

2017 European guideline for the screening, prevention and initial management of hepatitis B and C infections in sexual health settings

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Abstract

This guideline updates the 2010 European guideline for the management of hepatitis B and C virus infections. It is primarily intended to provide advice on testing, prevention and initial management of viral hepatitis B and C for clinicians working in sexual health clinical settings in European countries. The guideline is in a new question and answer format based on clinical situations, from which population/intervention/comparison/outcome questions were formulated. Updates cover areas such as epidemiology, point-of-care tests for hepatitis B, hepatitis C risk and ‘chemsex’, and HIV pre-exposure prophylaxis and hepatitis B. We have also included a short paragraph on hepatitis E noting there is no evidence for sexual transmission. The guideline has been prepared in accordance with the Europe protocol for production available at <http://www.iusti.org/regions/europe/pdf/2017/ProtocolForProduction2017.pdf>

Keywords

Diagnosis, Europe, hepatitis B, hepatitis C, immunisation, standard of care

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Introduction and methodology

This guideline is an update of the Europe guideline published in 2010¹ and provides guidance for best practice in the diagnosis, prevention and initial management of viral hepatitis B and C. It is primarily intended for use in sexual health settings, but can be applied or adapted for use in other settings in Europe where sexually transmitted infection (STI) assessments are undertaken. The purpose of this guideline is to help improve the health of people attending sexual health clinics by encouraging high standards of care in relation to viral hepatitis. The guideline offers recommendations on best practice regarding viral hepatitis for both men and women, including adolescents.

We have no longer attempted to provide detailed guidance on the specialist antiviral management of established chronic hepatitis B or C. Since our 2010 guideline was published, WHO has produced its first comprehensive treatment guidelines for both hepatitis B and C.^{2,3} The European Association for the Study of the Liver (EASL) also published a major update to its

evidence-based advice for management of hepatitis C in September 2016.⁴

In this 2017 version, we have changed the format to try and mirror real-life situations by posing a series of questions a physician might ask about hepatitis screening, prevention and initial management in the sexual health clinic. We have updated the sections on initial management of hepatitis B and C in line with new evidence and national guidelines and other sections have

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been updated to reflect new evidence and practice. New topics include:

- advice on use of point-of-care tests for hepatitis B,
- comment on HIV pre-exposure prophylaxis (PrEP) and hepatitis B,
- updated recommendations for hepatitis C advice, testing and prevention in the light of ‘chemsex’ (use of drugs in a sexualised setting),
- a complete list of countries with intermediate-to-high endemicity for hepatitis B and C to guide decision making in the clinic, and
- brief advice regarding hepatitis E.

The guideline is predominantly based on what the authors believe constitutes reasonable practice, based on best evidence. Evidence is sometimes cited from other settings outside sexual health care where necessary. The recommendations are graded using a modified GRADE system (http://www.iusti.org/regions/europe/pdf/2013/Levels_of_Evidence.pdf).

Detailed protocol for production is found at <http://www.iusti.org/regions/europe/pdf/2017/ProtocolForProduction2017.pdf>

Hepatitis B virus infection

Background

Hepatitis B is caused by a highly-infectious hepadna (DNA) virus. Despite the availability of a vaccine, hepatitis B virus (HBV) infection is endemic, estimated to affect 240 million people worldwide, with very high hepatitis B surface antigen (HBsAg) carriage rates (up to 20%) particularly in south and east Asia.² High carriage rates (up to 10%) are also found in some regions of Central and South America and Africa.

The European Centre for Disease Prevention and Control (ECDC) recently published a comprehensive systematic review of published studies of hepatitis B prevalence in the European Union/European Economic Area (EU/EEA).⁵ In the general population chronic carriage varies across Europe from 0.1% in Ireland to 4.4% in Romania. Prevalence in men who have sex with men (MSM) was reported as very low in Estonia and UK but 1.4% in France, and in persons who inject drugs (PWID) up to 6.3% in Portugal. Prevalence in the general migrant population was as high as 17.4% in those from South-East Asia. Overall, ECDC estimates overall prevalence in the EU/EEA to be 0.9% (95% CI 0.7–1.2), or 4.7 million HBsAg-positive cases.

Testing

In patients attending sexual health and dermatovenereology services in WHO Europe region, who should be tested for past or current hepatitis B infection and what laboratory tests should be used?

Recommendations:

- If the local general prevalence of hepatitis B carriage is <2%, a risk assessment should guide testing for hepatitis B. Testing should be offered to MSM, PWID, sex workers, HIV-positive individuals, people from countries with intermediate and high HBV endemicity (see Table 1), sexual partners of HBsAg-positive or risk group patients and those presenting after needlestick injury (1A).
- In settings with higher local geographic prevalence (>2%, see Table 1), we suggest all attenders be offered testing for hepatitis B unless they are known to be immune (by documented resolved natural infection or by immunisation) (2D).
- In **asymptomatic** patients, initial testing with antibody against hepatitis B core antigen (anti-HBcore) or HBsAg or both is acceptable. If any test is positive, order additional serology to assess stage of infection and infectivity, see Figure 1 and Table 2 (1A).
- In **symptomatic** patients (e.g. acute icterus, highly elevated serum transaminase) where acute hepatitis B is suspected, test for the presence of HBsAg. If positive, proceed to test other HBV markers (Table 2, Figure 1), and order liver function tests (LFTs) and clotting to confirm stage of infection and severity of the hepatitis (1A).
- Measure antibody against hepatitis B surface antigen (anti-HBs) in people at risk (as defined above) to determine serological protection, including those who have been vaccinated for HBV during universal vaccination campaigns in childhood (2B).
- Point-of-care tests for hepatitis B have lower specificity and sensitivity than whole blood testing. If used, patients should be made aware of this and offered whole blood testing, especially if at recent risk (1B).

Discussion:

- HBV transmission occurs through infected body fluids including blood, semen, vaginal secretions, breast milk and saliva,⁶ and is associated with unprotected sex (homosexual^{7–9} and heterosexual^{10,11}), sharing of needles, syringes or other drug paraphernalia among PWID,^{9,12,13} (unscreened) blood or blood products,^{14,15} non-sterile invasive

Table 1. Intermediate- to high-endemic countries for hepatitis B (estimated anti-HBV prevalence in general population >2.0%) by UN region.

Africa	All African countries except the Seychelles
Americas	
Caribbean	All Caribbean Islands
Central America	Belize
South America	Colombia, Ecuador, French Guyana, Guiana, Peru, Suriname
Northern	Greenland
Asia	
Central Asia	Kazakhstan, Kyrgyzstan, Tajikistan, Turkmenistan, Uzbekistan
Eastern Asia	China, Mongolia, North Korea
Southern Asia	Bangladesh, Bhutan, Pakistan Sri Lanka
SE Asia	Brunei, Cambodia, Myanmar, Philippines, Singapore, South Korea, Taiwan, Vietnam
Western Asia	Armenia, Azerbaijan, Cyprus, Georgia, Oman, Saudi-Arabia, Syria, Turkey, Yemen
Europe	Albania, Belarus, Bulgaria, Greece, Kosovo, Moldova, Romania, Russian Federation
Oceania	New Zealand + all Pacific islands

Note: Data may not be complete for all countries. The purpose of this table is solely to help decide on an offer of risk-based testing where patients originate from or disclose risk in the countries cited.

(medical) procedures^{16,17} and being born or breastfed from an HBV-infected mother.^{18,19}

- HBV epidemiology differs markedly between areas of high and intermediate endemicity, where vertical transmission (from mother to child) results in the majority of chronic HBV infections and areas with low endemicity where transmission is restricted to sexual or blood-borne routes.^{6,20–22}
- Acute HBV is asymptomatic in nearly all infants and children, 10–50% of adults and in a large proportion of people co-infected with HIV. Acute fulminant hepatitis is rare (<1%). Spontaneous resolution occurs in <10% of newborns from hepatitis B ‘e’ antigen (HBeAg)-positive mothers, >70% of newborns from antibody against hepatitis B ‘e’ antigen (anti-HBe)-positive mothers and 90–95% of adults, but is less likely in people with HIV or other forms of immunosuppression.^{22–26}
- Detection of anti-HBcore in the absence of HBsAg and anti-HBs (isolated core antibody) might be the result of either resolved HBV infection with waned anti-HBs titres,^{27,28} or false-positive anti-HBcore reactivity (in a low-risk population approximately 15%).^{29,30} In rare cases, anti-HBcore in the absence of HBsAg represents occult HBV infection (OBI): chronic HBV infection with intermittent very low HBV viremia and low (<200 IU/mL) or no anti-HBs-titers. OBI does not progress to liver disease and is not infectious to sexual partners.^{30–32}
- The number of point-of-care test platforms for hepatitis B is increasing but quality remains variable and in general they will have lower sensitivity and specificity compared to whole blood testing carried out by a trained laboratory technician.^{33,34}

Prevention

In patients not known to be already infected with or immune to hepatitis B, what clinically effective interventions can reduce the ongoing risk of acquisition of hepatitis B infection?

Recommendations:

- Take a comprehensive social and sexual history to fully identify risk factors and consider which are modifiable. Be aware that some risks or routes of transmission may not be readily disclosed. Ascertain patient knowledge and discuss safer sex and methods of transmission of hepatitis B. Support this with provision of written or trusted website information (1D).
- In at-risk patients who have not been previously vaccinated, offer vaccination with either monovalent hepatitis B vaccine or combined A&B vaccine if recommended locally. In most settings, the ultra-rapid 0, 1, 3 weeks, 12-month vaccination course is recommended to improve adherence (1A).
- Health care providers should ensure there are robust recall mechanisms in place to help completion of the scheduled vaccine course (1B). Patients should be given a personal record card documenting the date, type and dose of vaccine received (1D).
- Where resources allow, and especially in those living with HIV infection, measure the anti-HBs response, and offer booster vaccinations of up to three further doses to those without detectable antibodies (i.e. <10 IU/L) 4–12 weeks after the primary course (1C).
- Patients should be advised that protection provided by monovalent vaccination is believed to

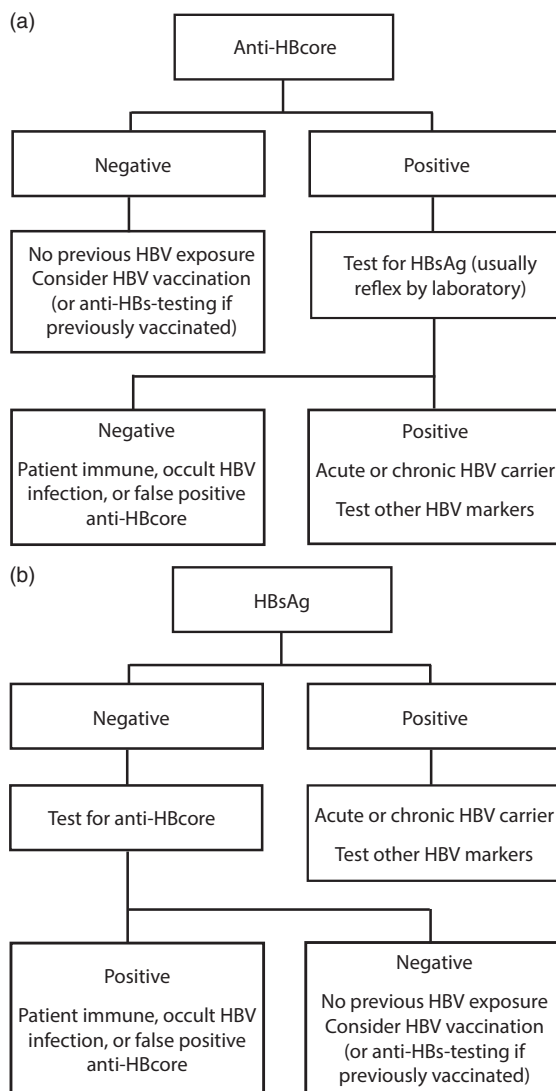


Figure 1. Flow charts for hepatitis B testing using either (a) serum anti-HBc or (b) HBsAg as initial test.

persist for >20 years once immunity has been confirmed (1B).

- In people living with HIV who have failed to respond to a primary course of hepatitis B vaccine, HBV revaccination with single- or double-dose vaccine is equally efficacious (1B). Revaccination can also be reattempted once CD4 cell count rises to >350 cells/ μ l (2C).

Discussion:

- Hepatitis B is transmitted easily by many types of sexual activity. Concordance rates (infection in both partners) of up to 18% in acute hepatitis B are reported.^{11,35}
- A careful sexual and social history is needed to identify possible risks for hepatitis B acquisition. Some behaviours are stigmatised especially in certain

jurisdictions and may not be disclosed on first enquiry. Key risk groups include:^{10,36-44}

- Unvaccinated/non-immune MSM especially those reporting multiple partners, unprotected anal sex and oro-anal sex ('rimming').
- Injecting drug users especially where there is lack of access to safer injecting equipment.
- Those injecting drugs in sexualised settings ('slamming/chemsex') which is characterised by frequent injection episodes over prolonged periods, and ceding control of injection to a third party, making safer injecting practice even harder to maintain.^{45,46}
- Men and women who engage in transactional sex (sex in return for money, goods or services).
- Other risks include vertical acquisition (infected mother to infant), receipt of unscreened blood and

Table 2. Serological and amino-transferase patterns at different stages of hepatitis B disease.

Disease stage	HBsAg	HBeAg	Core IgM	Core total	HBV-DNA	Anti-HBe	Anti-HBs	ALT
Acute early	+	+	+	+	+	-	-	↑↑↑
Acute resolving	+	-	+	+	+	±	-	↑↑
Chronic immune tolerant	+	+	-	+	+	-	-	↔
Chronic immune active	+	+	-	+	+	-	-	↑
Chronic (HBeAg-)	+	-	-	+	+	±	-	↑
Chronic (inactive)	+	-	-	+	±	+	-	↔
Occult	-	-	-	+	±	±	±	↔
Resolved (immune)	-	-	-	+	-	±	+	↔
Vaccinated	-	-	-	-	-	-	+	↔

HBsAg: hepatitis B surface antigen; HBeAg: hepatitis B 'e' antigen; HBV-DNA: hepatitis B deoxyribonucleic acid; ALT: alanine transaminase; anti-HBe: antibody against hepatitis B 'e' antigen; anti-HBs: antibody against hepatitis B surface antigen.

↔ normal range; ↑ slightly raised; ↑↑ moderately raised; ↑↑↑ very raised.

blood products, non-sterile acupuncture and tattoo needles and occupational needlestick injuries.

- Hepatitis B acquisition can be reduced by using condoms for penetrative anal and vaginal sex and reducing sexual partner numbers. PWID can greatly reduce risk by adopting safer injecting practices, avoiding sharing needles and injecting paraphernalia.^{36,39}
- Hepatitis B acquisition is highly preventable through immunisation. The 'ultra-rapid' vaccination course (0, 1, 3, 52 weeks) provides immunity more quickly and is preferred in those at immediate risk. It makes recall and dose completion easier. Other courses (e.g. 0, 1, 2, 12 months or 0, 1, 6 months) produce a slightly higher response rate.⁴⁷⁻⁵¹ The ultra-rapid vaccination schedule (0, 1, 3 weeks) leads to an anti-HBs antibody response in only 80% of recipients 4-12 weeks after the third dose. This rises to 95% just prior to the 12-month booster dose.
- HIV-positive patients may not respond as well to vaccination with overall response rates varying widely from 7% to 88% depending on setting. Antibody titres can be lower than in HIV-negative individuals, and response correlates with CD4 cell count, lowest-ever CD4 cell count and HIV viral load. Possible strategies for improving response for non-responders are using larger (double) or more frequent doses or recommencing vaccination if the CD4 cell count rises above 350 cells/mm³. Recent evidence suggests that in HIV+ vaccine non-responders, HBV revaccination with single- or double-dose vaccine is equally efficacious.⁵²
- Completion of all recommended hepatitis B vaccine doses and measurement of response is difficult to achieve in sexual health-care settings, where overall three-dose completion rates are typically around 60-70%. Vaccination can be started at a first visit while awaiting results of initial serological screening.

Structured recall systems, including those driven by electronic record systems making use of mobile technology, may increase completion rates and antibody measurement in some groups but are not universally effective.⁵³ Particular care should be paid after service reconfigurations, which can inadvertently adversely affect completion rates.⁵⁴

Acute HBV

In patients attending sexual health and dermatovenereology services in WHO Europe region found to have markers of acute hepatitis B infection, what management is required in that setting and what patient information, health advice and public health action can reduce sequelae of infection and minimise risk of onward transmission?

Recommendations:

- Clinically assess the patient including documented physical examination. Look for signs of encephalopathy and disordered clotting. Ensure referral for or undertake appropriate tests to assess severity of the hepatitis including tests for liver cell damage (bilirubin, alkaline phosphatase, transaminases), synthetic function (coagulation parameters, serum cholinesterase, albumin, glucose), renal function and a full blood count. Imaging is not usually required (1A).
- Test for other STIs including HIV. Ensure referral for or undertake tests to exclude other causes of infectious hepatitis: hepatitis A virus (HAV), hepatitis C virus (HCV), hepatitis D virus (HDV), hepatitis E virus (HEV) serology (1B).
- Refer for hospital admission in case of signs of fulminant hepatitis such as disordered clotting, encephalopathy, renal dysfunction (1A).
- Depending on setting refer onwards for linkage into appropriate care or arrange local follow-up to

ensure sero-reversion and absence of any co-infection (1D).

- Discuss and advocate practicing safer sex until the patient has become non-infectious (HBsAg negative) or their partners have been successfully vaccinated with proven sero-protection (1A).
- Patients should be given a detailed explanation of their condition with particular emphasis on the implications for the health of themselves and their partner(s) and routes of transmission of infection (1D).
- Partner notification should be performed and documented, remembering the incubation period can be as long as 180 days (1D).
- Specific hepatitis B immunoglobulin (HBIG) 500 IU intramuscularly may be administered to a non-immune contact after a single unprotected sexual exposure or parenteral exposure/needlestick injury if the source is known to be infectious. This works best within 12 h of exposure, ideally should be given within 48 h and is of no use after more than seven days (1A).
- An accelerated course of hepatitis B vaccine (at 0, 1, 3 weeks or 0, 1, 2 months with a booster at 12 months in either course) should be offered to all non-immune sexual and household contacts (including children), even where HBIG has been given. Vaccination theoretically will provide some protection from disease when started up to six weeks after exposure (1A).
- Contacts who have previously been vaccinated and achieved immunity should have a single booster dose, with no HBIG (1B).
- Practitioners should adhere to local regulations regarding public health reporting of acute hepatitis B infection (1C).

Discussion:

- Acute hepatitis B can present between 30 and 180 days after exposure. There can be a prolonged viral replication phase before symptoms develop. Patients can present with a prodromal illness which can be mistaken for gastroenteritis, before developing more typical signs of liver infection such as nausea, right upper quadrant pain and jaundice. Patients can be acutely co-infected with multiple hepatitis viruses at the same time or can present with additional hepatitis virus infection sequentially due to differing incubation periods.
- Patients found to have acute hepatitis B infection need to be assessed for the severity of the infection and for co-infection by appropriate clinical examination and tests to determine the best management. Fulminant hepatitis is rare (<0.5–1%) but can

present with encephalopathy and occur some weeks after initial symptoms. Patients should be referred for assessment of hepatitis severity if local expertise is not available.^{14,23,24,26}

- Severe acute infection can be treated with antivirals such as lamivudine or entecavir, but this would usually be under the direction of an appropriately qualified hepatology specialist.^{55,56}
- Follow-up is needed to ensure that HBsAg is cleared and that there is no emerging evidence of co-infection, remembering that incubation period for hepatitis C may differ and that there may be ongoing risk.
- Partner notification will allow identification of partners who require advice on safer sex (condoms, no sharing of sex toys, etc.) and post-exposure prophylaxis (PEP). Choice of appropriate PEP requires accurate identification of the earliest possible exposure, as specific HBIG is of no value more than seven days after risk. It is important to consider household contacts and children.^{11,36,37,39,57–64}
- Adequate information about the pathomechanisms of the disease will promote understanding and insight into required risk-reduction means.^{7,9–11,13,18,19,21,24,36–40}
- There is clear evidence for the efficacy of hepatitis B vaccine and specific HBIG for the prevention of hepatitis B. With risk of ongoing exposure an ultra-rapid vaccination schedule (0, 1, 3 weeks with a booster at 12 months) is preferred.^{13,18,19,27,39,41,57–64}

Chronic HBV

In patients found to have markers of chronic hepatitis B infection, what management is required in that setting and what patient information, health advice and public health action can reduce sequelae of infection and minimise risk of onward transmission?

Recommendations:

- Arrange referral to a hepatologist or other suitable specialist for more detailed molecular testing (e.g. HBV-DNA level), exclusion of hepatitis co-infections, liver cancer screening, ongoing disease monitoring and assessment for therapy (1D).
- Offer vaccination against hepatitis A if non-immune (1D).
- Patients should be given a detailed explanation of their condition with particular emphasis on the long-term implications for the health of themselves and their partner(s). This should include information about alcohol reduction. This should be

reinforced by giving them clear and accurate written or trusted website information (1C).

- Patients found to have chronic hepatitis B who are considering sexual PrEP for HIV with tenofovir/emtricitabine should be advised of the risk of hepatitis flares especially with event-based dosing (1D).
- Partner notification should be performed and documented and the outcome documented at subsequent follow-up. Trace contacts as far back as any episode of jaundice or to the time when the infection is thought to have been acquired although this may be impractical for periods of longer than two or three years (1D).
- They should be advised of the need to disclose to new sexual partners, and partners encouraged to be vaccinated (1D).
- Ensure arrangements made to test and vaccinate children who have been born to infectious women if the child was not vaccinated at birth (1C).
- For screening of other nonsexual partners who may be at risk, proceed with case finding according to local procedures (1C).
- If pregnant, inform the woman about the risk of vertical (mother to infant) infection transmission and the need for monitoring and intervention to prevent this (1C).
- Advice for MSM and HIV+MSM should include use of condoms, gloves for fisting, single-person-only sex toys/condoms on sex toys and changed between partners. They should be advised not to share lube and avoid group sex situations such as 'chem-sex' parties (2D).
- Practitioners should adhere to local regulations regarding public health reporting of chronic hepatitis B infection (1C).

Discussion:

- Chronic hepatitis B has long-term complications such as cirrhosis and liver cancer but is treatable with agents such as tenofovir, entecavir, lamivudine or pegylated interferon.⁶⁵⁻⁷³ Patients should therefore see an experienced specialist who can assess the patient for treatment.
- Factors that would make HBV-related liver disease worse include viral hepatitis infections, HIV and alcohol. Prevention can be instituted, such as vaccination against hepatitis A, if necessary.⁷⁴⁻⁸⁴
- Discussion on safer sex and of the ways to prevent infection are also likely to be effective.^{57,58} Many MSM do not see injecting during 'chemsex' situations as being risky⁸⁴ whereas the reality is that acquisition of blood-borne virus infections is as high as for other forms of injecting drug use.
- Hepatitis D (HDV) is an incomplete ribonucleic acid (RNA) virus that requires the hepatitis B outer coat. HBV/HDV coinfection increases the risk of fulminant hepatitis and progression to cirrhosis, so all patients with hepatitis B should receive hepatitis D testing.^{23,85}
- The advent of PrEP for HIV with a combination of tenofovir and emtricitabine may mean some patients with chronic hepatitis B may unwittingly take PrEP unaware of the possibility of this causing a hepatitis flare, especially when started and stopped. The licence for Truvada[®] (Gilead Sciences Inc., Foster City, CA, USA) use in the USA and Europe has a specific warning about the use of Truvada in chronic hepatitis B. Very limited evidence suggests continuous Truvada-based PrEP may be safe in chronic hepatitis B where the person has near-normal transaminase levels and is non-cirrhotic.⁸⁶

Contacts

In patients reporting contact with someone known or suspected to have infectious hepatitis B, what is the best approach to testing, immunisation and health advice to gain maximal reassurance for the patient and reduce the potential risk of onward transmission?

Recommendations:

- Enquire about previous hepatitis B testing and vaccination. If status unclear, test for evidence of pre-existing HBV infection and immunity (see earlier section *Hepatitis B: Testing*). Do not delay actions below while awaiting results (1A).
- Likely or known to be non-immune:
 - Specific HBIG 500 IU intramuscularly may be administered to a non-immune contact after a single unprotected sexual exposure or parenteral exposure/needlestick injury, especially if the donor is highly infectious (hepatitis B deoxyribonucleic acid [HBV-DNA] >2000 IU/mL). This works best within 12 h of exposure, ideally should be given within 48 h and is of no use after more than seven days (1A).
 - An accelerated course of hepatitis B vaccine (at 0, 1, 3 weeks or 0, 1, 2 months with a booster at 12 months in either course) should be offered to all non-immune sexual and household contacts, including to those given HBIG. Vaccination theoretically will provide some protection from symptomatic and chronic infection when started up to six weeks after exposure (1A).
- Contacts who have previously been vaccinated and achieved immunity (anti-HBs >10 IU/L) should have

a single booster dose as soon as possible, with no HBIG (1A).

- Avoid sexual contact, especially condomless vaginal or anal penetrative sex, until vaccination has been successful (anti-HBs titres >10 IU/L) (1D).

Discussion:

- The risk of acquiring hepatitis B varies according to the nature of the risk and the infectivity of the source. Highest risk is when the source has a HBV-DNA viral load >2000 IU/mL and when the exposure is unprotected penetrative vaginal or anal sex or parenteral exposure.^{6–17}
- In the absence of intervention, vertical transmission occurs in 90% of pregnancies where the mother is hepatitis B e antigen positive and in about 10% of surface antigen-positive, e antigen-negative mothers. Most (>90%) infected infants become chronic carriers.¹⁹
- Hepatitis B can be transmitted sexually, both through vaginal and anal sex. The rate of transmission from a chronic carrier is proportional to the HBV viral load.^{11,13,21,25}
- Rapid hepatitis B vaccination will prevent most cases of acute HBV but HBIG will provide additional protection and is needed especially if the patient exposed is immunocompromised or the donor is highly infectious (HBV-DNA >2000 IU/mL).^{47–52,60–64}
- Screening for hepatitis B in the recipient at baseline will provide information on whether they have any immunity, which in turn will dictate the need for any further vaccine doses. However, do not wait for laboratory results before deciding to administer immunoglobulin and vaccination.

HCV infection

Background

Hepatitis C is an RNA virus in the flaviviridae family. It is endemic worldwide with overall prevalence estimated to be 1.6% (95% CI 1.3–2.1), with much higher prevalence in west and central sub-Saharan Africa and Central Asia, where prevalence exceeds 4%.⁸⁷ Within this broad geographic spread, HCV preferentially affects specific risk groups, such as PWID, recipients of infected blood products and tattoos, people with HIV infection, and children born to mothers with HCV infection. Some 15–45% of people infected clear the virus naturally, leaving an estimated 80.2 (95% CI 64.4–102.9) million people globally who are HCV viraemic (chronic HCV), and so at risk of complications and onward transmission.^{3,87}

Complications include cirrhosis and hepatocellular carcinoma.

In 2016, ECDC published a systematic review of published studies informing country-specific prevalence for the whole European region.⁵ Anti-HCV prevalence in the general population was 5.9% (95% CI 5.2–6.6) in Italy and above 2% in Romania, Latvia, Greece, Slovakia. The prevalence of HCV among MSM ranged from very low in Italy to 4.7% in Estonia; in PWID from 13.8% in Malta to 84.3% in Portugal. The overall estimated EU/EEA prevalence is 1.1% (95% CI 0.9–1.4), corresponding to around 5.6 million antibody against HCV (anti-HCV)-positive cases.

HCV has been classified into seven genotypic groups which have important differences in response to currently available treatments, with the exception of the newest ‘pan-genotypic’ agents. Genotype 1 accounts for just under half of all infections. Direct-acting antiviral (DAA) treatments have revolutionised the management of hepatitis C, offering ability to cure >90% of patients with a 12–24-week course of oral tablets. Traditional interferon-based treatments have been relegated from first line status in any situation in both WHO and European treatment guidance.^{3,4}

Testing

In patients attending sexual health and dermatovenereology services across WHO Europe region, who should be tested for past or current HCV infection and what laboratory tests should be used?

Recommendations:

Who to screen

- We recommend a risk-based approach to HCV testing in the sexual health setting. Local public health guidance may suggest testing in additional situations and should be followed. We suggest testing in the following groups:
 - People who currently or in the past injected any type of drugs, including steroids, (novel) psychoactive substances, image and performance enhancing drugs (IPEDs), and melatonin (1A).
 - People who have exchanged sex for money, goods or favours (1B).
 - People with a past history of needlestick injury where the source was known to have hepatitis C or injected drugs (1A).
 - MSM who have additional risk factors including HIV infection, report of traumatic sexual practice (e.g. fisting), diagnosis of lymphogranuloma venereum (LGV) or syphilis, previous resolved or treated hepatitis C infection, engaging in ‘chemsex’ (1B).

Table 3. Intermediate to high-endemic countries for hepatitis C (estimated anti-HCV prevalence in general population >2.0%) by UN region.

Africa	Angola, Benin, Burkina Faso, CAR, Cameroon, Chad, Congo, DRC, Egypt, Equatorial Guinea, Gambia, Ghana, Ivory Coast, Gabon, Guinea, Guinea-Bissau, Liberia, Mali, Niger, Nigeria, Senegal, Sierra Leone, Togo, Western Sahara
Americas	Greenland, Puerto Rico
Asia	
Central Asia	Kazakhstan, Kyrgyzstan, Tajikistan Turkmenistan, Uzbekistan
Eastern Asia	Mongolia
Southern Asia	Pakistan
SE Asia	Cambodia, Thailand, Taiwan
Western Asia	Armenia, Azerbaijan, Georgia, Israel, Iraq, Yemen
Europe	Belarus, Estonia, Greece, Italy, Latvia, Lithuania, Moldova, Romania, Russian Federation, Slovakia, Ukraine
Oceania	—

Note: Data may not be complete for all countries. The purpose of this table is solely to help decide on an offer of risk-based testing where patients originate from or disclose risk in the countries cited.

- People from countries of intermediate to high hepatitis C endemicity (>2%; see Table 3) (2C).
- Recipients of suspected unsafe blood products (e.g. prior to 1990 or poor donor screening) (1A).
- Current and past prisoners (2C).
- Patients with symptoms of acute hepatitis or found to have deranged liver function as part of a routine liver disease workup (1A).
- Patients who are living with HIV infection should be screened for HCV according to current recommendations of the European AIDS Clinical Society Guideline.⁸⁸ In 2016, they recommended HCV testing at HIV diagnosis, and every year thereafter, irrespective of alanine transaminase (ALT) level (1B).
- Additional HCV testing of no more than once every three months should be considered in HIV-positive MSM who report HCV-related sexual risk factors, in particular traumatic sexual practices, those diagnosed with LGV and/or syphilis, and previous (resolved) HCV infection (2B).
- HIV-negative MSM do not require routine HCV screening, but HCV testing should be considered at least yearly for MSM who report HCV-related sexual risk factors, and in particular MSM who require HIVPEP or are eligible for or taking HIV PrEP (2D).

How to test

- If suspected HCV exposure was >3 months ago, test for HCV antibody. If this is positive, detection of hepatitis C virus ribonucleic acid (HCV RNA) by a sensitive molecular method or hepatitis C virus antigen (HCV Ag) confirms active HCV infection (1A).
- If suspected HCV exposure was <3 months ago, HCV antibody may not have developed. Testing for HCV Ag or HCV RNA allows for earlier detection of infection where resources and facilities allow (2C).
- In patients who have previously-resolved HCV infection (spontaneously or by treatment) HCV Ag or HCV RNA testing is required to detect re-infection (1A).
- Consider HCV Ag or HCV RNA testing for all immunocompromised patients at risk for HCV, including people with HIV, as HCV antibody takes longer to develop (up to 12 months) or may even not form at all (1D).

Discussion:

- The median time to develop detectable anti-hepatitis C antibody after infection is 65 days, with >90% of infected individuals HCV antibody positive by three months. Seroconversion can be delayed for up to nine months or not even occur at all, particularly in the context of HIV infection and/or other forms of immunosuppression.^{14,89–92}
- Newer automated HCV Ag tests provide a sensitive, specific, semi-quantitative and cheaper alternative to HCV RNA molecular testing for early detection of active HCV infection. Although its lower limit of detection (700–1100 IU/mL) is about 100× higher compared to HCV RNA detection, the doubling-time of HCV viral load after infection (10.8 h) suggests only an extension of the diagnostic window of 3–4 days.^{93–96} EASL guidelines support use of HCV Ag testing and recommend use of RNA tests with a lower limit of ≤15 IU/mL.
- In clinical practice, elevated ALT levels are often used as a trigger to initiate HCV screening, but ALT levels remain normal or rapidly normalise in

up to 71% of HCV-infected patients, even during acute infection.^{90,96,97} HCV testing should therefore be considered based on risk rather than solely with abnormal LFTs.

- Sexual transmission is almost completely confined to HIV-positive MSM and is associated with multiple partners, unprotected anal sex, a known HCV-positive sexual partner, recent ulcerative STIs in particular LGV and syphilis, potentially traumatic sexual practices (e.g. group sex, the use of sex toys, fisting and bleeding during sex), the use of anal enema and/or the use of recreational drugs before or during sex.^{3,98–103} Commercial sex work has been associated with increased HCV prevalence.¹⁰
- Previous exposure to HCV does not confer sterilising immunity, and the risk of re-infection and super-infection is high with continuing risk behaviour.^{104–107}
- Heterosexual transmission is extremely rare (maximum incidence rate <0.07% per year), but the rate may increase in the presence of HIV, with anal sex or vaginal intercourse during menses, commercial sex work or a high number of sexual partners, rough sexual techniques or concurrent STI.^{107,108}
- Although HIV is not a prerequisite for sexual transmission of HCV, HIV-negative MSM in Europe remain largely unaffected.^{109–111} However, recent studies among high-risk HIV-negative MSM, especially men who meet criteria for PEP and PrEP, underline the risk of HCV spreading to the HIV-negative population.^{112–114}
- Blood–blood contact is the most efficient way to transmit HCV. PWID who share needles should be routinely tested for HCV, but also sharing other injection paraphernalia or straws while snorting causes an elevated risk for HCV.^{115–117} In this context, the increased popularity of slamming at chemsex parties (injection of recreational drugs in a highly sexualised setting) might fuel the HCV epidemic among MSM, both as a result of parenteral transmission and the loss of attention to safe sex while under the influence of drugs.^{45,84,98,99} Mephedrone injection, at least in the UK, is linked to significantly higher risk of hepatitis C markers.¹¹⁸ Prevalence of blood-borne viruses is also rising among those injecting IPEDs.⁴⁶

Prevention

In patients attending sexual health and dermatovenereology services not known to have current HCV infection, which clinically effective interventions can be delivered in that setting to reduce ongoing risk of acquisition of HCV in sexualised settings?

Recommendations

- Ensure access to harm reduction programs for PWID, and educate on the risk of sharing needles, injection paraphernalia and straws while using recreational drugs and/or steroids (1B).
- There is a lack of evidence-based behavioural interventions that reduce HCV-related risk behaviour. Nevertheless advocate safer sex and provide accurate, accessible and tailored information to increase HCV awareness and knowledge on HCV transmission routes and clinical complications (1D).
- Provide accessible HCV testing for people at risk and linkage to appropriate care for those infected with HCV to reduce onward transmission of HCV (1D).
- Promote partner referral and lift stigma around HCV to facilitate disclosure of HCV status, thereby preventing onward HCV transmission (1D).

Discussion:

- Needle and syringe programs, opiate substitution therapy and other drug dependence treatment, especially in combination with social–medical care will reduce parenterally-transmitted infections, including HCV among PWID.^{87,119–122}
- Sexual transmission requires the exchange of HCV-infected body fluids (most likely semen and/or blood) across mucosal surfaces and therefore the use of condoms, and not sharing lubricant, gloves, toys or other objects (including insertive partners in the setting of group sex) will likely prevent sexual transmission of HCV and other STIs.^{3,98–103}
- There is evidence of low understanding of HCV acquisition risk among affected communities including MSM and those living with HIV infection. HCV risk assessments need to be personalised with full discussion of an individual's sexual practices as well as use of recreational or sexualised drug use, and any other injecting drug use (e.g. for bodybuilding); practitioners need to be cognisant of local epidemiology and prevalent risk behaviours.^{123–125}
- In the era of interferon-free DAA therapy, HCV treatment for prevention can be a cost-effective measure to reduce the burden of HCV, including PWID, prison settings and in MSM with higher-risk sexual practice.^{4,126–129}
- MSM may be re-infected after successful treatment and therefore practitioners should offer retesting where a new risk arises (see *Testing*).¹⁰⁵
- There is some evidence in support of 'treatment optimism', where the availability of effective treatments

for both HIV and hepatitis C results in continuous or renewed sexual high-risk behaviour. Alternative strategies in sexual health counselling and the implementation of behavioural health prevention measures in both HIV-positive and HIV-negative MSM may be required.^{114,128}

- Since 1991 donated blood has been screened for HCV and blood products rendered almost incapable of transmitting infection in (nearly) all European countries.^{14,130} Patients should be warned about receipt of parenteral blood products from countries with ineffective blood product screening.
- There is no effective HCV vaccine currently available.¹³¹
- Primary prevention includes action to eliminate discrimination and gender violence and to increase access to medical and social services for vulnerable people. Sexual health services should consider ways of addressing these objectives within their own local political context.¹³²

Acute HCV

In patients attending sexual health and dermatovenereology services across WHO Europe region found to have markers of acute hepatitis C infection, what management is required in that setting, and what patient information, health advice and public health action can reduce sequelae of infection and minimise risk of onward transmission?

Recommendations:

- Clinically assess the patient and arrange or ensure referral for appropriate tests of the severity of the hepatitis including transaminases and LFTs, such as clotting, cholinesterase, protein, coagulation and serology of other infectious hepatitis (HAV, HBV, HDV, HEV serology) (1A).
- Screen for other STIs (including syphilis, LGV and HIV), particularly in MSM (1A).
- Patients with acute HCV should be followed with four-weekly HCV RNA quantitation to detect spontaneous clearing of the disease. We recommend referral to a specialist centre with access to DAA treatments for assessment, monitoring and treatment and access to clinical trials of treatment of early infection, especially in those with a higher risk of onward transmission (1A).
- Refer for clinical admission in case of signs of (rare) fulminant hepatitis (1A).
- If HCV RNA persists for more than six months refer to an appropriate centre for management of chronic hepatitis C (1A).

- Patients should be given a detailed explanation of their condition with particular emphasis on the implications for the health of themselves and their partner(s) and routes of transmission of infection (1D).
- Sexual transmission, although rare should be discussed, particularly in an MSM/HIV-positive setting. Discuss and advocate practicing safer sex including use of condoms, gloves for fisting, single-person-only sex toys/condoms on sex toys and changed between partners. Also not to share lube and avoid group sex situations particularly in chemsex settings (1D).
- Transmission through drug use should be discussed, recognising that some patients using injectable drugs in sexualised settings (chemsex) may not identify themselves as injecting drug users (1D).
- Partner notification should be performed and documented (1B).
- Hepatitis C infection should be reported to local health authorities according to local public health and/or legal regulations (1D).
- Women should be informed of the possible risk of vertical transmission in pregnancy and if wishing to conceive should be referred to consider therapy prior to conception or advised to await possible natural resolution (1D).

Discussion:

- Elevated transaminases together with clinical symptoms, such as B-symptoms, fatigue, lack of energy and potential risks of infection might be indicators of an acute hepatitis C. Specific antibody/antigen-testing for verifying the diagnosis is available, but might not differentiate between acute and chronic forms of an HCV infection.^{4,133–138}
- DAA therapy is highly effective and generally well tolerated, but restricted to chronic HCV infection^{126–129} based on clinical trial data and European Medicines Agency/Food and Drug Administration approval.
- Early treatment of hepatitis C can be effective and linkage into appropriate care should be made where available. Treatment may be based on a failure to show a viral load reduction by at least 2 log₁₀ at week 4 or those who have a positive viral load at week 12.^{4,135–141}
- The course of the disease, including potential clearing and difference between acute and chronic HCV, should be discussed to facilitate management and referral decisions.^{4,133–141}
- Sexual HCV transmission commonly is associated with high-risk sexual behaviour with risk of acquiring other STIs.^{51,103,106,111,142–144}

- Use of safer-sex practices (condoms, no sharing of toys, gloves, lube, etc.) will prevent sexual transmission of HCV.¹³⁵
- Tailored health promotion about HCV might provide a means to increase HCV awareness and disrupt its negative image, thereby providing a means to discuss sexual practices and reconsider risk-reduction procedures.^{84,103,111,143,144}
- Partner notification may be considered where resources allow especially if a sexual route of acquisition is suspected (2C).
- The infection should be reported to local health authorities depending on local legal regulations (1D).
- Women should be informed of the possible risk of vertical transmission in pregnancy and if wishing to conceive should be referred to consider therapy prior to conception (1D).

Chronic HCV

In patients attending sexual health and dermatovenereology services across WHO Europe region found to have markers of chronic hepatitis C infection, what management is required within that setting, and what patient information, health advice and public health action can reduce sequelae of infection and minimise risk of onward transmission?

Recommendations:

- Clinically assess the patient and perform appropriate tests including transaminases and LFTs, such as clotting, cholinesterase, protein, coagulation and serology for other infectious hepatitis (HAV, HBV (±HDV), HEV) (1A).
- We recommend vaccination against HAV and HBV if not immune (1B).
- Screen for other STIs (including syphilis, LGV and HIV), particularly in MSM (1A).
- Arrange referral to a specialist centre with access to DAA treatments for assessment, monitoring including HCC screening, treatment and access to clinical trials (1A).
- Patients should be given a detailed explanation of their condition with particular emphasis on the implications for the health of themselves and their partner(s) and routes of transmission of infection (1D).
- Sexual transmission, although rare should be discussed, particularly in an MSM/HIV-positive setting. Discuss and advocate practicing safer sex including use of condoms, gloves for fisting, single-person-only sex toys/condoms on sex toys and changed between partners. Also not to share lube and avoid group sex situations particularly in chemsex settings (1B).
- Transmission through injecting drug use should be discussed, including risks of sharing injecting paraphernalia, mindful that not all patients will disclose potentially stigmatised behaviour. Patients who disclose injecting drug use should be directed to needle exchange resources and safer injecting locations where available (1B).

Discussion:

- Chronic HCV infection is defined by a course of >6 months, a clear differentiation between acute and chronic HCV infection commonly only can be done via this time criterion.^{4,90,97,102,136–147}
- Sexual HCV transmission commonly is associated with high-risk sexual behaviour and therefore acquisition of other STIs is not uncommon.^{51,103,106,111,142–144}
- Sexual transmission of HCV commonly is associated with sexualised recreational drug taking with poly-drug use common. Injecting of novel psychoactive substances is increasingly reported, with users injecting multiple times per day during multi-day sessions of drug-taking. Patients using drugs in these settings may not self-identify as injecting drug users and may have less appreciation of risk of onward transmission of hepatitis C. Local drug services may be tailored to opioid substitution therapy. A careful history and informed guidance is needed to help modify risk in these settings.^{45,84,98,99}
- Use of safer-sex practices (condoms, no sharing of toys, gloves, lube, etc.) will prevent sexual transmission of HCV.¹³⁶
- Partner notification in the setting of chronic hepatitis C, especially where the source of transmission is unclear, may yield few identifiable contacts. A public health approach based on knowledge of local epidemiology to identify all those at risk to come forward for testing is likely to be more effective.^{148,149}
- Tailored health promotion about HCV might provide a means to increase HCV awareness and disrupt its negative image, thereby providing a means to discuss sexual practices and reconsider risk-reduction procedures.^{84,103,111,143,144}
- Vertical transmission may occur in up to 5.8% of pregnancies in women with HCV mono-infection and 10.8% of those with HIV co-infection.^{150–154}
- DAA therapy is highly effective and generally well tolerated, but in many jurisdictions funding is restricted to chronic HCV infection only. Additional restrictions (level of fibrosis) might

apply in selected countries.^{126–129} EASL guidance covers treatment in detail.⁴ In particular, these new guidelines recommend treatment should be considered without delay in individuals at risk of transmitting HCV, including injecting drug users, MSM with high risk sexual practice and women wishing to conceive.⁴

- Acute fulminant hepatitis can occur during hepatitis A co-infection.^{155,156}

Contacts

In patients reporting contact with someone known or suspected to have hepatitis C infection, what is the best approach to testing and health advice to gain maximal reassurance for the patient and reduce the potential risk of onward transmission?

Recommendations:

- Screen for evidence of past or current HCV infection as well as for HIV, HBV and STIs (1D). It can take three or more months to seroconvert to HCV-antibody positive. If available, HCV-RNA or HCV-antigen assays can detect the infection as early as four weeks after exposure and can be used after high-risk exposure.
- Sexual transmission risk during the window period should be discussed. It seems likely that if condoms are used consistently then sexual transmission will be avoided, but given the very low rates of transmission outside of HIV co-infection, monogamous partners may choose not to use them (1D).
- Sexual contacts with HIV should be advised of higher risk of sexual transmission, with regular testing and condom use encouraged (1D).
- There insufficient evidence of risk–benefit and cost-effectiveness to support use of DAA agents as PEP (1B).
- There is currently no available vaccine or immunoglobulin preparation that will prevent HCV transmission.

Discussion:

- Heterosexual sexual transmission of hepatitis C is uncommon.^{103,107,140} Sexual transmission has been seen particularly in the last 10 years amongst MSM in the setting where one of the partners is HIV-positive and is linked to unprotected anal sex. Co-factors include concurrent STIs such as herpes, syphilis and LGV and also related to traumatic sex.^{103,111,141,157,158}

- The choice of assay depends on availability and risk of exposure.^{90,95} In previous years, it was especially urgent to identify acute HCV infection as pegylated interferon works best within the first six months.^{143,159} However, with the advent of DAAs for the treatment of HCV, the time when treatment is instituted is becoming less important.¹⁵⁹
- Prevention still centres around safer-sex (condoms) and the identification of infection.

Hepatitis E virus

In patients attending sexual health and dermatovenereology services in WHO Europe region, what advice should be given to patients concerned about hepatitis E infection?

Recommendations:

- Patients can be advised that HEV is not likely to be transmitted sexually or by human-to-human contact (2B).
- There does not appear to be an increased prevalence in those at higher risk of STIs so we do not recommend any targeted testing of HEV in the sexual health clinic setting (2C).
- HEV virus testing should be considered as part of the routine workup for patients presenting with clinical hepatitis or raised transaminases (1A).

Discussion:

- Hepatitis E causes acute hepatitis (and very rarely chronic hepatitis) which, according to genotype, can be mainly faeco-orally or food transmitted. There is no evidence to date for sexual transmission.¹⁶⁰

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Appendix I

Search Strategy

The 2016 guideline updates the previous guideline by searching Medline 2011–2016 for ‘hepatitis B’, ‘hepatitis C’, ‘hepatitis D’ and ‘Delta virus’ and limited to ‘human’ with specific reference to the eight formulated PICO questions.

Other current hepatitis guidelines were also reviewed for consistency and for information not captured in our searches.

The protocol for production for Europe Guideline is at <http://www.iusti.org/regions/europe/pdf/2017/ProtocolForProduction2017.pdf>

Levels of evidence and grading of recommendations. The GRADE System as adopted by Europe Guidelines Group

Please see http://www.iusti.org/regions/europe/pdf/2013/Levels_of_Evidence.pdf