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# Sexually acquired hepatitis

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**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.[1 2] 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.[3] 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.[4–6] Parenteral spread can also occur in injecting drug users, haemophiliacs using contaminated factor VIII, and other recipients of blood products.[7–11]

### 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.[12–15] Outbreaks are mainly confined to large cities including Melbourne, New York, London, Amsterdam, and Tokyo.[12–18] However, the majority of MSM do not seem to be at increased risk, nor is there evidence for heterosexual spread of HAV.[19–21] 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.[2] 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.[2] 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%).[2 22 23] 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.[24–26]

### 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.[2 3] Liver function abnormalities are similar for all

**Table 1** World Health Organization defined patterns of hepatitis A endemicity[2]

| | |
|---|---|
| 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) | Typically peaks at 500–10000 IU/l in the first few weeks. |
| Serum bilirubin | 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)[27 28 66]

| Virus type | Acute infection | Chronic infection | Recovered/immune |
|---|---|---|---|
| Hepatitis A | IgM anti-HAV+ve | Does not occur | IgG anti-HAV +ve<br>IgM anti-HAV -ve |
| Hepatitis B | IgM anti-HBc +ve,<br>HBsAg +ve, HBeAg +ve<br>HBV-DNA +ve | IgM anti-HBc -ve (+ve low titre in flares)<br>HBsAg +ve, HBeAg + or -ve<br>HBV-DNA+ or -ve | IgG anti-HBc +ve (NB some tests measure combined IgG and IgM)<br>IgG anti-HBs +ve (may become negative)<br>HBsAg -ve |
| Hepatitis C | IgG anti-HCV +ve by ELISA and RIBA tests (but may take up to 3 months or more).<br>HCV-RNA +ve by PCR | As for acute infection | Antibody negative or IgG anti-HCV +ve by ELISA and RIBA tests.<br>HCV-RNA -ve by PCR |
| Hepatitis D | IgG and IgM anti-HDV +ve<br>HDAg +ve,<br>HDV-RNA +ve<br>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.[2 27 28]

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.[2 29] Normal human immunoglobulin may be given to non-immune close personal contacts, as may HAV vaccine.[30 31] 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.[32] Universal vaccination of children in developing countries is now being considered although is currently prohibitively expensive.[2]

## 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.[33 34] Other non-sexual routes of spread include horizontal transmission in institutions for patients with learning difficulties[35] and parenteral exposure such as occurs among injecting drug users, or those infected nosocomially.[36 37]

### Sexual transmission

HBV is very efficiently transmitted sexually during heterosexual and male homosexual contact.[38–41] Heterosexual transmission occurs in many situations which includes sex with female sex workers in many resource-poor countries.[42–45] 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.[34 35] The importance of heterosexual transmission varies

**Table 4** Worldwide prevalence of hepatitis B, C, and D carriage[33 34 79–82 87–89]

| 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.<br>Currently 350 million chronic carriers | Africa, Asia, and South America 5–10%.<br>China and Taiwan 10–20% | Mother to infant (vertical)<br>Child to child<br>Sexual |
| C | 170 million carriers — 3% of the world's population. | 2–5% of the population in most resource poor countries.<br>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.[34] 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.[46 47] 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.[47]

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%.[39 40 48–55] Transmission of HBV in homosexual men correlates with duration of sexual activity, number of partners, oro-anal and genito-anal sexual contact.[51 52] Despite the availability of an effective vaccine, HBV continues to be a significant problem in homosexual men in developed countries.[53–55] There is relatively little published work on homosexual transmission of HBV in the tropics with the exception of parts of Latin America.[56–58] 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%.[56–58]

### Clinical presentation

As with HAV, acute infection of children with HBV is largely asymptomatic[59 60] and this situation accounts for the majority of HBV infections in resource-poor countries.[33] 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.[60 61] 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%.[59] 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.[33 59] 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.[33]

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.[62–64] About 10% of those with cirrhosis get liver cancer[65] 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.[33] 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.[66] 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).[66] The most sensitive test of all is the HBV DNA assay,[66] which can be used to clarify issues if the antibody and antigen tests are not completely helpful (for example, in HBeAg negative replicative infection),[67] 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,[68–71] but the expense of these drugs has limited their use in resource-poor countries to a few healthcare settings.[72] 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.[73 74] However, although the prognosis of liver disease in HIV/HBV co-infection may be worse,[75] 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.[74] Once cirrhosis and liver cancer have developed, death is inevitable outside of those settings where liver transplantation and chemotherapy are available.[33] 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.[76] Similarly in China, the country with the largest number of HBV carriers, it is hoped that it will be virtually eradicated within a lifetime.[77] Certainly vaccination and consistent condom use will prevent most cases of sexually transmitted hepatitis B if advised to those at risk.[39 40 78]

## 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).[79–82] Rarely, vertical (mother to infant) spread may also occur.[79]

### 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.[48 79 83 84]

### 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.[79] 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.[79] 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%.[79] 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.[79 85] 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%).[85]

### 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).[79] 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.[86]

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.[79]

## HEPATITIS C

### Epidemiology (table 4)

Parenteral transmission is the predominant route of transmission in most resource-poor countries.[87–89] 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.[90] 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.[91–93] There is also evidence for homosexual spread.[94] 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.[95–97] Conversely, research in Thailand, Argentina, and Egypt does link HCV spread to heterosexual sex, particularly in relation to HIV infection.[89 98 99] 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.[87 100 101] Fulminant hepatitis is rare except for hepatitis A superinfection of chronic HCV disease.[102] However, about 80% of patients develop chronic (>6 months) infection and spontaneous recovery is rare in such people.[87 100 101] 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.[87 100 101]

### 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.[103] 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.[87 103] 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.[103]

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.[87] However, it is wise to vaccinate HCV carriers against hepatitis A and B to prevent the severe consequences of co-infection with these viruses.[87 100 101 102] 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.[104]

## REFERENCES


1 **Shapiro CN**, Margolis HS. Worldwide epidemiology of hepatitis A virus infection. *J Hepatol* 1993;**18**(suppl 2):S11–14.
2 **World Health Organization**. *Hepatitis A*. Department of Communicable Disease Surveillance and Response. Geneva: WHO, December 2001 (www.who.int/emc-documents/hepatitis/docs/whocdscredc2007.html).
3 **Fathalla SE**, Al-Jama AA, Al-Sheikh IH, *et al*. Seroprevalence of hepatitis A virus markers in eastern Saudi Arabia. *Saudi Med J* 2000;**21**:945–9.
4 **Lee SD**. Asian perspectives on viral hepatitis A. *J Gastroenterol Hepatol* 2000;**15**(suppl)G94–9.
5 **Polz-Dacewicz MA**, Policiewicz P, Badach Z. Changing epidemiology of hepatitis A virus infection—a comparative study in central eastern Poland. *Med Sci Mon* 2000;**6**:989–93.
6 **Das K**, Jain A, Gupta S, *et al*. The changing epidemiological pattern of hepatitis A in an urban population of India: emergence of a trend similar to the European countries. *Eur J Epidem* 2000;**16**:507–10.
7 **Grinde B**, Stene-Johansen K, Sharma B, *et al*. Characterisation of an epidemic of hepatitis A virus involving intravenous drug abusers—infection by needle sharing? *J Med Virol* 1997;**53**:69–75.
8 **Shaw DD**, Whiteman DC, Merritt AD, *et al*. Hepatitis A outbreaks among illicit drug users and their contacts in Queensland, 1997. *Med J Aust* 1999;**170**:584–7.
9 **Stene-Johansen K**, Skaug K, Blystad H, *et al*. A unique hepatitis A virus strain caused an epidemic in Norway associated with intravenous drug abuse. *Scand J Infect Dis* 1998;**30**:35–8.
10 **Chudy M**, Budek I, Keller-Stanislawski B, *et al*. A new cluster of hepatitis A infection in hemophiliacs traced to a contaminated plasma pool. *J Med Virol* 1999;**57**:91–9.
11 **Soucie JM**, Robertson BH, Bell BP, *et al*. Hepatitis A virus infections associated with clotting factor concentrate in the United States. *Transfusion* 1998;**38**:573–9.
12 **Henning KJ**, Bell E, Braun J, *et al*. A community-wide outbreak of hepatitis A: risk factors for infection among homosexual and bisexual men. *Am J Med* 1995;**99**:132–6.
13 **Leentvaar-Kuijpers A**, Kool JL, Veugelers PJ, *et al*. An outbreak of hepatitis A among homosexual men in Amsterdam 1991–1993. *Int J Epidemiol* 1995;**24**:218–22.
14 **Katz MH**, Hsu L, Wong E, *et al*. Seroprevalence of and risk factors for hepatitis A infection among young homosexual and bisexual men. *J Infect Dis* 1997;**175**:1225–9.
15 **Villano SA**, Nelson KE, Vlahov D, *et al*. Hepatitis A among homosexual men and injection drug users: more evidence for vaccination. *Clin Infect Dis* 1997;**25**:726–8.
16 **Stewart T**, Crofts N. An outbreak of hepatitis A among homosexual men in Melbourne. *Med J Aust* 1993;**158**:519–21.
17 **SundkvistT**, Aitken C, Duckworth G, *et al*. Outbreak of acute hepatitis A among homosexual men in East London. *Scand J Infect Dis* 1997;**29**:211–2.
18 **Takechi A**, Hatakeyama S, Kashiyama T, *et al*. Outbreak of hepatitis A infection amongst men who have sex with men. *Journal of the Japanese Association for Infectious Diseases* 2000;**74**:716–9.
19 **Nandwani R**, Caswell S, Boag F, *et al*. Hepatitis A seroprevalence in homosexual and heterosexual men. *Genitourin Med* 1994;**70**:325–8.
20 **Corona R**, Stroffolini T, Giglio A, *et al*. Lack of evidence for increased risk of hepatitis A infection in homosexual men. *Epidemiol Infect* 1999;**123**:89–93.
21 **Minuk GY**, Ding LX, Hannon C, *et al*. The risks of transmission of acute hepatitis A and B virus infection in an urban centre. *J Hepatol* 1994;**21**:118–21.
22 **McIntyre N**. Clinical presentation of acute viral hepatitis. *Br Med Bull* 1990;**46**:533–47.
23 **Sciot R**, Van Damme B, Desmet VJ. Cholestatic features in hepatitis A. *J Hepatol* 1986;**3**:172–81.

24 **Fagan EA**, Williams R. Fulminant viral hepatitis. *Br Med Bull* 1990;**46**:462–80.
25 **Willner IR**, Uhl MD, Howard SC, *et al*. Serious hepatitis A: an analysis of patients hospitalised during an urban epidemic in the United States. *Ann Intern Med* 1998;**128**:111–4.
26 **Vento S**, Garfano T, Renzini C, *et al*. Fulminant hepatitis associated with hepatitis A virus superinfection in patients with chronic hepatitis C. *N Engl J Med* 1998;**338**:286–90.
27 **McPherson RA**. Laboratory diagnosis of human hepatitis viruses. *J Clin Lab Anal* 1994;**8**:369–77.
28 **Stapleton JT**. Host immune response to hepatitis A virus. *J Infect Dis* 1995;**171**(suppl 1):S9–14.
29 **Polish LB**, Robertson BH, Khanna B, *et al*. Excretion of hepatitis A virus (HAV) in adults: comparison of immunologic and molecular detection methods and relationship between HAV positivity and infectivity in tamarins. *J Clin Microbiol* 1999;**37**:3615–17.
30 **Winokur PL**, Stapleton JT. Immunoglobulin prophylaxis for hepatitis *A*. *Clin Infect Dis* 1992;**14**:580–6.
31 **Mele A**. Efficacy of hepatitis A vaccine in prevention of secondary hepatitis A infection: a randomized trial. *Lancet* 1999;**353**;1136–9.
32 **Brook MG**. Clinical Effectiveness Group. National guideline for the management of the viral hepatitides A, B and C. *Sex Transm Infect* 1999;**75**(Suppl 1):S57–64.
33 **World Health Organization**. *Hepatitis B*. Fact Sheet WHO/204. Geneva: WHO, October 2000 (www.who.int/inf-fs/en/fact204.html).
34 **Yao GB**. Importance of perinatal versus horizontal transmission of hepatitis B virus infection in China. *Gut* 1996;**38**(suppl 2):S39–42.
35 **Van Damme P**, Cramm M, Van Der Auwera J-C, *et al*. Horizontal transmission of hepatitis B virus. *Lancet* 1995;**345**:27–9.
36 **Alter MJ**, Hadler SC, Margolis HS, *et al*. The changing epidemiology of hepatitis B in the United States. *JAMA* 1990;**263**:1218–22.
37 **Singh J**, Gupta S, Khare S, *et al*. A severe and explosive outbreak of hepatitis B in a rural population in Sirsa district, Harayana, India: unnecessary therapeutic interventions were a major risk factor. *Epidemiol Infect* 2000;**125**:693–9.
38 **Struve J**, Giesecke J, Lindh G, *et al*. Heterosexual contact as a major route for transmission of acute hepatitis B among adults. *J Infect* 1990;**20**:111–21.
39 **Francis DP**, Hadler SC, Thompson SE, *et al*. The prevention of hepatitis B with vaccine. Report of the Centers for Disease Control multi-center trial among homosexual men. *Ann Intern Med* 1982;**97**:362–6.
40 **Szmuness W**, Stevens CE, Zang EA, *et al*. A controlled clinical trial of the efficacy of the hepatitis B vaccine (Heptavax B): a final report. *Hepatology* 1981;**1**:377–85.
41 **Szmuness W**, Much I, Prince AM, *et al*. On the role of sexual behavior in the spread of hepatitis B infection. *Ann Intern Med* 1975;**83**:489–95.
42 **Hyams KC**, Phillips IA, Tejada A, *et al*. Three-year incidence study of retroviral and viral hepatitis transmission in a Peruvian prostitute population. *J Acq Immune Defic Synd* 1993;**6**:1353–7.
43 **Hyams KC**, Phillips IA, Tejada A, *et al*. Hepatitis B in a highly active prostitute population: evidence for a low risk of antigenemia. *J Infect Dis* 1990;**162**:295–8.
44 **Bratos MA**, Eiros JM, Orduna A, *et al* . Influence of syphilis in hepatitis B transmission in a cohort of female prostitutes. *Sex Transm Dis* 1993;**20**:257–61.
45 **Hyams KC**, Krogwold RA, Brock S, *et al*. Heterosexual transmission of viral hepatitis and cytomegalovirus infection among United States military personnel stationed in the western Pacific. *Sex Transm Dis* 1993 **20**:36–40.
46 **Kura MM**, Hira S, Kohli M, *et al*. High occurrence of HBV among STD clinic attenders in Bombay, India. *Int J STD AIDS* 1998;**9**:231–3.
47 **Jacobs B**, Mayaud P, Changalucha J, *et al*. Sexual transmission of hepatitis B in Mwanza, Tanzania. *Sex Transm Dis* 1997;**24**:121–6.
48 **Mele A**, Franco E, Caprilli F, *et al*. Hepatitis B and delta virus infection among heterosexuals, homosexuals and bisexual men. *Eur J Epidem* 1988;**4**:488–9.
49 **Hoffman B**, Kryger P, Pedersen NS, *et al*. Sexually transmitted diseases, antibodies to human immunodeficiency virus and subsequent development of acquired immunodeficiency syndrome. Visitors of homosexual sauna clubs in Copenhagen: 1982–1983. *Sex Transm Dis* 1988;**15**:1–4.
50 **Coleman JC**, Waugh M, Dayton R. Hepatitis B antigen and antibody in a male homosexual population. *Br J Vener Dis* 1977;**53**:132–4.
51 **Keefe EB**. Clinical approach to viral hepatitis in homosexual men. *Med Clin North Am* 1986;**70**:567–86.
52 **Coutinho RA**, Schut BJ, Albrecht-Van Lent NA, *et al*. Hepatitis B among homosexual men in the Netherlands. *Sex Transm Dis* 1981;**8**(suppl 4):333–5.
53 **Gilson RJC**, de Ruiter A, Waite J, *et al*. Hepatitis B virus infection in patients attending a genitourinary medicine clinic: risk factors and vaccine coverage. *Sex Transm Infect* 1998;**74**:110–15.
54 **Hart GJ**, Dawson J, Fitzpatrick RM, *et al*. Risk behaviour, anti-HIV and anti-hepatitis B core prevalence in clinic and non-clinic samples of gay men in England 1991–2. *AIDS* 1993;**7**:863–9.
55 **SeageGr**, Mayer KH, Lenderking WR, *et al*. HIV and hepatitis B infection and risk behaviour in young gay and bisexual men. *Public Health Rep* 1997;**112**:158–67.
56 **Oliveira ML**, Bastos FI, Tellos PR, *et al*. Prevalence and risk factors for HBV, HCV and HDV infections among injecting drug users from Rio de Janeiro, Brazil. *Braz J Med Biol Res* 1999;**32**:1107–14.
57 **Oliveira LH**, Silva IR, Xavier BL, *et al*. Hepatitis B infection among patients attending a sexually transmitted diseases clinic in Rio de Janeiro, Brazil. *Memorias do Instituta Oswaldo Cruz* 2001;**96**:635–40.
58 **Rodriguez L**, Collado-Mesa F, Aragon U, *et al*. Hepatitis B virus exposure in human immunodeficiency virus seropositive Cuban patients. *Memorias do Instituta Oswaldo Cruz* 2000;**95**:243–5.
59 **McIntyre N**. Clinical presentation of acute viral hepatitis. *Br Med Bull* 1990;**46**:533–47.
60 **Hyams KC**. Risks of chronicity following acute hepatitis B virus infection: a review. *Clin Infect Dis* 1995;**20**:992–1000.
61 **Brook MG**., Chan G., Yap I, *et al*. Randomised controlled trial of lymphoblastoid interferon alfa in Europid men with chronic hepatitis B virus infection. *BMJ* 1989;**299**:652–6.
62 **Zarski JP**, Bohn B, Bastie A, *et al*. Characteristics of patients with dual infection by hepatitis B and C viruses. *J Hepatol* 1998;**28**:27–33.
63 **Chu CM**, Yeh CT, Liaw YF. Fulminant hepatic failure in acute hepatitis C: increased risk in chronic carriers of hepatitis B virus. *Gut* 1999;**45**:613–7.
64 **Vento S**, Garfano T, Renzini C, *et al*. Fulminant hepatitis associated with hepatitis A virus superinfection in patients with chronic hepatitis C. *N Engl J Med* 1998;**338**:286–90.
65 **Chiaramonte M**, Stroffolini T, Vian A, *et al*. Rate of incidence of hepatocellular carcinoma in patients with compensated viral cirrhosis. *Cancer* 1999;**85**:2132–7.
66 **Gitlin N**. Hepatitis B: diagnosis, prevention and treatment. *Clin Chem* 1997;**43**:1500–6.
67 **Badur S**, Akgun A. Diagnosis of hepatitis B infections and monitoring of treatment. *J Clin Virol* 2001;**21**:229–37.
68 **Janssen HL**, Gerken G, Carreno V, *et al*. Interferon alfa for chronic hepatitis B infection: increased efficacy of prolonged treatment. The European Concerted Action on Viral Hepatitis (EUROHEP). *Hepatology* 1999;**30**:238–43.
69 **Main J**, Brown JL, Howells C, *et al*. A double-blind, placebo-controlled study to assess the effect of famciclovir on virus replication in patients with chronic hepatitis B virus infection. *J Vir Hepat* 1996;**3**:211–15.
70 **Dienstag JL**, Schiff ER, Wright TL, *et al*. Lamivudine as initial treatment of chronic hepatitis B in the United States. *N Engl J Med* 1999;**341**:1256–63.
71 **Tsiang M**, Rooney JF, Toole JJ, *et al*. Biphasic clearance kinetics of hepatitis B virus from patients during adefovir dipivoxil therapy. *Hepatology* 1999;**29**:1863–9.
72 **Yao GB**. Management of hepatitis B in China. *J Clin Virol* 2000;**61**:392–7.
73 **Lin SM**, Sheen IS, Chien RN, *et al*.. Long-term beneficial effect of interferon therapy in patients with chronic hepatitis B virus infection. *Hepatology* 1999;**29**:971–5.
74 **Dore GJ**, Cooper DA, Barrett C, *et al*. Dual efficacy of lamivudine treatment in human immunodeficiency virus/hepatitis B virus-coinfected persons in a randomized controlled study (CAESAR). The CAESAR Coordinating Committee. *J Infect Dis* 1999;**180**:607–13.
75 **Colin JF**, Cazals-Hatem D, Loriot MA, *et al*. Influence of immunodeficiency virus infection on chronic hepatitis B in homosexual men. *Hepatology* 1999;**29**:1306–10.
76 **Huang K**, Lin S. Nationwide vaccination: a success story in Taiwan. *Vaccine* 2000;**18**(suppl 1):S35–8.
77 **Zhao S**, Xu Z, Lu Y. A mathematical model of hepatitis B virus transmission and its application for vaccination strategy in China. *Int J Epidemiol* 2000;**29**:744–52.
78 **Bhave G**, Lindan CP, Hudes ES, *et al*. Impact of an intervention on HIV, sexually transmitted diseases and condom use among sex workers in Bombay. *AIDS* 1995;**9**(suppl 1):S21–30.
79 **World Health Organization**. *Hepatitis delta*. Department of Communicable Disease Surveillance and Response, CSR. Geneva: WHO, December 2001 (www.who.int/emc-documents/hepatitis/docs/whocdscrncs20011.html).
80 **Flodgren E**, Bengtsson S, Knotsson M, *et al*. Recent high incidence of fulminant hepatitis in Samara, Russia: molecular analysis of prevailing hepatitis B and D strains. *J Clin Microbiol* 2000;**38**:3311–6.
81 **Manock SR**, Kelley PM, Hyams KC, *et al*. An outbreak of fulminant hepatitis delta in the Waorani, an indigenous people of the Amazon basin of Ecuador. *Am J Trop Med Hyg* 2000;**63**:209–13.
82 **Niro GA**, Casey JL, Gravinese E, *et al*. Intrafamilial transmission of hepatitis delta virus: molecular evidence. *J Hepatol* 1999;**30**:564–9.
83 **Liaw YF**, Chiu KW, Chu C, *et al*. Heterosexual transmission of hepatitis delta virus in the general population of an area endemic for hepatitis B virus infection: a prospective study. *J Infect Dis* 1990;**162**:1170–2.
84 **Smith HM**, Alexander GJ, Webb G, *et al*. Hepatitis B and delta virus infection among "at-risk" populations in south east London. *J Epidem Com Health* 1992;**46**:144–7.
85 **Fattovich G**, Giustina G, Christensen E, *et al*. Influence on hepatitis delta virus infection on morbidity and mortality in compensated cirrhosis type B. The European Concerted Action on Viral Hepatitis (Eurohep). *Gut* 2000;**46**:420–6.
86 **Modahl LE**, Lai MM. Hepatitis delta virus: the molecular basis of laboratory diagnosis. *Critical Reviews in Clinical Laboratory Science* 2000;**37**:45–92.
87 **World Health Organization**. *Hepatitis C*. Geneva: WHO, October 2000. (www.who.int/inf-fs/en/fact164.html)
88 **Sun CA**, Chen HC, Lu SN, *et al*. Persistent hyperendemicity of hepatitis C virus infection in Taiwan: the important role of iatrogenic risk factors. *J Med Virol* 2001;**65**:30–4.
89 **Habib M**, Mohamed MK, Abdel-Aziz F, *et al*. Hepatitis C virus infection in a community in the Nile delta: risk factors for seropositivity. *Hepatology* 2001;**33**:248–53.
90 **European Paediatric Hepatitis C Virus Network**. Effects of mode of delivery and infant feeding on the risk of mother to child transmission of hepatitis C virus. *Br J Obstet Gynaecol* 2001;**108**:371–7.

91 **Dienstag JL**. Sexual and perinatal transmission of hepatitis C. *Hepatology* 1997;**26**(suppl 1):66S–70S.
92 **Goldberg D**, McIntyre PG, Smith R, *et al*. Hepatitis C among high and low risk pregnant women in Dundee: unlinked anonymous testing.*Br J Obstet Gynaecol* 2001;**108**:365–70.
93 **Feldman JG**, Minkoff H, Landesman S, *et al*. Heterosexual transmission of hepatitis C, hepatitis B and HIV-1 in a sample of inner city women. *Sex Transm Dis* 2000;**27**:338–42.
94 **Osella AR**, Massa MA, Joekes S, *et al*. Hepatitis B and C virus transmission among homosexual men. *Am J Gastroenterol* 1998;**93**:49–52.
95 **Maida MJ**, Daly CC, Hoffman I, *et al*. Prevalence of hepatitis C infection in Malawi and lack of association with sexually transmitted diseases. *Eur J Epidemiol* 2000;**16**:1183–4.
96 **Smikle M**, Dowe G, Hylton-Kong T, *et al*. Hepatitis B and C viruses and sexually transmitted disease patients in Jamaica. *Sex Transm Infect* 2001;**77**:295–6.
97 **Matee MI**, Lyamuya EF, Mbena EC, *et al*. Prevalence of transfusion-associated viral infections and syphilis among blood donors in Muhimbili Medical Centre, Dar Es Salaam, Tanzania. *East Afr Med J* 1999;**76**:167–71.
98 **Luksamijarulkul P**, Khemnak P, Pacheun O, *et al*. Human immunodeficiency virus and hepatitis C virus infections among patients attending sexually transmitted disease clinics, Regional 2, Thailand. *Asia-Pacific J Pub Health* 2000;**12**:41–5.
99 **Fainboim H**, Gonzlaez J, Fassio E, *et al*. Prevalence of hepatitis viruses in an anti-human immunodeficiency virus-positive population from Argentina. A multicentre study. *J Virol Hepat* 1999;**6**:53–7.
100 **Hoofnagle J**. Hepatitis C: the clinical spectrum of disease. *Hepatology* 1997;**26**(suppl 1):15S–20S.
101 **Seeff LB**. Natural history of hepatitis C. *Hepatology* 1997;**26**(suppl 1):21S–28S.
102 **Vento S**, Garfano T, Renzini C, *et al*. Fulminant hepatitis associated with hepatitis A virus superinfection in patients with chronic hepatitis C. *N Engl J Med* 1998;**338**:286–90.
103 **Gretch DR**. Diagnostic tests for hepatitis C. *Hepatology* 1997;(suppl 1):43S–47S
104 **Manns M**, McHutchison JG, Gordon SC, *et al*. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. *Lancet* 2001;**358**:958–65.