Clinical Medicine 2011, Vol 11, No 2: 184–9

Therapy for chronic viral hepatitis: current indications, optimal therapies and delivery of care

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Chronic infection with hepatitis B virus (HBV) or C virus (HCV) is a major cause of cirrhosis or hepatocellular carcinoma (HCC). End-stage liver disease (ESLD) secondary to chronic infection with HBV and HCV is a major and increasing cause of morbidity and mortality. Effective treatments exist, capable of curing or arresting the progression of liver disease, reducing both the incidence of symptomatic liver disease and the mortality.

Most of the 180,000 people infected with HBV and the 200,000–400,000 infected with HCV in the UK are unaware of their diagnosis and likely to remain asymptomatic until they develop end-stage liver cirrhosis or HCC, conditions with a relatively poor prognosis. Furthermore, many of those known to be infected have not been referred for therapy because the benefits of these relatively new therapies have not been fully realised in primary healthcare. The earlier in the course of the infection the cases are identified the greater the benefits.

The prevalence of these infections is increasing in the UK. The numbers diagnosed with chronic viral hepatitis and developing ESLD are rising year on year. In 2008 in England over 8,000 new diagnoses of HCV were made and over 17,000 hospital admissions attributed to HCV.[1]

The management of chronic viral hepatitis involves:

- excluding coexisting risks for chronic liver disease
- screening for infection with other blood-borne viruses such as HIV
- detecting complications of cirrhosis
- education to reduce viral transmission
- drug treatment to prevent disease progression.

This article reviews:

- the indications for treatment
- current treatment options licensed for treatment of chronic HBV and HCV infections and the rationale behind their use
- the need to actively seek out those infected
- approaches to achieving case identification.

These topics present challenges, not just for physicians but also for those responsible for providing and planning healthcare at local and national levels.

Chronic hepatitis B

Immune recognition of HBV occurs a variable time period after infection (immune tolerance phase) leading to clearance of infected hepatocytes (immune clearance phase) with loss of HBe antigen (HBeAg) and development of anti-HBe.[2] This phase may be protracted, in which case hepatic necroinflammation can result in progressive liver fibrosis. After seroconversion to the HBeAg-negative phase, hepatic inflammation is minimal (immune control phase) and fibrosis does not progress unless there are mutations in the viral genome. The best documented of these, the precore mutation, permits the virus to escape from immune control (immune escape phase), with a rise in viral DNA titres and a recrudescence of hepatic inflammation and fibrogenesis (HBeAg-negative hepatitis) (Fig 1).[3] Clearance of chronic HBV, spontaneously or with treatment, is rare and the therapeutic aim is suppression of viral replication to a serum viral DNA level below the limit of detection of available assays. Viral suppression leads to reduced hepatic inflammation with normalisation of transaminases, and aims to prevent progression to cirrhosis and HCC. Viral suppressive therapy must be maintained for many years because the half-life of the virus-infected hepatocyte is longer than 100 days.[4] Even if clearance of HB surface antigen (HBsAg) and the development of anti-HBs occurs, viral DNA persists in the nucleus of infected hepatocytes.

Treatment

International consensus guidelines for the management of HBV have been published recently.[5]

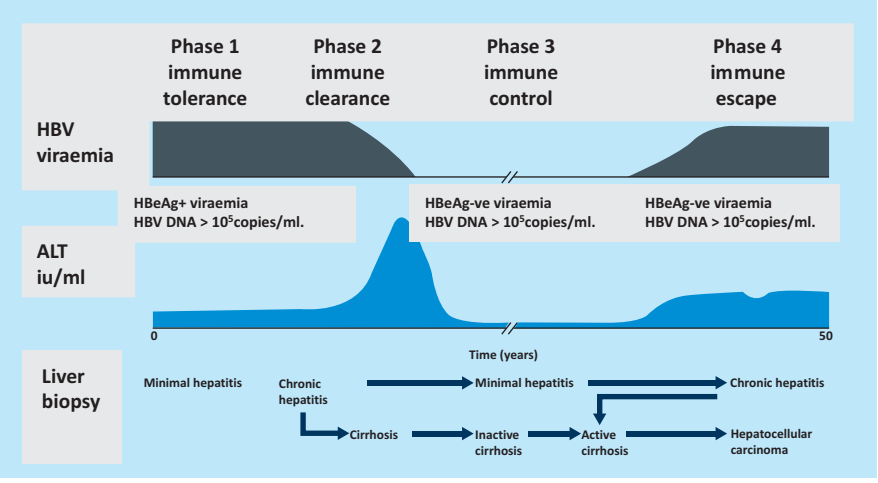


Fig 1. Stages of disease in patients with chronic hepatitis B virus (HBV) infection. ALT =

The indications for therapy are summarised in Table 1. Clinicians need to be aware that some patients with apparently low risk of progressive liver disease can be proven to have advanced fibrosis on liver biopsy[6] and therefore should undergo liver biopsy if they have significant viral replication (>2,000 IU/ml).

Two classes of drugs are licensed and approved for the treatment of HBV:[7–9]

1 *Pegylated interferon* (PEG-IFN) may be used to upregulate the immune response to the virus. Favourable response to IFN is more likely with HBV genotype A or B, lower viral load (DNA <106 IU/ml), alanine aminotransaminase more than twice the upper limit of normal, female gender, age less than 50 years and acquisition of infection in adulthood. IFN has the advantage of a clearly defined treatment duration, usually 6–12 months. Sustained viral suppression with normalisation of liver function tests is achieved after one year's treatment in approximately 30% of HBeAg-positive and 15% of HBeAg-negative patients.
2 *Nucleotide/nucleoside analogues* are the second class of agents licensed for treatment of HBV. They include lamivudine, adefovir, tenofovir and entecavir (Table 2). These drugs are generally well tolerated and require minimal monitoring, but optimal treatment duration is unclear. A trial of drug withdrawal may be attempted for HBeAg-positive patients who become HBeAg-negative on treatment, but for most patients treatment should be considered long term.

Rates of drug resistance are high with lamivudine (up to 70% after five years). For this reason, the current National Institute for Health and Clinical Excellence (NICE) recommendations are to initiate treatment with newer agents with potent rapid antiviral activity and low risk of resistance (entecavir and tenofovir). There is crossover in viral resistance mutations which are archived in the liver, so sequential use of antiviral agents is not encouraged. The management of

Table 1. Indications for drug treatment of chronic hepatitis B according to guidelines published by the European Association for the Study of the Liver.[5]

	Hepatitis		Cirrhosis	
	HBeAg+	HBeAg−	Compensated	Decompensated
ALT	>ULN	>ULN	Any value	Any value
Viral load	>2,000 IU/ml	>2,000 IU/ml	Detectable	Detectable
Liver biopsy	Moderate/severe inflammation and/or fibrosis			

ALT = alanine aminotransferase; ULN = upper limit of normal.

Table 2. Characteristics of oral agents recommended for treatment of chronic hepatitis B Adapted with permission from BMJ Publishing Group Ltd.[10]

	Lamivudine	Adefovir	Tenofovir	Entecavir
Class	L-nucleoside	Acyclic nucleoside phosphonates		Deoxyguanosine analogue
Dose	100 mg/day	10 mg/day	345 mg/day	500 µg/day
Side effects	Rare	Renal impairment, phosphate loss		Rare
Response at 1 year in HBeAg+ patients (%)				
HBeAg seroconversion	16–21	12	21	21
HBV undetectable	36–44	13–21	80	67
Resistance	24	0	0	<1
Response at 1 year in HBeAg- patients (%)				
HBV undetectable	72	63	93	90
Resistance	21	0	0	<1
Prescription cost for 1 year's treatment (£)				
	1,015	3,664	3,094	4,404

Key points

- Chronic infection with hepatitis B virus (HBV) and C virus (HCV) is common, with approximately 500,000 individuals infected in the UK
- Long-standing liver inflammation causes progressive fibrosis resulting in cirrhosis
- Chronic viral hepatitis is frequently asymptomatic until end-stage liver disease is present
- Referral for specialist assessment is recommended for all patients with potentially progressive disease
- The aim of antiviral therapy for HBV is control of viral replication; this can be achieved by immune stimulation with pegylated-interferon (PEG-IFN) or nucleoside/nucleotide analogues. These National Institute for Health and Clinical Excellence (NICE)-recommended therapies prolong life
- NICE-recommended combination therapy with PEG-IFN and ribavirin can cure HCV in the majority of patients; it should be offered to all patients unless there are contraindications to therapy
- Most patients with chronic viral liver disease have either not been diagnosed or not been referred for assessment for therapy. Populations where the risk of viral hepatitis is increased above that in the general population should be actively screened for HBV and HCV. This should include those with past or current intravenous drug use, past exposure to blood or blood products prior to 1991 and first-generation migrants from countries with a prevalence of HBV or HCV above 2%

KEY WORDS: antiviral therapy, hepatitis B, hepatitis C, viral screening

escape mutants should be with addition of appropriate second-line agents.

Chronic hepatitis C

Treatment

The aim of current treatment regimens for chronic hepatitis C is sustained virological response (SVR), defined as undetectable serum HCV RNA six months after the end of therapy. Clearing HCV prevents progression of fibrosis, reducing the risk of hepatic decompensation and HCC, but does not confer protective immunity against re-infection with HCV.[11] The current standard of care is combination therapy with PEG-IFN-α and ribavirin.[12,13] NICE has approved a single course of treatment for 48 weeks for genotypes 1 or 4 and 24 weeks for genotype 2 or 3 HCV, with SVR (cure) rates of approximately 45% and 80%, respectively.[14] Combination antiviral therapy is expensive, but treatment at all stages of HCV infection, including mild fibrosis, is cost-effective.[15]

Treatment in decompensated cirrhosis should be undertaken only in specialist centres with access to liver transplantation. Duration of treatment may be shortened for selected patients with an undetectable viral load after four weeks of treatment (rapid virological response). Response may be improved with 72 weeks of therapy in patients with genotype 1 infection who have a slow initial response but treatment beyond 48 weeks is not currently funded.[16]

Treatment response rates are lower for those with higher baseline viral load, more advanced liver disease, higher body mass index, ongoing excessive alcohol use, non-Caucasians, co-infection with HIV and patients unable or unwilling to take full treatment courses.

Current recommendations are to offer combination therapy to all patients with chronic HCV who do not have contraindications to treatment (see below).[15] Those with mild disease and unfavourable genotypes or a predicted poor chance of treatment response may choose to defer treatment until newer agents are available. Such decisions should be made on an individual basis.

Adverse events

IFN is associated with side effects in approximately 75% of those treated, most commonly non-specific flu-type symptoms such as myalgia, arthralgia, fatigue, headache and fever.[11] It is also associated with a risk of myelosuppression, autoimmune conditions and neuropsychiatric illness, including depression, anxiety and psychosis.

The major side effect associated with ribavirin is haemolytic anaemia. Ribavirin is potentially teratogenic, so effective contraception is imperative during treatment and for six months after the completion of therapy.

Contraindications

Treatment is contraindicated in people with major uncontrolled depression, previous solid organ transplant (other than liver transplantation), autoimmune conditions known to be exacerbated by IFN therapy, untreated thyroid disease or any severe concurrent illness associated with a significantly reduced life expectancy.

New agents

A number of novel agents are under development for the treatment of HCV.[17] Inhibitors of the viral protease given in combination with PEG-IFN and ribavirin yield SVR rates of 80% in treatment of genotype 1 infection. SVR was seen in 50% of subjects treated with telaprevir in combination with PEG-IFN and ribavirin who had failed previous standard antiviral therapy.[18] It is likely that protease inhibitors will be licensed for use in the UK within the next two years, but neither the optimal indications for their use (ie treatment-naïve patients or non-responders to previous therapy) nor the cost of treatment are yet known.

Identifying patients who need treatment for chronic viral hepatitis

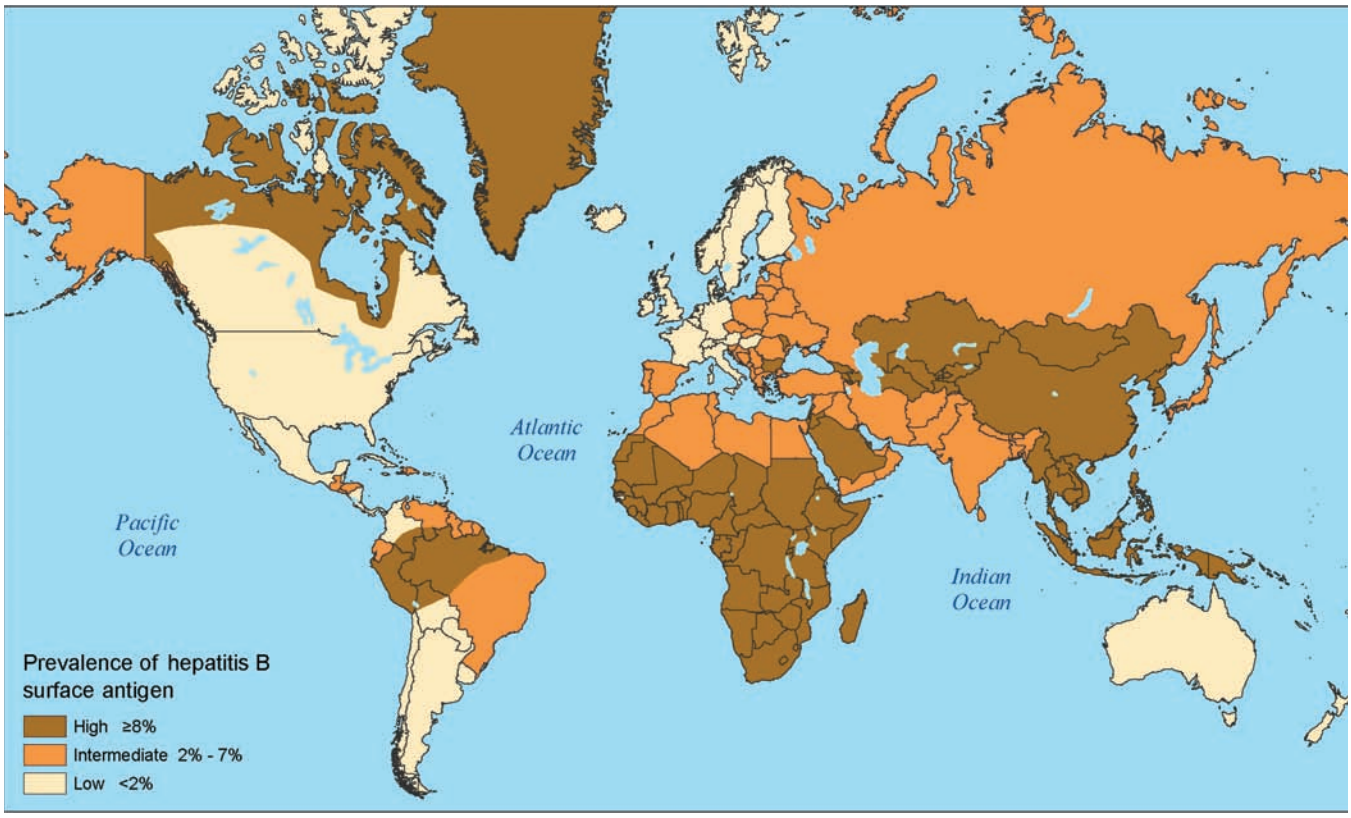
Those in whom active infection is diagnosed (HBsAg-positive, or HCV RNA-positive) should be referred for a specialist opinion on whether or not treatment is warranted. The question facing physicians and policy makers is how best to identify those infected with chronic viral hepatitis in order to ensure optimal use of healthcare resources.

The natural course of HBV infection differs between those infected in infancy, in whom chronic infection is almost universal, and those who acquire the infection in adulthood in whom the rate of chronic HBV is only 5%.[10] Approximately 20% of those infected with HCV clear the virus, irrespective of age.[11] Knowing the age at infection is important since the risk of liver damage increases with duration of infection. Thus a 30-year-old who acquired HBV sexually aged 25 years is less likely to have severe liver disease than a vertically infected 30-year-old.

Routes of infection

Both HBV and HCV are spread by contact with blood and blood products. All UK blood donors are now screened but patients who received blood products prior to September 1991 are potentially at risk of HCV. Injecting drug use is the major cause of transmission of HCV in the UK. It has been suggested that the prevalence of HCV may have decreased as a result of safer injecting practices and needle-exchange programmes but the magnitude of this effect is open to debate. A study in injecting drug users in the South of England found an incidence of new antibody to HCV of 41.8 cases per 100 person-years.[19] The risk of sexual transmission is much greater with HBV than HCV, particularly in men who have sex with men.

Worldwide the most common routes of infection with HBV are vertical transmission at the time of delivery or horizontal spread from infected family members in infancy. Transplacental spread may occur in pregnant women with very high levels of HBV viraemia. HBV and HCV are endemic throughout most of Asia and Africa, with seroprevalence several-fold higher than the UK rates of approximately 0.5% for both



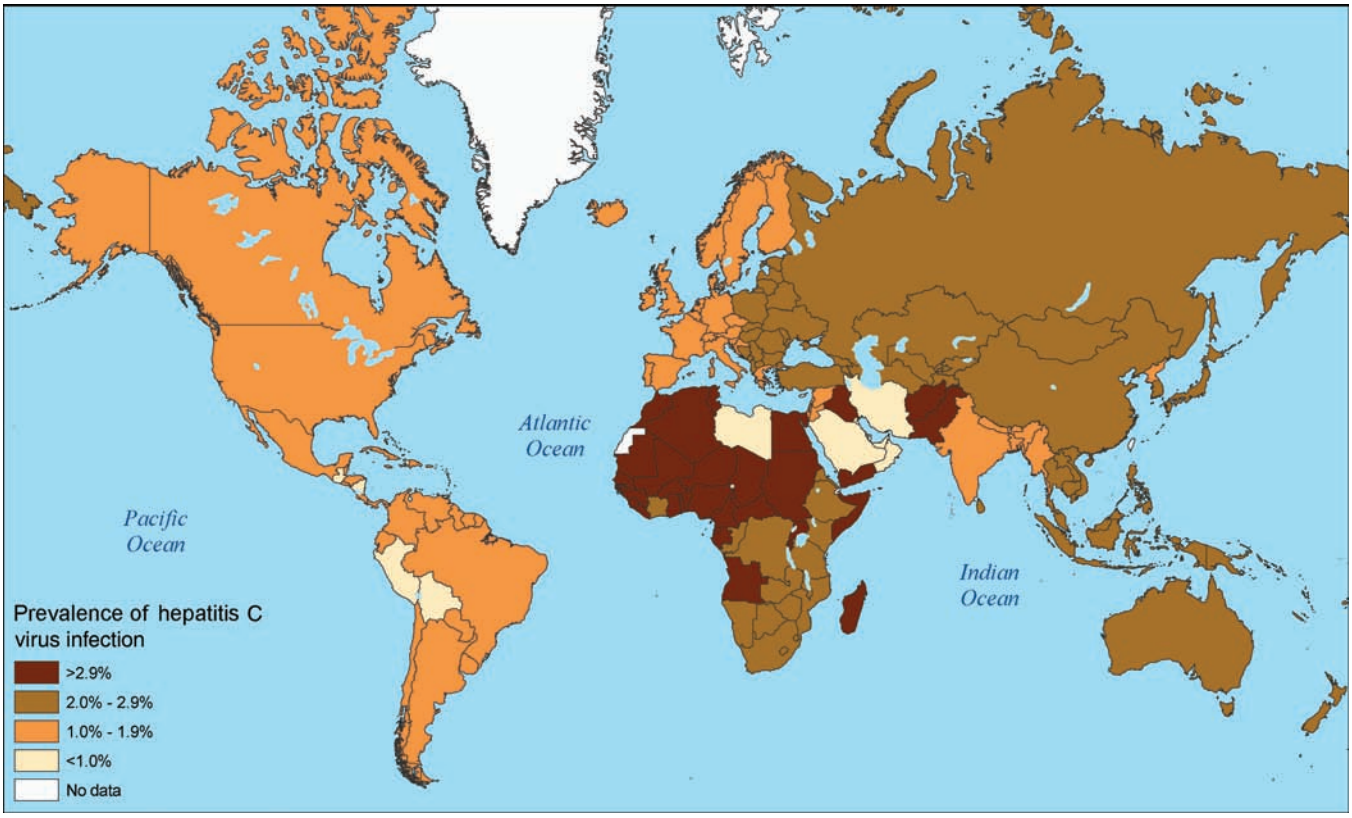


Fig 2. Global prevalence of (a) hepatitis surface antigen and (b) chronic hepatitis C infection. Reproduced with permission of the Centers for Disease Control and Prevention.[20,21]

HBV and HCV (Fig 2). Prevalence rates vary by region and have changed over time, so the rate of infection in immigrants is difficult to estimate from the country of origin alone.[22] Only 300 of the 7,700 new cases of chronic HBV diagnosed each year acquire the infection in the UK, the rest acquiring the chronic infection overseas.[7]

Screening

Testing for HBV and HCV infection is recommended for anyone with elevated liver transaminases.[6] Screening is recommended in high-risk groups, including those who received blood products prior to the introduction of screening, anyone who has ever used intravenous (iv) drugs, sex workers, the sexual partners of anyone with HBV or HCV, and men who have sex with men.

Unlike a number of countries including Canada, Australia and the USA there is no programme of screening of immigrants to the UK. However, consideration is being given to testing migrants from high prevalence countries, where HBV or HCV prevalence exceeds 2% in the general population, at a time when they are first registered with general practitioners after settling in the UK. Earlier detection of infection and commencement of antiviral therapy would be expected to reduce the rate of symptomatic end-stage viral liver disease and contribute to stopping the currently increasing mortality from liver disease.

Conclusions

Chronic infection with HBV and HCV is common and the incidence is increasing. The long interval between infection and development of irreversible fibrosis and HCC offers an opportunity for case identification and therapeutic intervention, thus reducing morbidity and mortality. Treatment is capable of curing HCV (an SVR) and suppressing HBV. Although expensive, it is cost-effective at reducing progression of liver disease and occurrence of HCC.

Both the general population and the medical profession need an increased awareness of the benefits afforded by modern antiviral therapy. In order to bring these benefits to the approximately 500,000 people with chronic viral hepatitis in the UK, increased activity needs to be directed to:

- encouraging referral of those cases already identified in primary care (but not yet referred for evaluation and treatment)
- improving case finding in the high-risk groups, particularly first-generation migrants from countries with a high prevalence (>2%) of either HBV or HCV and those with previous exposure to infected blood as a result of past or current iv drug use or transfusion with blood or blood products prior to testing of such products.

The cost of providing these services is likely to increase significantly in the future if increasing numbers of patients are to be treated, but the cost of leaving these patients untreated until they present with decompensated cirrhosis or HCC is even higher. Further work is required in order to clarify the optimal methods for detecting those infected with chronic viral hepatitis in order to minimise future morbidity and mortality.

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Managing alcohol dependence and alcohol-related liver disease: a problem for the hepatologist, psychiatrist or economist?

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Alcohol misuse is a major issue for medical and social agencies alike. Although the harmful effects of excessive consumption are well publicised, one-quarter of adults in England still consume alcohol at hazardous or harmful levels.[1] A global alcohol strategy has recently been agreed by the World Health Organization,[2] supported in Britain by extensive guidance from the National Institute for Health and Clinical Excellence (NICE),[3–5] parliamentary committees[6,7] and non-governmental organisations – but to whom does this advice apply?

The sobering facts

Most adults in Britain drink alcohol and do so responsibly.[1] However, some 33% of men and 16% of women drink hazardously – that is, at a level which increases their risk of alcohol-related harm, while 6% of men and 4% of women drink to an extent that is mentally or physically harmful.[8,9] In 2007, 9% of men and 4% of women in England were dependent on alcohol (Table 1).[10]

Alcohol misuse is associated with a wide variety of physical health problems and is also causally linked to accidents, injuries and poisoning. There was a total of 863,300 alcohol-related hospital admissions in England in 2007–8, of which 222,600 were for diseases wholly attributable to alcohol. Two-thirds of these admissions were for mental/behavioural disorders due to alcohol use, while 30,100 were for alcohol-related liver injury.[11,12] Men make up almost two-thirds of the admissions. There are significant differences in admission ages for conditions that are wholly or partly alcohol-related (Fig 1).[11,12]

Table 1. Adult drinking behaviour by gender (individuals in England aged ⩾16 years).[1]

	Variable	Men (%)	Women (%)
Population drinking levels*	Drank alcohol on at least one day the previous week	72	57
	Drank some alcohol every day the previous week	13	7
	aged ⩾65 years	22	12
	aged 16–24 years	3	2
	Drank ⩾8 units (men) or ⩾6 units (women) on at least one day the previous week		
	aged ⩾65 years	3	3
	aged 16–24 years	32	25
Hazardous drinking**	Men >21 <50 units/week Women >14 <35 units /week	31	20
Harmful drinking**	Men >50 units/week Women >35 units/week	9	6
Dependent drinking+	Severity of Alcohol Dependence Questionnaire	9	4

Sources:
* General Household Survey, 2007.[8]
**General Household Survey, 2006.[9]
+Adult Psychiatric Morbidity Survey, 2007.[10]