse transcription, and quantification, thus reducing false-false rates. negative, identifying patients with HDV earlier and controlling transmission in a timely manner.

The global health system with the SARS-CoV-2 pandemic has had a negative impact on the development of assistance programs for other diseases. Considering that millions of people live with chronic HBV, the health care emergency in relation to SARS-CoV-2 has strongly undermined screening, management and treatment programs for diseases associated with HBV and HDV around the world. To date, no epidemiological data on HBV/HDV co-infection during the SARS-CoV-2 pandemic are available and few data on HBV infection are reported in the literature, although HBsAg positive individuals are at high risk of acquiring HBV infection. SARS-CoV-2 (SAGNELLI, 2021).

The literary analysis of the articles observed evidenced the need for more studies to better understand the HDV infection; determine the

epidemiology of HDV infection among HBV patients; and to evaluate new treatment strategies in infected people to reduce the risk of liver complications and mortality. These are knowledge gaps that need to be overcome in order to understand and manage the complex mechanisms of VHD infection.

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