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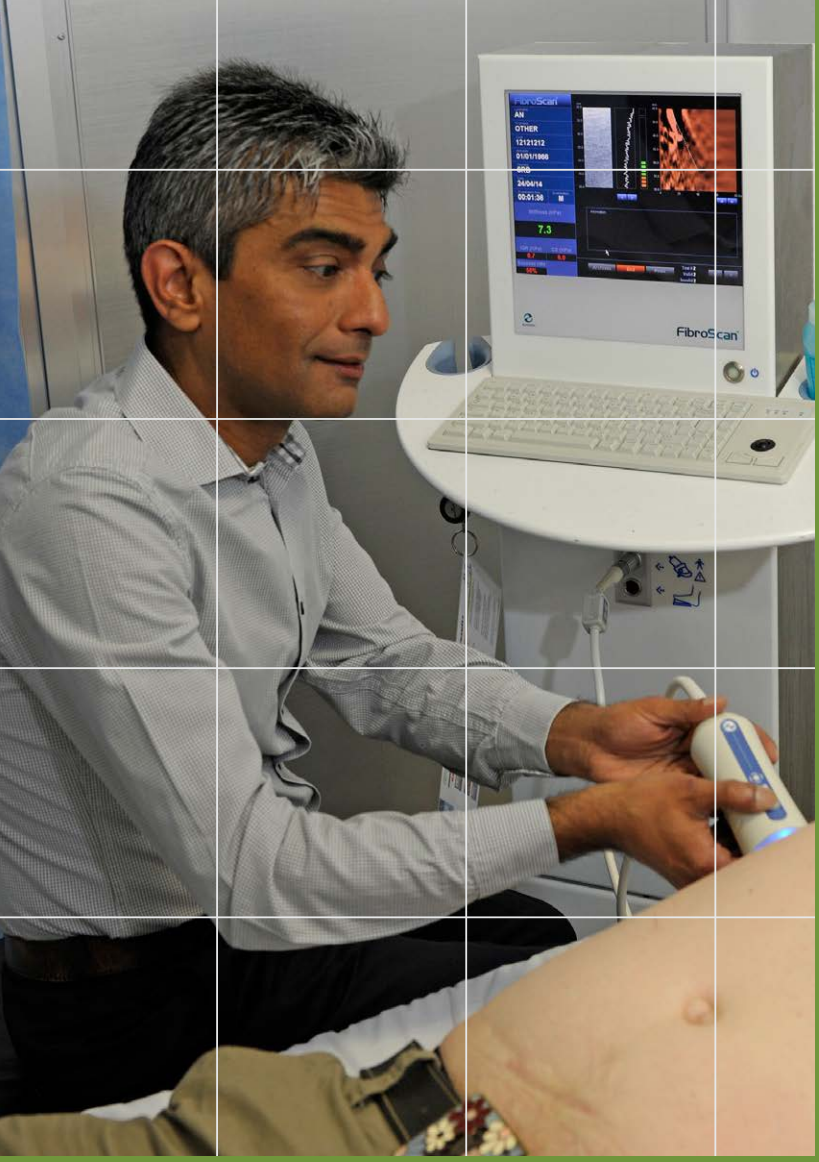

How To establish a viral hepatitis clinic

heptrislide

HEPTRIslide is a free, online, searchable, downloadable slide library with many presentations about viral hepatitis.

Access it at **www.justrislide.com**

JUSTRI is a UK-based not-for-profit organisation, dedicated to providing resources and education for those with and working with HIV and viral hepatitis.
See our work at **www.justri.org**

Additional information on viral hepatitis is available at: **www.aidsmap.com**, **www.hepatitisc.uw.edu**, **www.natap.org**, **www.i-base.info**, **www.hep-druginteractions.org** and at other sites listed in the **Further Information** section of this guide

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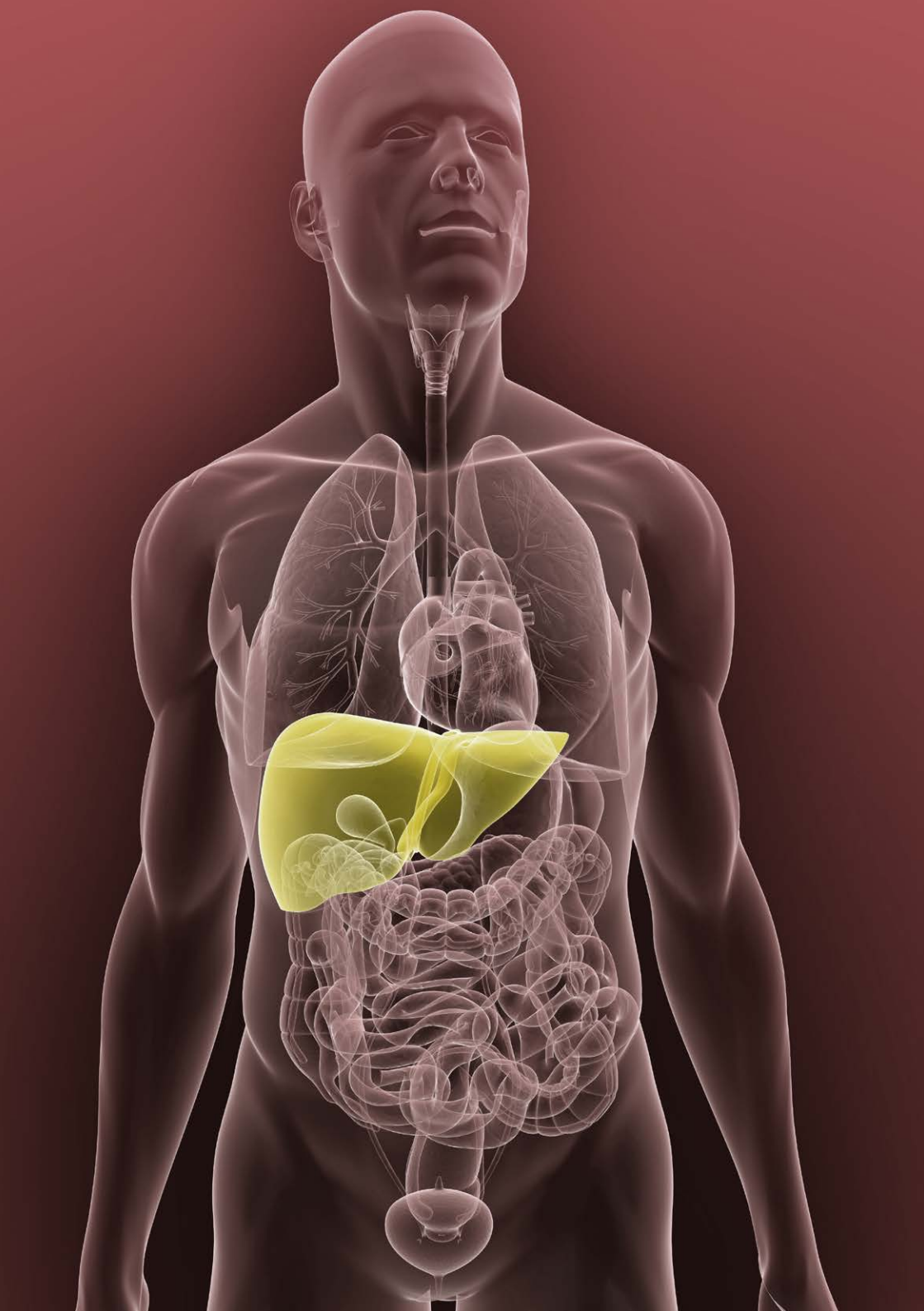

Section 1: Introduction

Welcome to the first edition of the JUSTRI guide for establishing and running a viral hepatitis clinic.

Viral hepatitis, comprising chronic hepatitis B (HBV) and C (HCV), affects over 500 million people globally and represent a public health problem in many countries. These infections contribute to 60% of deaths from liver cirrhosis and 75% of cases of primary liver cancer (hepatocellular carcinoma [HCC]) worldwide. In the context of HIV infection, co-infection with HBV and HCV is extremely common. In the era of effective antiretroviral therapy, liver disease – mostly as a result of chronic viral hepatitis – is the single biggest cause of non-AIDS death in HIV-infected individuals.

HBV is vaccine preventable and treatable with both interferon-based therapies and oral nucleoside and nucleotide agents, thus halting progression to cirrhosis and HCC. HCV infection is curable with an appropriate combination of pegylated interferon-alpha, ribavirin and the newer, direct-acting antivirals (DAAs). In the next few years, a range of oral therapies will become available for the treatment of chronic HCV; these will offer many more patients globally the opportunity to cure their HCV infection.

Whilst the development of therapies for HBV over the past decade has helped build a momentum for the treatment of this infection, it is the new opportunity of more easily curing HCV that is mobilising the medical and political establishments to take both of these diseases more seriously. The diagnosis and treatment of HIV infection provides an excellent template for organising services for the individual patient with viral hepatitis, as well as affected communities, while technological advances in diagnosing and monitoring of viral hepatitis and liver damage allow for better management of these conditions. There will be rapid changes in this area during the next few years as many novel therapies are about to be licensed for use. It is vital, therefore, that clinical services are developed to deal with the needs of the patient with viral hepatitis in a variety of different healthcare settings.

The time is now right to set in place infrastructure, appropriately skilled personnel and pathways of care to manage chronic viral hepatitis infection.

This is a practical guide designed to be used by doctors, nurses, managers and others who organise and deliver care to individuals infected with viral hepatitis, including those co-infected with HIV. It provides the basis for setting up and running a dedicated clinical service and has been developed using the model of an established viral hepatitis clinic based at the Royal Free Hospital, London, UK, which currently provides care for over 5000 HBV and HCV mono-infected and 650 HIV and HBV/ HCV co-infected patients. Of course, this model will need to be modified for your own setting and needs.

How to use this guide

We hope that reading this guide will help you to have a clear understanding of the issues involved in establishing a dedicated viral hepatitis clinic and that by sharing the information with your colleagues and other health professionals the care you provide will be improved.

The lines of communication between physicians, nurses, patients and those who work with all aspects of viral hepatitis are opening up and this needs to continue as it will benefit all involved.

The subject of viral hepatitis is a constantly changing field and there are many online sources in the **Further Information** section of this guide that provide a wealth of scientific and general information about the disease. Don't be afraid of using the internet to find things out – we all do nowadays! However, information provided on the internet is of varying quality and should be read with caution. As with all printed information, please check for updates to this guide, especially if reading it after December 2015; the latest version will always be available online at **www.justri.org**.

A large number of individuals, some living with viral hepatitis with and without HIV, have contributed to this guide and we welcome any comments, corrections and ideas or suggestions for inclusion in future editions; please send these to **home@justri.org**.

JUSTRI and the authors of this guide welcome you to contact them if you wish to establish a viral hepatitis clinic or for advice on the running of your clinic. Through our JUSTRI Skills Exchange programme, (see **www.justri.org**), we offer training in areas needed to provide the best care for those with viral hepatitis – please get in touch with us at **home@justri.org** to find out more.

Why have dedicated viral hepatitis clinics?

There are several advantages of having a clinic dedicated specifically to the management of viral hepatitis. These include:

- HBV and HCV may both cause multi-system manifestations, so it is important to have dedicated clinics with expertise in managing all aspects of these infections
- Co-infection with HIV is common; thus, there is a need to test for and manage all blood-borne viruses effectively in a single setting
- Management of these viruses requires expertise in a wide range of areas such as harm-reduction, partner notification and partner/household testing and vaccination, which is best delivered by a dedicated team
- Antiviral therapy is evolving rapidly and this increases the importance of developing a dedicated multi-disciplinary team with expertise in effectively treating these infections

Basics of chronic viral hepatitis

HEPATITIS B

HBV is a DNA virus of the *Hepadnaviradae* family and it is estimated that there are over 350 million people chronically infected with HBV worldwide.

Transmission occurs only between humans, both vertically and horizontally, parenterally or within households, and is associated with the sharing of toothbrushes, razors and towels. There is no evidence that it can be be transmitted by sharing cooking and eating utensils or by sleeping in the same bedroom.

In Africa and Asia, mother-to-child and horizontal transmission in early childhood are the commonest routes of infection. Early childhood transmission occurs by household transmission, as described above, and via sharing of chewing gum or partially eaten sweets amongst children. Breast feeding is not thought to transmit HBV, although HBV DNA can be detected in colostrum. The question of transmission through blood sucking insects remains controversial. In the rest of the world, sexual transmission in adult life predominates.

If infection is acquired in early life chronicity develops in the vast majority of individuals. In adult infections, clearance of the primary infection is usual in immune competent individuals.

HBV is integrated into the human genome. An important replicative intermediate is also found in the hepatocyte as a covalently coiled, closed circular DNA and – similar to HIV – infection once established is life-long.

Disease activity, in terms of liver inflammation and fibrosis, results from the interplay between the virus and the host immune system. For many patients, the immune system is able to control viral production and these individuals will sustain very little liver damage over their normal life span. However, in others, there is progressive liver damage leading to cirrhosis and HCC. Progression to end-stage liver disease and HCC occurs over a period of many years, although it appears to be faster if the patient is co-infected with HIV. HBV is unique in that it can cause HCC without progressive cirrhosis in some individuals. This is common in sub-Saharan Africa where co-factors such as aflatoxins in the diet may lead to this occurring.

Table 1 shows the different stages of HBV infection. It is important to be able to ascertain at what stage of infection your patient is, as the need for treatment will very much depend on a number of factors, including HBV DNA levels, histological liver damage (stage and grade), alanine transaminase (ALT) levels, hepatitis 'e' antigen (HBeAg) status and the age of the patient.

TABLE 1: STAGES OF HEPATITIS B VIRUS (HBV) INFECTION

Stage of infection	Surface antigen (HBsAg)	'e' antigen (HBeAg)	IgM anti-core antibody	IgG anti-core antibody	HBV DNA	Anti-HBe antibody	Anti-HBs antibody	Alanine trans-aminase
Acute (early)	+	+	+*	+*	+	-	-	↑↑↑
Acute (resolving)	+	-	+	+	-	+/-	-	↑↑
Chronic (immune tolerant)	+	+	-	+	++	-	-	N
Chronic (immune active)	+	+	-	+	+	-	-	↑
Chronic (HBeAg negative)	+	-	-	+	+	+/-	-	↑
Chronic (inactive carrier)	+	-	-	+	-	+	-	N
Resolved (immune)	-	-	-	+	-	+/-	+/-	N
Successful vaccination	-	-	-	-	-	-	+	N

* In very early infection, the HBV IgM anti-core antibody test may be negative and, by definition, so may the IgG anti-core antibody test

N=normal

HEPATITIS D (hepatitis delta)

Delta virus is a defective RNA virus-like agent that infects hepatocytes and can only complete viral replication in the presence of hepatitis B surface antigen (HBsAg). Therefore, this infection occurs only in the presence of HBV, either as a co-infection or a super-infection. While transmission is commonly via the parenteral route, especially in injecting drug users (IDUs), transmission through contact with infected blood during sex may also occur. Infection with HDV leads to severe liver damage in the presence of HBV and must always be tested for in patients with chronic HBV infection.

HEPATITIS C

HCV is an RNA virus from the *Hepacivirus* genus of the family *Flaviviridae*, which also includes West Nile virus, dengue virus, tick-borne encephalitis virus and yellow fever virus. It is estimated that globally there are in excess of 180 million people chronically infected with HCV.

Transmission is parenteral, primarily by transfusion of infected blood products, sharing of needles and injecting drug use paraphernalia or unsafe medical practices. Heterosexual sexual transmission and mother-to-child HCV transmission appear to be relatively rare. More recently, an epidemic of acute HCV has developed amongst mainly HIV-positive men who have sex with men (MSM). This is thought to be associated with mucosal-traumatic sexual practices, such as fisting, and injecting drug use. Sharing of implements for intra-nasal drug use may also contribute to the transmission of HCV.

HCV mainly infects liver cells but can also infect lymphocytes and probably cells within the brain. Clinical disease caused by this virus has many manifestations, including autoimmune diseases, glomerulonephritis, sweats, fatigue and depression. Progression to end-stage liver disease occurs within 20–30 years in 20%–30% of patients. However, several factors increase the risk of progression to cirrhosis or end-stage liver disease – the most important being continued alcohol and drug abuse and HIV co-infection. Patients with HIV/HCV co-infection are more likely to progress to end-stage liver disease and have a faster rate of progression than those who are HCV mono-infected.

Unlike HBV and HIV, HCV is an RNA virus that does not integrate into the host genome, so treatment of HCV leads to

cure. Up to 80% of HCV infections lead to chronicity, irrespective of age when the infection was acquired. HCV exists as distinct genotypes numbered 1 to 6, which vary in distribution globally. For example, genotype 1 is the commonest in Western Europe and the USA, whereas almost all infections in Egypt are with genotype 4. There appears to be no major difference in disease manifestations and liver disease progression amongst the various genotypes.

Until recently, a combination of pegylated interferon-alpha and ribavirin was the mainstay of HCV therapy. However, responses to this therapy, especially in genotype 1 and 4 HCV, were generally poor and these drugs are also associated with significant side effects. Over the last few years, there has been considerable progress in the development of DAAs to treat HCV infection. These agents directly target viral and host proteins and enzymes involved in successful HCV. Several of the DAAs are already licensed for use in combination with pegylated interferon-alpha and ribavirin. Interferon-free regimens will become a reality in 2014 and ribavirin may prove to not be an essential component of some HCV treatment drug combinations.

Section 2: The Viral Hepatitis Clinic

People living with viral hepatitis, with or without HIV co-infection, should expect their healthcare to be delivered according to the current national standards and the most up-to-date, local, professional guidelines.

The number of patients with viral hepatitis that you look after in your individual setting will determine how you best provide for their specific needs. If you only have a few viral hepatitis patients it may not be feasible to develop all the services discussed in this guide in a single clinic environment. What is described in this guide is an optimal approach and may need to be modified for your own circumstance. It may be easier to develop a network of practitioners who have an understanding and interest in viral hepatitis, create smooth referral pathways and maintain clear lines of communication to ensure that care is both comprehensive and holistic.

What do you need?

1. SPACE

You need a consultation room with an examination couch that flattens to allow full physical examination of the patient. There should be sufficient privacy to allow patients to feel comfortable to frankly discuss their life-style, risk behaviours and drug and alcohol use. There should be sufficient space or facilities for blood-taking, including from patients with difficult access.

2. EQUIPMENT

- A FibroScan® machine (with up-to-date calibration records)
- FibroScan® report sheets (See **Appendix 1**)
- Ultrasound gel
- Patient information resources such as:
  - » Guides to viral hepatitis and HIV
  - » Treatment information
  - » Risk reduction information
  - » Information about community support
- Equipment for blood taking, including for patients with difficult access, i.e. smaller needles or those required for femoral arterial blood sampling
- Sexually transmitted infections self-screening kits for high-risk MSM and others (throat and rectal self-swabs plus urine pots for *Chlamydia trachomatis* and gonorrhoea)

3. STAFF AND TRAINING

The clinic requires doctors trained in the management of viral hepatitis, with a good understanding of liver function tests and the common manifestations of liver disease, and nurses with training or experience in viral hepatitis, who are interested and keen to work in the clinic. It is important to develop a positive team mentality.

All healthcare professionals who work in the viral hepatitis clinic's specialist services should not only develop and maintain their skills, but should also be helped to disseminate their expertise through teaching, training and sharing of best practice. Management of viral hepatitis is rapidly undergoing unprecedented change due to treatment advances; this means that all those working in this area should regularly update their knowledge. Training and experience in areas other than viral hepatitis can also be invaluable in running a viral hepatitis clinic, including:

- HIV skills in adherence, management of drug-drug interactions and side-effects of treatment and care of patients with co-infection
- Experience in managing drug and alcohol misuse
- Mental health experience/training
- Counselling and motivational skills to work with challenging behaviours and support harm minimisation

A wide range of advice and training can be found through the online resources in the **Further Information** section of this guide.

4. LABORATORY SERVICES

Good laboratory support with sufficient turn-around times to safely manage care and make timely treatment decisions is essential. Forging a strong relationship with laboratory staff and working collaboratively for the patients' benefit strengthens any viral hepatitis service. Access to fast-turnaround serological testing for HBV and HCV is necessary and near-patient or 'point-of-care' testing for HBV and HCV, endorsed by the WHO, will be available in the near future. Testing for basic liver function; HBV serology and DNA quantification; HCV serology, genotype and RNA quantification; together with facilities for viral sequencing for resistance mutations should, at the very least, be available at regional reference laboratories.

How to run the clinic

The clinic should operate a multi-disciplinary team (MDT) approach so that all key personnel, as well as the patient, are involved in treatment decisions and kept informed at all times. This could take the form of a formal MDT or through good communication between all those involved in the care.

The clinic should provide a range of services to accommodate both the planned and unplanned nature of the illness and treatment. These should include:

- A clinic with booked appointments scheduled every 1–2 weeks
- Working week daily emergency or 'walk-in' services (for problems that arise at short notice and between appointments)
- Strategies in place for out-of-hours access for emergencies
- Virtual or e-clinics with email consultation may be an option, especially when distance is a problem

The frequency of booked clinics will depend on your patient caseload, with appointment slots for new patient referrals and those in routine follow-up. New referrals should be accepted from within the hospital, from other services (other hospitals, primary care, and other agencies such as drugs services and directly from patients themselves, i.e. self-referral). New patient slots should be at least 30 minutes long to allow sufficient time for a full initial assessment, history and examination.

How the clinic operates will vary according to your local needs and resources; however, division of the patient assessment can speed-up the process. One method is for the nurse (if trained) to perform the FibroScan® and blood tests and the doctor to take the history and examine the patient. In this way, all data can be assimilated by the end of the consultation and a treatment and follow-up plan made and discussed before the patient leaves the clinic.

Patients need variable amounts and types of information when they come to clinic. Nurses are often best placed to assess information needs and provide resources on transmission, prevention, treatment and support.

A summary of the clinic visit should be entered into shared notes and copies sent securely with the patient's consent to key personnel involved in their care. It is a good idea to give or send copies of correspondence to the patient themselves (with their consent) to keep them central to any decision-making.

The relationship between HIV and viral hepatitis can be complex and benefits from clinic services that provide an integrated approach to care, management and treatment. Historically, management of HIV-associated viral hepatitis has been fragmented, leading to poor user involvement and unacceptable delays in patients accessing care and treatment. In an ideal situation, a joint clinic should be set-up with staff having expertise in both HIV and viral hepatitis, as well as in the complications of end-stage liver disease, to plan care for both conditions in a single patient consultation. However, in the absence of a joint clinic *per se*, care may need to be provided across sites, in which case the goal is to adopt an integrated approach through clear communication and shared decision making between the patient and the key care providers.

Which services should you provide or link to?

Some of these services can be delivered in the viral hepatitis clinic whereas others will need you to develop partnerships within your hospital or elsewhere in order to provide comprehensive care.

1. IMAGING AND ENDOSCOPY SERVICES

Liver imaging forms a crucial part of viral hepatitis diagnosis and monitoring. The imaging department should be capable of organising ultrasound-guided liver biopsies to assess changes in liver disease progression that can guide the timing of initiating treatment. All patients with liver cirrhosis should have 6-monthly liver ultrasounds to assess the risk of HCC, as well as an endoscopy every 1–2 years to screen for oesophageal varices. Whatever imaging is undertaken, there must be systems in place for these images to be reviewed and interpreted by the clinician managing the patient within a suitable time-frame. This is particularly relevant if the imaging is performed away from the clinic site.

2. VIROLOGY

Of all the laboratory support services needed to run a viral hepatitis clinic, a good link with virology is probably the most important. This includes having access to a range of diagnostic tests to support the clinic and its particular population, in order to make speedy diagnoses, initiate treatment and manage treatment decisions based on response to therapy. Short turnaround times from blood sampling to acting on results can be achieved by reducing transit times for blood samples to reach the laboratory, and by having systems in place that allow direct access to results that allows prompt decision-making.

3. ONCOLOGY SERVICES

HCC is one of the serious consequences of chronic viral hepatitis infection. Whilst screening should be in place to try and identify lesions early, it is also important to link in with a liver specialist, pathologist, radiologist, hepatobiliary oncologist and surgeon with expertise in managing HCCs. Early lesions are curable with hepatic resection or transplantation, and even with late presenting lesions, a good quality of life may be achieved with local ablative therapies and/or chemotherapeutic agents. All patients with HCC should have their care discussed at a multidisciplinary meeting.

4. OTHER SPECIALISTS

Patients treated for HCV may at times require referral to other specialists depending on the nature of their treatment. These include ophthalmologists, an essential requirement for patients receiving interferon-based treatments to perform a baseline eye-check to establish the condition of the retinal circulation since there is a small risk of haemorrhage during therapy, and dermatologists for management of complex rashes or the exacerbation of pre-existing problems, such as psoriasis, during treatment.

5. TRANSPLANT SERVICES

Patients with severe liver damage may be considered suitable transplant recipients, including those with HIV provided that their CD4+ cell count is greater than 200cells/mm^3 and their HIV is controlled on antiretroviral therapy. Maintaining a good relationship with the liver transplant team puts patients awaiting transplant in the best position in terms of the necessary pre-transplant 'work-up'.

6. PSYCHOLOGY AND PSYCHIATRY

Some patients may have mental health problems that pre-date their diagnosis of viral hepatitis and that could have made them more vulnerable to acquiring viral hepatitis. There is a high incidence of mental health problems in viral hepatitis patients, which may be exacerbated by drug and alcohol use, may be unmasked by interferon therapy and can be worse in those with HIV co-infection or advanced liver disease.

Quick and easy-to-complete tools to assess mental health such as the Hospital Anxiety and Depression Scale (HADS) tool (**Appendix 2**) should be used in the clinic to provide an instant baseline 'anxiety and depression score' against which future changes can be measured. It also helps to identify those patients who need onward referral to psychology and psychiatry services. Patients often benefit from access to psychological support to explore and address important issues that have an impact on their health, wellbeing and treatment decisions. These may include affective disorders, anxiety and the side effects of interferon-based treatment.

7. DRUGS AND ALCOHOL SERVICES

Drug and alcohol misuse are both frequently encountered in patients with viral hepatitis; therefore, they should ideally have direct access to appropriate drugs and alcohol services or be referred to them from the clinic. These services should also be able to refer patients easily to the viral hepatitis clinic. Drug misuse most commonly involves current or previous injecting drug use, a significant risk factor for acquiring both viral hepatitis and HIV. In addition, recreational drug use can be associated with high risk-taking behaviour contributing to sexually acquired viral hepatitis (most commonly acute HCV amongst MSM).

High alcohol intake not only further damages an already damaged liver but also drastically reduces the likelihood of successful treatment of viral hepatitis.

Simple screening tools can be used to assess alcohol intake in patients attending the clinic. The FAST screening tool (**Appendix 3**) takes a few minutes to complete and provides an objective framework within which to discuss what some health professionals find an awkward topic. The immediate scoring system helps to identify problem areas that act as signposts for interventions aimed at reducing or stopping alcohol use.

Drugs and alcohol services can offer risk-reduction counselling, information on safer drug use (including access to needle-exchange services) and management of drug and alcohol misuse through supportive detoxification programmes and/or provision of replacement therapy.

8. SEXUAL HEALTH AND CONTRACEPTIVE SERVICES

The majority of patients with HBV, and a growing number of MSM with HCV, will have acquired their infection sexually. All patients should be supported to maintain good sexual health, including being given advice to avoid acquiring new sexually transmitted infections (STIs). STI screening should be offered to all new patients as part of their medical assessment and annually thereafter, as well as at other times when necessary or requested by the patient. Investigation, diagnosis and treatment for STIs should form a regular part of health monitoring. It is important to develop a good relationship with those who provide sexual health services as they will often be the ones to diagnose new patients with viral hepatitis.

Higher-risk populations, such as MSM, may benefit from using easy-to-use self-swab kits for STI screening and, more importantly, also from receiving risk-reduction counselling since there is growing evidence of re-exposure and re-infection of HCV after treatment in the absence of behaviour change.

Ribavirin as part of HCV treatment is a potential teratogen in women on therapy, or if their male partners are being treated with this drug. Therefore, pregnancy prevention counselling is essential in the lead up to, during and for 6 months after treatment has finished to avoid possible drug-related birth defects. Dual contraception is the method of choice to prevent pregnancy; for example, an oral hormonal contraceptive plus condoms or an intra-uterine device plus condoms. Women patients (or female partners of male patients regardless of their hepatitis status) need to be prescribed contraception in the clinic or referred to services that can provide it.

9. PHARMACY

A good relationship with your pharmacist is essential due to the complex nature of the new drugs being used to treat viral hepatitis. This is particularly important for patients with co-morbidities and co-infections due to the increased risk of drug–drug interactions, in particular when HCV drugs are prescribed alongside anti-HIV therapy.

The most up-to-date information on interactions can be found at **www.hep-druginteractions.org**. Collaboration with a pharmacist is also advisable when dose adjusting in severe liver or kidney disease and when introducing drugs to improve or avoid anaemia and neutropenia secondary to ribavirin or interferon therapy.

10. GENERAL AND FAMILY PRACTITIONERS

It is helpful to work with general practitioners (GPs)/primary care teams, with the patient's consent, to keep all parties informed of treatment and management decisions by letter or secure email. Patients should be copied in on all correspondence to ensure that they are always involved and aware of planning and decision-making in their treatment and care.

Primary care teams can provide expert management of general health issues that underpin specialist care. In addition, depending on how services are funded locally, some referrals to other specialists may need to be made via primary care.

11. COMMUNITY AND PEER SUPPORT

Where these are available, community and peer support services can provide invaluable help, and it is well worth developing these if they are not already in place. The usefulness of being able to talk through problems, treatments and issues with other people who have viral hepatitis and/or HIV and are experts in managing their condition and in negotiating health services cannot be over-estimated. Whether as one-to-one support or in a group setting, they can provide help that is not easily available through health services but which can help people with their diagnosis, symptoms and side effects, by just talking or by providing physical relief using approaches such as acupuncture or massage.

Section 3: The Patient

All patients with viral hepatitis in your care should be invited and encouraged to come to the viral hepatitis clinic on a regular basis. They should be given written information on where the clinic is, what services are provided and what they can expect to take place during a routine visit.

Who needs to be tested?

HBV and HCV share common routes of infection but the rate of transmission varies between the two viruses and by their route of acquisition. The frequency with which viral hepatitis screening should be performed is summarised separately below for HBV (**Table 2**) and HCV (**Table 3**). It is always advisable to consult local guidelines but the World Health Organization (WHO) website also has a summary of the widely available recommendations, which are not population specific at: **www.who.int/csr/disease/hepatitis/HepatitisB_whocdscsrlyo2002_2.pdf** for HBV and **www.who.int/csr/disease/hepatitis/Hepc.pdf** for HCV.

HBV SCREENING

Effective HBV immunisation programmes are vital to protect those who are as yet not infected and at risk of HBV infection. Their serologic response to vaccination should be monitored and booster doses administered appropriately. Successful vaccination negates the need for continued screening based on risk factors.

All patients seropositive for HBsAg must be tested for co-infection with HIV and HDV at baseline with consideration for repeat testing if they are at ongoing risk of contracting these infections and have an unexplained rise in liver aminotransferase levels.

TABLE 2: SCREENING RECOMMENDATIONS FOR HBV

Who to test	Comments
At-risk individuals with prior HBV vaccination and an adequate vaccine response	Repeat screening should be considered if the HBsAg status is unknown immediately prior to and at any point after adequate vaccination
At-risk individuals with an inadequate vaccination response (non-responders)	Screening is recommended as per the recommendations for each continuing risk factor If a 'true' non-responder after repeat vaccination courses, annual screening should be considered
Migrants from/travellers to areas with intermediate and high endemic risk (HBsAg seroprevalence ≥2%)	Recommended at least once if currently living in a low seroprevalence area and no other continuing risk
Pregnant women	Recommended in the first trimester for all pregnant women Consider in the third trimester if at high risk of recent HBV acquisition
Children born to HBsAg-positive mothers	Recommended at least once
People living with HIV, HCV or other liver disease	Recommended at least once if no ongoing risk
Men who have sex with men	Recommended annually if inadequate vaccine response
Sexual partners of individuals infected with HBV	Recommended annually if inadequate vaccine response
Household contact (shares a kitchen, bathroom, bedroom or sitting room) with someone infected with HBV	Recommended annually if inadequate vaccine response

»

TABLE 2 (continued)**: SCREENING RECOMMENDATIONS FOR HBV**

Who to test	Comments
Injecting drug users	Recommended annually if inadequate vaccine response
Anyone who has had a tattoo, body piercing or acupuncture by an unregulated provider or someone using non-sterile needles	Recommended at least 6 months after last potential exposure
Healthcare or public safety workers at risk of contact with blood or blood-contaminated body fluids	Recommended annually if inadequate vaccine response
Prisoners	Recommended at the beginning of incarceration
Blood/blood product transfusion recipient in areas where routine screening is inadequate or recipient prior to effective measures to deactivate HBV in blood/blood products	Recommended at least 6 months after last potential exposure
Recipient of healthcare in countries where the risk of iatrogenic infection is high due to the use of unsterilised equipment	Recommended at least 6 months after last potential exposure
Haemodialysis patients	Recommended at 6-monthly intervals
Transplant recipients if transplanted from a donor with prior HBV exposure or infection	Consider at 6 months following transplantation
Individuals with unexplained raised alanine transaminase or aspartate transaminase levels	Recommended at least once

HCV SCREENING

Screening programmes for HCV are vital since there are clear benefits to early diagnosis and treatment in those individuals who fail to spontaneously clear the virus. The window period to develop HCV IgG antibodies is estimated to be around 6 months but delayed seroconversion is common, especially in the context of HIV infection. Furthermore, since HCV antibodies generally remain throughout life, screening for re-infection requires the testing for and detection of HCV RNA.

TABLE 3: SCREENING RECOMMENDATIONS FOR HCV

Who to test	Comments
Migrants from/travellers to areas with intermediate or high endemic risk (chronic HCV prevalence ≥2%)	Recommended at least once if currently living in a low seroprevalence area and no other continuing risk
Pregnant women	Consider in the first trimester if there is another risk factor for HCV infection
Children born to mothers with chronic HCV	Recommended at least once
People living with HIV, HBV or liver disease	Recommended at least once if no continuing risk
HIV-infected men who have sex with men	Recommended annually
Sexual partners of individuals infected with HCV	Recommended annually
Injecting drug users	Recommended annually
Drug users who share insufflation (snorting) equipment/paraphernalia	Consider annually

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TABLE 3 (continued)**: SCREENING RECOMMENDATIONS FOR HCV**

Who to test	Comments
Anyone who has had a tattoo, body piercing or acupuncture by an unregulated provider or someone using non-sterile needles	Recommended at least 6 months after last potential exposure
Healthcare and public safety workers at risk of contact with blood or blood-contaminated body fluids	Recommended annually
Incarcerated individuals including those detained in immigration removal centres	Recommended at baseline, annually and 6 months following incarceration
Blood/blood product transfusion recipients in areas where routine screening is inadequate	Recommended at least 6 months after last potential exposure
Recipient of healthcare in countries where the risk of iatrogenic infection is high due to the use of unsterilised equipment	Recommended at least 6 months after last potential exposure
Haemodialysis patients	Recommended at 6-monthly intervals
Individuals with unexplained raised alanine transaminase or aspartate transaminase levels	Recommended at least once
The US Centers for Disease Control and Prevention recommend testing of birth cohort 1945–1965 to identify HCV in 'baby boomers'	Recommended at least once

Risk reduction

All persons at risk should be provided with information on how HBV and HCV are transmitted and, specifically, how they may reduce their risk of acquiring or transmitting these infections (**Table 4**). As routes of acquisition are also similar to those for HIV, risk-reduction advice should encompass all three infections but provide specific information related to the transmission of the confirmed underlying hepatitis virus of the index case.

Useful resources for patient information translated into a number of languages are available at:

www.hepb.org.uk/information/resources/hepatitis_b_leafletsandbookletsD

www.hepbandcni.net/content/hepatitis-c-public-information-leaflets

Partner/household testing

For both viruses, all sexual and household contacts should be screened as part of a partner notification strategy. For HBV, there should be active vaccination and follow-up of all contacts, both sexual and household. Partner notification is an effective approach to help those at high risk of viral hepatitis to:

- Be screened for viral hepatitis and other diseases
- Receive appropriate health promotion education and counselling for risk reduction
- Be directed to or engaged with risk-reduction programmes, including HBV vaccination

For specific guidance on partner notification, the following is a useful resource: **www.ssha.info/wp-content/uploads/ha_manual_2004_section_a.pdf**

HBV vaccination

Vaccination is a key strategy for tackling HBV, both within high-risk groups and at population level. While effective immunisation programmes from birth are in place in some countries, practice varies significantly between countries. You should use your local country-specific vaccine strategy. It is recommended that all individuals considered at high risk of acquiring HBV be vaccinated as per appropriate vaccination schedules. It is worth noting that there is evidence for the benefits of more rapid schedules; **www.who.int/ith/vaccines/hepatitisB/en/index.html**.

TABLE 4: RISK-REDUCTION ADVICE

Risk	Risk-reduction advice
Sexual	Safe and effective use of condoms, including changing condoms between partners in the context of group sex Avoid sexual practices resulting in trauma and contact with blood Use gloves for fisting Avoid sharing sex toys
Mother-to-child transmission	Use of maternal HBV antivirals in the third trimester for those with high levels of HBV DNA Give HBV immunoglobulin/vaccination to neonate Temporarily avoid breastfeeding if nipples are cracked and sore
Injecting drug users	Avoid sharing any injecting paraphernalia, including needles, syringes, spoons etc. Engage with needle exchange programmes Engage with drug services and methadone-replacement programmes
Sharing of 'snorting' or insufflation drug taking paraphernalia (HCV only)	Use own straw for drug insufflation and do not share
Tattoos/piercings/acupuncture	Use regulated providers
Sharing of razors and toothbrushes	Use own razors and toothbrushes and do not share them. Ensure safe storage away from children

Section 4: Assessments

General

All patients seen in a viral hepatitis clinic should have the following assessments at baseline for severity of liver disease and at appropriate intervals determined by their clinical need.

1. CLINICAL HISTORY

Taking a detailed history of risk factors for infections and comorbidities as well as a full drug history will ensure appropriate management of patients with viral hepatitis. It should include information about:

- Symptoms
- Any history of jaundice
- Any history of blood transfusion
- Likely time and source of infection to assist with partner notification and determine the chronicity of infection
- Medication history, including that of hepatotoxic medications
- Current medication with an assessment made of potential drug–drug interactions prior to treatment
- Co-morbidities such as diabetes and cardiovascular disease
- Risk factors for progression of liver disease such as obesity, older age, male gender, alcohol abuse, HIV infection
- Family history of viral hepatitis, liver disease or HCC
- Psychiatric history
- Drug and alcohol history, including injecting or inhaled drug use

2. PHYSICAL EXAMINATION

The clinical examination should look for features suggestive of liver disease. These include jaundice, palmar erythema, spider naevi, hepatomegaly, splenomegaly, gynaecomastia, ascites, liver flap and confusion.

3. BLOOD TESTS

- Full blood count – low platelet levels can be an indicator of cirrhosis
- Coagulation screen
- Liver function tests: levels of ALT and AST (markers of liver inflammation), alkaline phosphatase, albumin and bilirubin
- Gamma-GT
- Alpha-fetoprotein (AFP) – levels may be raised with acute hepatitis, in cirrhosis and with HCC
- Renal function
- Hepatitis A, B and C screening to assess co-infection and immunity
- HDV antibody testing for all who test HBsAg seropositive
- HIV testing (this is vital as some drugs used for HBV will result in HIV resistance developing if not given as combination antiretroviral therapy)
- Autoimmune screen, including tissue autoantibodies
- Thyroid function and thyroid antibodies if pegylated interferon-alpha use is being considered
- Cæruloplasmin
- Ferritin
- Cryoglobulins in patients with symptoms of neuropathy, renal impairment, skin rash or lymphoma
- Complement components 3 and 4 (C3 and C4) levels in patients with suspected cryoglobulinaemia

4. ASSESSMENT OF LIVER DAMAGE

Risk factors for hepatic fibrosis progression include pre-existing cirrhosis, older age, male gender, alcohol abuse, raised ALT levels, steatosis of the liver and HIV infection.

A liver ultrasound should always be performed, as well as non-invasive testing for hepatic fibrosis using one or more of the following tests:

- A FibroScan® (use appropriate disease-specific cut-offs) . See training videos at **www.youtube.com/results?search_query=fibroscan**
- Non-commercial routine blood panels: aspartate aminotransferase (AST): platelet ratio index (APRI), Forn's index, FIB-4
- Commercial blood panels: FibroTest (**www.en.wikipedia.org/wiki/FibroTest**), ELF test

Liver biopsies are taken less frequently nowadays but are specifically useful where there is doubt as to the underlying cause of liver damage or where 'non-invasive' tests give inaccurate or unreliable results. In assessing biopsies an appropriate histological grading and staging score should be used of which the METAVIR score is the most commonly used.

The METAVIR score helps interpret the liver biopsy by providing a reliable way to quantify what is seen under the microscope. This scoring system assigns two standardised numbers: one to represent the degree of inflammation and the other the degree of fibrosis. The intensity of necroinflammatory lesions is graded on a four-point scale from A0 to A3, while fibrosis is graded on a five-point scale from F0 to F4.

Fibrosis score:

F0 = *no fibrosis*

F1 = *portal fibrosis without septa*

F2 = *portal fibrosis with few septa*

F3 = *numerous septa without cirrhosis*

F4 = *cirrhosis*

In those with evidence of cirrhosis on the above tests, an endoscopy should be performed to identify portal hypertensive gastropathy and/or oesophageal varices. A specialist Hepatology referral is required if any of these three conditions are found.

Screening for HCC in patients with cirrhosis should be undertaken every 6–12 months with liver ultrasound and an AFP blood test. Chronic HCV patients should have HCC screening if there is any evidence of cirrhosis. In chronic HBV, screening for HCC should be performed in African patients >25 years of age, Asian patients >40 years of age, and in those with a family history of HCC. In those with a normal ultrasound but a high index of suspicion for HCC (for instance with an AFP >200ng/mL), assessment with a second imaging modality – either an MRI scan or a triple-phase CT scan of the liver – is required.

Assessment of HBV infection

For those with identified active HBV infection, the following should be performed:

- HBV DNA quantification
- HDV (delta virus) antibody testing

Assessment of HCV infection

In addition to the general assessments above, the following should be performed:

- HCV antibody-POSITIVE patients should have a confirmatory HCV RNA test, as some may previously have been infected and cleared the virus
- HCV antibody-NEGATIVE patients who have a history of HCV exposure or persistently raised transaminase levels should be offered HCV RNA testing as they may be infected but have not yet developed antibodies to HCV
- HCV genotyping – this will determine treatment options
- HCV RNA viral load

Prior HCV treatment history and details about response to therapy are important factors in deciding future treatment options. The reasons for discontinuation, intolerance or virological failure of HCV treatment should be noted, as well as previous side effects of treatment. A record should be made of all, if any, previous treatments and if so, with what agents and for how long. Is the patient willing to re-try therapy and, if so, on what basis?

All patients with chronic HCV should be assessed for the possibility of commencing therapy. Those without contraindications should be offered to start treatment, with counselling about potential side-effects and rates of sustained virological response (SVR) based upon individual prognostic indicators such as age, viral genotype and stage of liver fibrosis.

Factors to consider before starting therapy

1. AUTOIMMUNE DISEASE

Underlying autoimmune disorders such as psoriasis, Crohn's disease, thyroid disease (especially in those with pre-existing anti-thyroid antibodies) and rheumatoid arthritis may be exacerbated during pegylated interferon-alpha therapy; these patients should be co-managed with a specialist. These problems may be less common with the use of DAAs.

2. CONCOMITANT CONDITIONS

- HBV, heavy alcohol use with or without other liver disease
- If a patient has features of autoimmune hepatitis, HCV treatment should be administered with caution
- Severe cardiac or pulmonary disease; pegylated interferon-alpha/ribavirin treatment can increase the risk of myocardial infarction in patients with poorly controlled coronary artery disease. Severe pulmonary disease may already have reduced life expectancy to <5 years, meaning HCV treatment may be of little added benefit
- Pegylated interferon-alpha/ribavirin-based HCV treatment can be problematic in those with renal impairment, and careful monitoring of renal function is required with dose adjustment of ribavirin as necessary

3. OTHER ISSUES

Adherence to HCV treatment is essential for optimal outcomes, for cure as well as for the prevention of HCV resistance (especially with DAAs). Pre-treatment counselling is important, and information should be given about the significant pill burden and frequent monitoring visits required during treatment.

Pregnancy testing should be performed prior to commencement of therapy, since ribavirin is potentially teratogenic and there are few data available on the safety of DAAs in pregnancy. Robust contraceptive advice should be given to both male and female partners (note oral contraceptives may be less efficacious during treatment with DAAs). Contraception should be used for the duration of treatment and for 6 months after completion.

TABLE 5: PRE-TREATMENT ASSESSMENTS IN PATIENTS WITH CHRONIC HCV INFECTION

Required assessments
Medical history, including complications of liver disease, presence of significant extra-hepatic disease including symptoms of chronic HCV affecting quality of life
Previous antiviral therapies and response
Psychiatric history, including past or ongoing psychiatric disorders; alcohol or drug misuse
Screening for depression using HADS (**Appendix 2**)
Biochemical markers of liver injury and assessment of hepatic function, including ALT and AST, alkaline phosphatase, albumin, bilirubin (including direct bilirubin) and prothrombin time
Haemoglobin, haematocrit, white blood cell count with differential, and platelet count
Thyroid-stimulating hormone and thyroid hormone levels
Tissue autoantibodies, including thyroid antibodies
Serum creatinine
Serum glucose
Serum urate (if being treated with telaprevir)
Ferritin, iron saturation and serum anti-nuclear antibodies (ANA)
Cryoglobulins or C3 and C4 protein levels in those with suspected cryoglobulinaemia or lymphoma
Pregnancy test (in women of childbearing age)
HIV serology

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TABLE 5 (continued)**: PRE-TREATMENT ASSESSMENTS IN … CHRONIC HCV INFECTION**

Required assessments
Serum HBsAg, HBV core antibody (anti-HBc), anti-HBs, Hepatitis A total antibody (anti-HAV [total]). HBV DNA and HDV antibody should be performed in those who test HBsAg seropositive
Quantitative HCV RNA measurement
HCV genotype
Electrocardiography in patients with pre-existing cardiac disease
Chest X-ray

Recommended assessments
Eye examination for retinopathy in patients with diabetes or hypertension, since this may be worsened by treatment with pegylated interferon-alpha
Urine toxicology screen for opiates, cocaine and amphetamines

VACCINATION

Ensure immunity to HBV from history of prior vaccination or documented serological evidence.

If immunity cannot be confirmed, start a course of HBV vaccination.

EDUCATION

Continued patient education about how to prevent onward transmission should be provided to minimise ongoing risk once treatment has been completed. This may have both individual and public health benefits.

SECTION 5: Treatment

Treatment of HBV

Treatment algorithms for HBV focus on the following key variables when deciding on who and when to treat:

- HBV DNA levels
- Serum transaminase levels
- Liver function abnormalities
- Degree of fibrosis/cirrhosis
- Co-infection with other viruses, including HCV, HDV and HIV

In the case of co-infection with HIV, specific guidance should be followed because of:

- Different response to treatment compared to HBV mono-infected individuals
- Risk of drug–drug interactions and overlapping toxicities
- Risk of partially treating HIV, thus compromising future treatment options for that infection

Since the timing and type of HBV treatment requires reviewing a number of factors and evaluations we suggest that you review the guidance offered in the **Guidelines for monitoring and treatment** section on the next page.

Treatment of HCV

The greatest challenge in treating those infected with HCV who are engaged in care, is the poor tolerance of currently available drugs, especially interferon. While DAAs are improving sustained virological response (SVR) rates, the currently licensed agents are limited to genotype 1 infection and are co-administered with pegylated interferon-alpha.

However, the landscape of HCV treatment strategies and options is rapidly changing and even within the next two years, a wider range of increasingly tolerable and curative treatment options will become available; see **www.justrislide.com/swfs/A3033.swf**.

Given its slow clinical course, the timing of HCV treatment depends on the patient's motivation. Other issues to consider are:

- The degree and likelihood of progression of liver fibrosis/cirrhosis
- The risk of infecting others, especially sexual partners
- Co-infection with HBV, HIV or, indeed, both
- Recent acquisition – although acute HCV treatment with pegylated interferon-alpha/ribavirin yields good SVR rates, the >90% cure rates in chronic HCV with the use of newer DAAs is likely to render this benefit irrelevant
- The benefits of waiting for the newer and more tolerable options to become available compared with the risk of fibrosis/cirrhosis progression

All treatment algorithms for HCV require close monitoring of HCV RNA levels,

with critical decisions to continue or discontinue therapy made at specific time intervals, which vary depending on the particular combination therapy given. The rationale for this is to avoid:

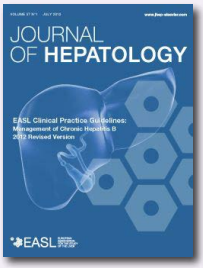
- Unnecessary patient exposure to poorly tolerated agents that will fail to achieve SVR
- Maintaining drug pressure that will reduce the emergence of genotypic resistance mutations that may compromise future treatment strategies

Specific guidance is also provided for the management of drug–drug interactions and drug toxicities, including the need for dose reduction in specific instances.

Guidelines for monitoring and treatment

Please see the relevant websites for updates as guidelines in viral hepatitis are constantly changing.

CURRENT GUIDELINES FOR THE MANAGEMENT OF HBV MONO-INFECTION AND HBV/HDV CO-INFECTION



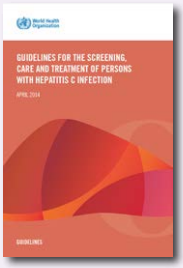
EASL: **www.easl.eu/_clinical-practice-guideline/issue-8-april-2012-revised-clinical-practice-guidelines-on-the-management-of-chronic-hepatitis-b**

BHIVA: **www.bhiva.org/hepatitis-2013.aspx**

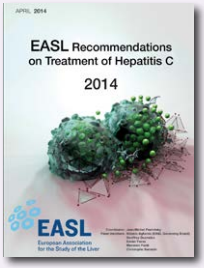
EACS: **www.eacsociety.org/Portals/0/Guidelines_Online_131014.pdf**

AASLD: **www.aasld.org/practiceguidelines/pages/guidelinelisting.aspx**

CURRENT GUIDELINES FOR THE MANAGEMENT OF HCV INFECTION



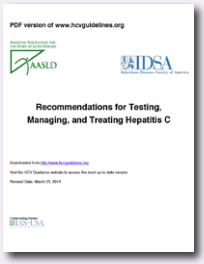
WHO: **www.who.int/hiv/pub/hepatitis/hepatitis-c-guidelines/en/**



EASL: **www.easl.eu/_newsroom/latest-news/easl-recommendations-on-treatment-of-hepatitis-c-2014**

BHIVA: **www.bhiva.org/hepatitis-2013.aspx**

EACS: **www.eacsociety.org/Portals/0/Guidelines_Online_131014.pdf**



AASLD: **www.aasld.org/practiceguidelines/pages/default.aspx**

Further Information: Web Links and Resources

British Liver Trust:
www.britishlivertrust.org.uk

Hep C Trust:
www.hepctrust.org.uk

HIV i-Base:
www.i-base.info/guides/hepc

'Path B' HBV information:
www.hepatitisinfo.org/managing-living/path-b

Hepatitis Drug Interactions:
www.hep-druginteractions.org

Hepatitis B Foundation
www.hepb.org

Hepatitis C Online
www.hepatitisc.uw.edu

EASL iLiver application:
www.easl.eu/_education/iliver

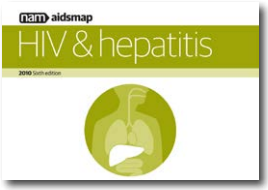
Hepatitis - NHS choices:
www.nhs.uk/conditions/Hepatitis.aspx

WHO - What is Hepatitis?:
www.who.int/features/qa/76/en/

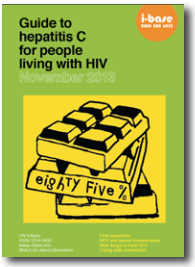
Drug and alcohol advice services:

Antidote: **www.londonfriend.org.uk/get-support/drugsandalcohol/**

Drink Aware: **www.drinkaware.co.uk**



nam aidsmap *HIV & hepatitis*:
www.aidsmap.com/booklets



i-Base *Hepatitis C for people living with HIV*:
www.i-Base.info

Appendices

Appendix 1 – FibroScan® report sheet

www.justri.org/how-to/fibroscan.pdf

Appendix 2 – Hospital Anxiety and Depression Scale (HADS) assessment tool

www.justri.org/how-to/hads.pdf

Appendix 3 – Fast Alcohol Screening Test (FAST)

www.nice.org.uk/niceMedia/documents/manual_fastalcohol.pdf

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