

## Sexually acquired hepatitis

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*Sex Transm Infect* 2002;**78**:235–240

Series editor: David Lewis

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Accepted for publication 28 June 2002

**Objectives:** To assess current knowledge of sexually transmitted viral hepatitis in relation to epidemiology, clinical presentation, management, and diagnosis with particular reference to resource-poor settings.

**Method:** A search of published literature identified through Medline from 1966 to October 2001, the Cochrane Library, and reference lists taken from each article obtained. Textword and MeSH searches for hepatitis A, B, C, D, E, G, delta, GB virus, GBV-C, and TT virus were linked to searches under the textword terms sex\$, prevent\$, and MeSH subheadings, microbiology, complications, drug therapy, therapy, diagnosis, epidemiology, transmission, and prevention and control.

**Conclusions:** In heterosexual relationships, hepatitis B is readily transmitted sexually and hepatitis C and D less so, with no evidence for sexual transmission of hepatitis A. Hepatitis types A–D are all transmissible sexually in male homosexual relationships under certain conditions. In resource-poor countries sexual transmission is generally only a significant route of transmission for hepatitis B.

Hepatitis B has been recognised as a sexually transmitted infection for over 25 years and more recent evidence supports sex as being one of the routes of transmission for hepatitis types A, C, and D. Although the viruses named hepatitis G, GB, and TT may also be sexually transmitted, current evidence suggests that these organisms do not cause disease and will not be discussed further. Similarly, hepatitis E will not be discussed further as there is no evidence for sexual transmission. The purpose of this article is to look at recent developments in our understanding of the sexually transmitted forms of viral hepatitis with reference to management in resource-poor settings.

### HEPATITIS A Epidemiology

This infection is usually transmitted by the faeco-oral route, including contaminated food and water, as well as by close personal contact.<sup>1,2</sup> It is prevalent worldwide and the World Health Organization (WHO) recognises three levels of hepatitis A virus (HAV) endemicity (table 1). In countries with high endemicity, over 90% of adults and over 80% of older children may show evidence of past infection in seroprevalence studies.<sup>3</sup> However, improving levels of sanitation in many countries in the last decade have led to a fall in childhood HAV infection with a concomitant rise in adults susceptible to symptomatic disease and outbreaks.<sup>4–6</sup> Parenteral spread can also occur in injecting drug users, haemophiliacs using contaminated factor VIII, and other recipients of blood products.<sup>7–11</sup>

### Sexual transmission

There are now numerous reports of HAV outbreaks among men who have sex with men (MSM). Infection correlates with visits to saunas and darkrooms, sex with anonymous partners,

group sex, oro-anal and digital-rectal intercourse, and number of partners.<sup>12–15</sup> Outbreaks are mainly confined to large cities including Melbourne, New York, London, Amsterdam, and Tokyo.<sup>12–18</sup> However, the majority of MSM do not seem to be at increased risk, nor is there evidence for heterosexual spread of HAV.<sup>19–21</sup> As HAV is largely a childhood infection in many countries, it should be no surprise that there is no evidence for sexual transmission as a significant route of infection in adults in resource-poor countries.

### Clinical presentation

Hepatitis A has an incubation period of 2–6 weeks for clinically apparent infection. Disease usually starts with a flu-like prodromal illness lasting for up to 2 weeks, followed by icteric hepatitis which lasts for a few weeks and rarely longer than 3 months.<sup>2</sup> However, disease manifestation is very much age related. For instance, only 5–20% of children under 5 years old will develop icteric disease, the rest having asymptomatic transient infection, and HAV related mortality is negligible in this age group.<sup>2</sup> Therefore, icteric hepatitis A is a relatively uncommon disease in highly endemic countries with very high rates of childhood infection. Adults infected with HAV are more likely to develop icteric hepatitis (75–90%) although mortality remains generally very low (0.3%).<sup>2,22,23</sup> The circumstance in which HAV infection has a significant mortality is when it occurs in older patients (over 40 years) or those with chronic liver disease, such as that due to hepatitis C, B, or alcohol.<sup>24–26</sup>

### Diagnosis and management

Acute hepatitis A cannot be distinguished clinically from that due to types B, C, D, or E although in most resource-poor countries HAV is the leading cause of acute icteric hepatitis in children.<sup>2,3</sup> Liver function abnormalities are similar for all

**Table 1** World Health Organization defined patterns of hepatitis A endemicity<sup>2</sup>

High	Developing countries with poor sanitary/hygienic conditions—parts of Africa, Asia, and central and South America. Infection mostly in children and therefore usually mild or asymptomatic. Incidence of disease may reach 150/100 000 population per year. Approximately one million cases per year in these areas.
Intermediate	Countries where sanitary conditions are variable—south and east Europe, parts of the Middle East. Many children escape infection, therefore clinical disease incidence may be high as infection occurs more frequently in adults.
Low	Countries with good sanitary and hygienic conditions—northern and western Europe, Japan, Australia, New Zealand, United States, and Canada. Infection rates are low and disease may occur among specific risk groups such as travellers. Disease incidence of 5–10/100 000/year

**Table 2** Biochemical features of acute viral hepatitis

Test	Notes
Serum aminotransferases (ALT, AST) Serum bilirubin	Typically peaks at 500–10000 IU/l in the first few weeks. 30–100 µmol/l. Mixed conjugated/unconjugated with bilirubinuria. Prolonged jaundice with rising bilirubin is seen in patients with the cholestatic variant. Beware other serious causes of acute jaundice in the tropics such as malaria, yellow fever and typhoid, all of which are usually accompanied by fever—a fever is normally absent in icteric viral hepatitis
Serum alkaline phosphatase	Usually normal or only mildly raised (<300 IU/l) except in the uncommon cholestatic variant of acute viral hepatitis. Epstein-Barr virus related hepatitis often presents with a moderately raised serum alkaline phosphatase level (300–500 IU/l) and aminotransferase levels <1000 IU/l. Very high alkaline phosphatase levels suggest biliary tract disease.
Prothrombin time	May be slightly prolonged by 1–5 seconds. Prolongation >5 seconds (INR >1.5) suggest impending hepatic failure.

**Table 3** Confirmatory serum tests for viral hepatitis (common patterns)<sup>27 28 66</sup>

Virus type	Acute infection	Chronic infection	Recovered/immune
Hepatitis A	IgM anti-HAV +ve	Does not occur	IgG anti-HAV +ve IgM anti-HAV -ve
Hepatitis B	IgM anti-HBc +ve, HBsAg +ve, HBeAg +ve HBV-DNA +ve	IgM anti-HBc -ve (+ve low titre in flares) HBsAg +ve, HBeAg + or -ve HBV-DNA+ or -ve	IgG anti-HBc +ve (NB some tests measure combined IgG and IgM) IgG anti-HBs +ve (may become negative) HBsAg -ve
Hepatitis C	IgG anti-HCV +ve by ELISA and RIBA tests (but may take up to 3 months or more). HCV-RNA +ve by PCR	As for acute infection	Antibody negative or IgG anti-HCV +ve by ELISA and RIBA tests. HCV-RNA -ve by PCR
Hepatitis D	IgG and IgM anti-HDV +ve HDAg +ve, HDV-RNA +ve With markers of acute/chronic hepatitis B infection	As for acute infection	Antibody, antigen, and RNA tests become negative within months of recovery.

types of acute viral hepatitis (table 2), but if resources allow, the diagnosis is confirmed by a serum antibody tests (table 3) using EIA.<sup>2 27 28</sup>

Most patients with acute icteric hepatitis will recover uneventfully on a regime of symptom control, rest, and adequate hydration and can usually be kept at home. In moderate/low endemicity countries there is a case for patient isolation, especially in patients with faecal incontinence, taking precautions against faeco-oral spread during the time of infectivity which is during the prodromal illness and for the first 2 weeks of jaundice.<sup>2 29</sup> Normal human immunoglobulin may be given to non-immune close personal contacts, as may HAV vaccine.<sup>30 31</sup> The vaccine may also be offered to those otherwise at risk such as non-immune travellers to endemic countries, MSM whose lifestyle puts them at risk, haemophiliacs, patients with chronic liver disease, or sewage workers.<sup>32</sup> Universal vaccination of children in developing countries is now being considered although is currently prohibitively expensive.<sup>2</sup>

## HEPATITIS B Epidemiology (table 4)

The majority of the world's hepatitis B virus (HBV) carriers have caught the infection through vertical transmission at birth and horizontal infection of children.<sup>33 34</sup> Other non-sexual routes of spread include horizontal transmission in institutions for patients with learning difficulties<sup>35</sup> and parenteral exposure such as occurs among injecting drug users, or those infected nosocomially.<sup>36 37</sup>

## Sexual transmission

HBV is very efficiently transmitted sexually during heterosexual and male homosexual contact.<sup>38–41</sup> Heterosexual transmission occurs in many situations which includes sex with female sex workers in many resource-poor countries.<sup>42–45</sup> Outside of prostitution, heterosexual transmission can still be important as shown by the 40% transmission rates to non-immune partners of patients with acute or chronic hepatitis B.<sup>34 35</sup> The importance of heterosexual transmission varies

**Table 4** Worldwide prevalence of hepatitis B, C, and D carriage<sup>33 34 79–82 87–89</sup>

Hepatitis type	Worldwide prevalence	Highest prevalence areas	Major routes of transmission in resource-poor countries
B	2 billion have been infected at some time in their life. Currently 350 million chronic carriers	Africa, Asia, and South America 5–10%. China and Taiwan 10–20%	Mother to infant (vertical) Child to child Sexual
C	170 million carriers — 3% of the world's population.	2–5% of the population in most resource poor countries. 10% in northern China and parts of Africa	Parenteral: reusable medical equipment, tattooing, traditional scarification and circumcision practices, blood products, injecting drug use
D	10 million carriers	Mediterranean basin, Middle East, central Asia, west Africa, Amazon basin, and some Pacific Islands. New areas identified in China, Japan, northern India, and Albania	Parenteral, injecting drug users. Horizontal, non-sexual, intrafamilial spread (exact mechanism is unknown)

from country to country. For instance in a Chinese seroprevalence study, most infection occurred in children under 5 years old but infection was also acquired by adults, some of whom are assumed to have acquired it sexually.<sup>34</sup> In both India and Tanzania, countries with a medium prevalence of chronic HBV (1–5%), higher rates are found in STD clinic attendees and correlate with other STDs, especially syphilis.<sup>46–47</sup> In fact, the Tanzanian study allowed an estimate of the proportion of hepatitis B that was sexually acquired in adults and was found to be 7.2% in men and 3.0% in women.<sup>47</sup>

Past studies of selected groups of homosexual men in the United States and Europe have found evidence of infection in 50% or more and HBsAg positive rates of up to 6%.<sup>39–40 48–55</sup> Transmission of HBV in homosexual men correlates with duration of sexual activity, number of partners, oro-anal and genito-anal sexual contact.<sup>51–52</sup> Despite the availability of an effective vaccine, HBV continues to be a significant problem in homosexual men in developed countries.<sup>53–55</sup> There is relatively little published work on homosexual transmission of HBV in the tropics with the exception of parts of Latin America.<sup>56–58</sup> In these countries there is evidence of very high rates of hepatitis B spread between homosexual men with indicators of present/past infection of over 40%.<sup>56–58</sup>

### Clinical presentation

As with HAV, acute infection of children with HBV is largely asymptomatic<sup>59–60</sup> and this situation accounts for the majority of HBV infections in resource-poor countries.<sup>33</sup> In adulthood many infections are asymptomatic, but 20%–35% of infections are marked by acute icteric hepatitis which tends to be more severe than that due to HAV. However, in the immunocompromised, including those who are HIV positive, asymptomatic acute infection is common.<sup>60–61</sup> For those with symptomatic disease, the incubation period is usually 6–12 weeks but can be as long as 6 months. HBV infection also causes fulminant hepatitis, chronic hepatitis, liver cirrhosis, and liver cancer. Approximately 1% of those with acute symptomatic infection will get fulminant hepatitis, marked by evidence of decompensated liver disease and leading to death in up to 50%.<sup>59</sup> Numerically far bigger is the problem of chronic infection, cirrhosis, and liver cancer. Ninety per cent of infants, 50% of preschool children, and 10% of adults with HBV will become chronically infected—that is, for more than 6 months.<sup>33–39</sup> Once chronic infection is established, this state may remain for decades and it is estimated that approximately 25% of chronically infected children will ultimately die of cirrhosis or liver cancer, usually from the fourth decade of life onwards and currently causing the death of about a million people annually.<sup>33</sup>

The majority of those with chronic infection have no symptoms until cirrhosis and decompensated liver disease develop in up to half of them when they experience abdominal ascites, jaundice, bleeding oesophageal varices and ultimately confusion, cachexia, and death. Both fulminant hepatitis and more rapidly progressive cirrhosis occur when chronic hepatitis B is complicated by hepatitis A, C, or D.<sup>62–64</sup> About 10% of those with cirrhosis get liver cancer<sup>65</sup> which presents with an enlarging liver, weight loss, and rapid progression to death.

### Diagnosis and management

Acute icteric hepatitis B is clinically similar for all types of viral hepatitis. Similarly, cirrhosis and liver cancer due to HBV cannot be distinguished on clinical grounds from those due to hepatitis C although HBV is the most common cause in most resource-poor countries.<sup>33</sup> A liver function test is available in many low resource healthcare settings and the pattern of abnormality for acute infection is similar for all types of viral hepatitis (table 2). Those with chronic hepatitis may have a normal liver function test apart from a mildly raised serum aminotransferase level (AST or ALT), although when cirrhosis

or cancer develop, the LFT becomes progressively more abnormal as does the serum prothrombin time.<sup>66</sup> HBV infection is confirmed by the presence of the serum surface antigen, a test which may be within the financial reach of many resource-poor settings, but to get more accurate assessment of the stage of infection more sophisticated and expensive assays for hepatitis B e antigen, and antibodies to the hepatitis B core, e and surface antigens needs to be done (table 3).<sup>66</sup> The most sensitive test of all is the HBV DNA assay,<sup>66</sup> which can be used to clarify issues if the antibody and antigen tests are not completely helpful (for example, in HBeAg negative replicative infection),<sup>67</sup> although the expense of this assay limits its use to only the most technologically sophisticated of laboratories.

The management of acute hepatitis is the same as that for hepatitis A. Chronic, HBeAg positive, infection can be cured in up to 50% of patients with drugs such as interferon alfa, lamivudine, famciclovir, and adefovir,<sup>68–71</sup> but the expense of these drugs has limited their use in resource-poor countries to a few healthcare settings.<sup>72</sup> HIV co-infection with HBV also complicates management in as much as therapy for HBV is less effective except in those with a high CD4+ lymphocyte count.<sup>73–74</sup> However, although the prognosis of liver disease in HIV/HBV co-infection may be worse,<sup>75</sup> this has not been entirely confirmed. There may be some advantage in prescribing lamivudine as part of any antiretroviral regimen, if available, in HIV/HBV co-infected patients in as much as the progression of liver disease may be delayed.<sup>74</sup> Once cirrhosis and liver cancer have developed, death is inevitable outside of those settings where liver transplantation and chemotherapy are available.<sup>33</sup> By far the most effective population strategy is universal vaccination, as advocated by the WHO. In Taiwan, widespread HBV vaccination, aiming particularly at infants and children has led to a 80% fall in chronic HBV carriage in children with similar decreases in childhood liver cancer. It is hoped that the HBV carrier rate in Taiwan will be <0.1% by 2010.<sup>76</sup> Similarly in China, the country with the largest number of HBV carriers, it is hoped that it will be virtually eradicated within a lifetime.<sup>77</sup> Certainly vaccination and consistent condom use will prevent most cases of sexually transmitted hepatitis B if advised to those at risk.<sup>39–40 78</sup>

## HEPATITIS D (DELTA VIRUS)

### Epidemiology

This RNA virus can only exist as a co-infection with hepatitis B but its geographic distribution is not uniformly identical to HBV (table 4). There are three main types of epidemiological pattern: endemic carriage (for example, Mediterranean basin, indigenous people in parts of South America), areas of mainly parenteral spread (for example, western Europe, North America) and areas with sudden epidemics (for example, in the Amazon basin, or central Africa).<sup>79–82</sup> Rarely, vertical (mother to infant) spread may also occur.<sup>79</sup>

### Sexual transmission

Several studies have shown sexual transmission of delta virus in both heterosexual couples and homosexual men and this route is significant both in endemic areas and in relation to injecting drug users in low prevalence countries.<sup>48 79 83 84</sup>

### Clinical presentation

Delta virus (HDV) can be first acquired concurrently with acute HBV infection or as a superinfection of a chronic HBV carrier. In acutely co-infected patients the incubation period is 3–7 weeks and there may be two bouts of clinical hepatitis due to each virus.<sup>79</sup> The acute infection is often quite severe and fulminant hepatitis is 10 times more likely than with other types of viral hepatitis with an 80% fatality rate.<sup>79</sup> Chronic infection occurs in only 5% of such patients. Superinfection of HDV in a HBV carrier causes an acute, severe, icteric hepatitis which again is associated with a high rate of fulminant disease

and also leads to chronic infection in 80%.<sup>79</sup> Chronic infection leads to a high rate of subsequent cirrhosis (up to 70%) which is usually more rapid in onset (40% in 6 years) than with HBV and can occur as little as 2 years after infection.<sup>79, 85</sup> The rate of progression to liver cancer in cirrhotics with HDV is also trebled compared to HBV alone (adjusted odds ratio of 3.2, 5 year risk 10% v 2–4%).<sup>85</sup>

### Diagnosis and management

Apart from the severity of infection, the only other clinically distinguishing feature is its propensity to cause acute hepatitis in known hepatitis B carriers (table 2).<sup>79</sup> Laboratory diagnosis can be established by a serum anti-HDV test (table 3) although the utility of this test in resource-poor settings is doubtful except to investigate epidemics. Antigen and RNA tests also exist but require a relatively high level of technological expertise.<sup>86</sup>

Management is along the same lines as HBV except that to date there is no effective antiviral therapy. However, this infection is largely preventable through HBV vaccination, condom use, sterile medical equipment, and the avoidance of equipment sharing in injecting drug users.<sup>79</sup>

## HEPATITIS C

### Epidemiology (table 4)

Parenteral transmission is the predominant route of transmission in most resource-poor countries.<sup>87–89</sup> It is unclear how important vertical (mother to infant) transmission is in HIV negative women but, as with all other situations, HIV co-infection markedly increases the rate of hepatitis C virus (HCV) transmission to over 9% and may also lead to spread through breast milk.<sup>90</sup> In developed countries the majority of carriers are injecting drug users, their partners, or those who have received untested blood or blood products

### Sexual transmission

HCV can be sexually transmitted (unprotected vaginal sex) but at a relatively low rate, probably 0.5–2% per year of a relationship or 5% of all heterosexual relationships. Transmission rates are markedly higher if the source patient is also HIV positive.<sup>91–93</sup> There is also evidence for homosexual spread.<sup>94</sup> However, these data are from studies in Europe and the United States. Studies on sexual transmission in resource-poor countries are less certain. For instance, reports from Malawi, Jamaica, and Tanzania did not show evidence of significant sexual spread of HCV in the general population.<sup>95–97</sup> Conversely, research in Thailand, Argentina, and Egypt does link HCV spread to heterosexual sex, particularly in relation to HIV infection.<sup>89, 98, 99</sup> As with hepatitis A, this evidence therefore suggests that sexual transmission may occur in resource-poor countries but at a rate that is relatively minor compared with other routes of spread.

### Clinical presentation

After an incubation period of up to 150 days, icteric hepatitis occurs in under 20% of acute infections, the rest being asymptomatic.<sup>87, 100, 101</sup> Fulminant hepatitis is rare except for hepatitis A superinfection of chronic HCV disease.<sup>102</sup> However, about 80% of patients develop chronic (>6 months) infection and spontaneous recovery is rare in such people.<sup>87, 100, 101</sup> Symptoms of chronic infection are rare until cirrhosis intervenes which happens in about 20% after 20 years. Liver cancer also develops in up to 5% of carriers after 20–30 years. Progression to cirrhosis is more likely and more rapid if there is co-infection with HIV, HBV, or a high alcohol intake.<sup>87, 100, 101</sup>

### Diagnosis and management

There is no way to distinguish acute icteric (table 2) and chronic HCV infection from other types of viral hepatitis on clinical grounds. Antibody tests are available (table 3) but

expensive. Usually, an ELISA is used for screening, and the positive test confirmed by a RIBA because of the high rate of false positive tests by the ELISA method.<sup>103</sup> It can take anything up to 9 months after exposure to HCV for the patient's antibody test to become positive although most are positive within 3 months.<sup>87, 103</sup> For settings with advanced technological facilities a polymerase chain reaction (PCR) assay can be used to determine if an antibody positive patient is an HCV carrier, although over 90% are.<sup>103</sup>

There is no effective vaccine and so prevention is centred around non-reusable medical equipment, education, testing of donated blood, and safer sex including condoms.<sup>87</sup> However, it is wise to vaccinate HCV carriers against hepatitis A and B to prevent the severe consequences of co-infection with these viruses.<sup>87, 100, 101, 102</sup> Approximately 50% of carriers can be cured using a treatment combination of pegylated interferon injections and ribavirin for 6–12 months, although this is very expensive and beyond the scope of most resource-poor countries.<sup>104</sup>

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