Clinical Guidance on the Use of Organs from Hepatitis C Viraemic Donors and Increased Infectious Risk Donors in Hepatitis C Negative Recipients

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Date of Approval: 25/5/20

Date for Review: 25/5/22

Introduction

National Health Service Blood and Transplant (NHSBT) has made great progress in increasing the number of transplants that happen year on year through their 'Taking Organ Transplantation to 2020' donor strategy. Nevertheless, a significant number of patients still die on the waiting list due the shortage of donor organs thus confirming the need to continuously review organs that have been discarded, to assess whether advances in medicine could enable such organs to be transplanted.

It is now apparent that greater use could be made of organs from Hepatitis C (HCV) infected donors. In the past, these organs have traditionally been discarded, or only used for HCV infected recipients. With the advent and licensing of highly effective and well tolerated direct-acting antiviral (DAA) therapy that can cure more than 95% of patients infected with HCV, regardless of genotype, kidneys from HCV infected donors may well safely be transplanted into HCV uninfected recipients. This approach could ultimately make more organs available for transplantation, and so reduce the morbidity and mortality of patients on solid organ transplant waiting lists.

Currently, renal transplantation occurs commonly in the face of disparity between donor and recipient viral status. The best examples of this would be CMV and EBV. Whilst the majority of adult recipients will be EBV positive and thus are likely to receive an EBV positive organ, for CMV, the prevalence of positivity is much lower and CMV negative recipients will commonly be offered a CMV positive organ. Transplantation in this setting proceeds because effective treatment is available.

The UK Advisory Committee on the Safety of Blood, Tissues and Organs (SaBTO) is responsible for making recommendations to the four UK governments regarding the use of organs for transplant. It recently issued revised guidance. The most relevant statement in the guidance reads as follows –

'HCV infection in the potential donor does not amount to an absolute contraindication to donation of material for life-preserving transplantation, however the net benefit of transplantation must be considered against the risk of not receiving that specific transplant. This risk/benefit analysis allows for the potential use of a transplant from a HCV infected donor to a non-infected recipient.'

This revised guidance allowed a UK Position Paper to be published on the appropriate use of Hepatitis C Virus (HCV) positive donors into hepatitis C negative recipients (ref). This has paved the way for the consideration of HCV positive donor organs for HCV negative recipients.

Patient Consent

Consent to receive a HCV D+ organ will be specifically discussed with the patient in the transplant assessment clinic (see Appendix 1). These patients will receive a patient

information leaflet (Appendix 2) and have the opportunity to think further about this option outwith the clinic environment before coming to a decision.

For those patients already on the transplant waiting list, they will receive the patient information leaflet which will be sent to them. They will then have the opportunity to discuss their options at their next transplant review appointment, at an appointment with their renal physician or at a separate appointment with the transplant team at the patient`s request.

Waiting list patients are entitled to refuse one of these organs at the time of transplant without penalty to their status on the national transplant waiting list. If a patient decides they do not want a kidney from a donor with hepatitis C, a record will be made of this and they will not be offered these kidneys.

If a patient expresses the wish that they would consider such a donor offer, this will be documented on their waiting list record and in Vitaldata and they may then be offered a kidney from a donor with hepatitis C.

If the wishes of the patient are not known at the time of a kidney offer from a donor with hepatitis C, the offer will be discussed first with the recipient`s nephrologist or the on call transplant nephrologist and, unless there are specific precluding circumstances, the kidney may still be offered to the patient

Pre- Transplant Patient Selection

The pre-transplant assessment pathway is outlined in Appendix 3.

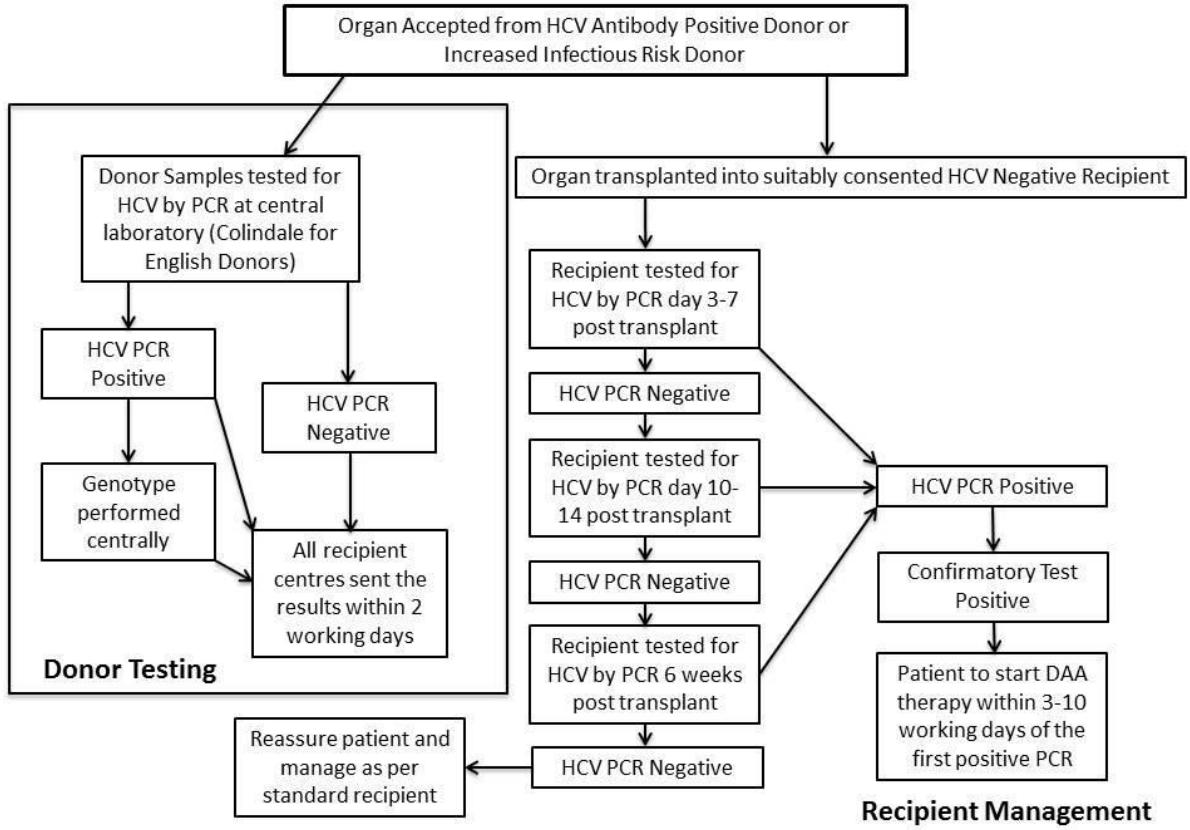
All consenting patients will have liver function tests and platelets checked during the transplant assessment process. If these investigations are normal or if the patient has only an isolated alkaline phosphatise rise, no further investigation would be required.

If there is LFT derangement or if the platelets are low, then a liver/spleen ultrasound will be undertaken.

- If the liver/spleen ultrasound is normal, no further investigation is required.
- If there is only evidence of fatty liver on ultrasound, hyaluronic acid level should be assessed. For patients with hyaluronic acid levels over 100ng/ml, a liver fibroscan is indicated.
- For patients with splenomegaly on ultrasound, a liver fibroscan is indicated.

For patients being assessed in Edinburgh, fibroscans can be arranged by contacting Dr Andy Bathgate, Consultant Hepatologist, who will arrange these directly. If the fibroscan suggests significant or advanced liver disease, then an opinion should be sought from Hepatology before the patient is considered for an HCV positive organ.

Management of the Recipient of a HCV D+ Organ



* *Option 1*- Donor Samples tested for HCV by PCR at central laboratory (Colindale for English Donors).
Option 2- Blood samples to be requested from Donor (Via Senior Nurse for Organ Donation) for testing for HCV by PCR/HCV Genotyping - Specialist Virology Centre, Royal Infirmary of Edinburgh, Little France

Figure 1. Proposal for Testing of Donors and Management of All Recipients in the UK HCV D+/R- scheme

Donor Testing

It is important to define the serological and virological status of the donor by both HCV antibody testing and HCV PCR testing. Genotyping will also be performed. HCV PCR testing will establish those who are actively viraemic. PCR testing is typically not available at the time of transplant. If the testing is performed in the central laboratory in Public Health England Colindale, then the recipient centre should be notified of the result within 2 working days. There is also the option to request that blood (serology/serum sample) via the Senior Nurse for Organ Donation (SNOD) to accompanies the kidney for subsequent testing at Specialist Virology Centre, Royal Infirmary of Edinburgh (this is likely to be the

arrangement for the first series of cases). Ideally, EDTA blood samples should be sent for analysis.

Treatment of HCV PCR Positive Recipient

Choice of agent

Two alternative regimens are deemed suitable as first line agents. These are either the combination of glecaprevir/pibrenatasvir (Maviret) or the combination of sofosbuvir/velpatasvir (Epclusa).

Duration of treatment

Either preparation would be given for 12 weeks in the context of HCV D+/R- transplants where the recipient subsequently has a positive HCV PCR on testing post transplantation. Both are pan-genotypic, which means that they can be started as soon as HCV PCR positivity is known, without having to wait for a HCV genotype.

Both have very acceptable drug to drug interaction profiles with standard anti- rejection drug therapy although exposure to the former is increased by ciclosporin, and it may also increase the levels of tacrolimus (CYP3A and P-glycoprotein inhibition); the latter is cautioned in patient with a eGFR <30 mL/min/1.73 m2 (please refer to the drug SPCs for details). Please read Appendix 4 for a detailed discussion on the DAAs, in particular to be made aware of clinically significant drug interactions.

Treatment will be directed by and given in liaison with the viral hepatology team. In the Royal Infirmary of Edinburgh, this will be Dr Andy Bathgate and Professor Peter Hayes and Senior Pharmacist, Katherine Davidson who are experienced in the management of HCV.

Response to Treatment (Sustained Virologic Response (SVR))

Sustained Virologic Repsonse (SVR) – this is a sustained virological response defined as negative PCR in blood >12 weeks (SVR 12) or >24 weeks (SVR 24) after completion of treatment. All patients should have SVR 12 result documented and in this cohort we will also aim for obtaining SVR 24 results given the fact they are immunosuppressed and late relapse may occur rarely in < 1% of patients (i.e between 12 and 24 weeks post treatment completion).

Management of poor response to treatment and suspected drug resistant HCV

In the rare (expected to be less than 2%) instances where the first course of treatment of HCV is not curative, recipients should be treated with a 12 week course of the combination of sofosbuvir/velpatasvir/voxaleprevir (Vosevi®) which has very high (>95%) rates of SVR even in those previously exposed to DAA therapy.

The risk of treatment failure with the licensed regimens is 1:2000. In the unlikely event of treatment failure with licensed regimens, alternative treatments can be used. In the rare case the patient becomes chronically infected with HCV, there is a 20% risk of cirrhosis at 20 years.

Special Additional Considerations

Given the theoretical concerns about the transmission of resistant HCV, the use of organs from donors known to have been treated for HCV with DAA within the last 6 months should be avoided unless there is clear documentary proof at the time of donation of an SVR12 result. Potentially donors engaging in increased infectious risk behaviour are at risk of re-infection post SVR and thus could still transmit HCV. The same donor and recipient testing outlined above should be followed if organs from such individuals are used. The table below indicates which donors should and should not be used for transplantation within the proposed policy

Donors who are Acceptable Within Proposed Policy	**Donors Not Recommended Within Proposed Policy**
HCV Ab positive with no history of treatment of HCV	Previously failed DAA therapy with on-going viraemia
HCV Ab positive with documented SVR after treatment	DAA therapy within last year without documented SVR (unless the recipient is at imminent risk of death or other features to suggest recipient unlikely to receive other offers of transplant)
Any HCV Ab negative donor who has exposed themselves to risk but who does not fulfil any of the unacceptable criteria	Multiple documented re-infection with HCV
Any HCV Ab positive donor whose HCV treatment history is unknown – **proceed with caution**	

Until more data is available, any organ from a donor who has been treated for HCV with DAAs but has not achieved SVR12 for any reason should not be considered for transplantation into a negative recipient unless the benefits outweigh the risks (e.g. in a clinically urgent transplant candidate). In such cases early liaison with an experienced HCV clinician with experience of transplantation is mandatory. Resistance testing of the virus at baseline prior to commencing treatment may be required and, in such cases, the timelines above may be relaxed. The choice of drug regimen in this scenario may have to be tailored in light of this information.

Sharing information about patients accepting a HCV positive kidney

If a patient has consented to receiving a HCV positive kidney, this should be documented on the Transplant Waiting List record (and VitalData).

Potential exposure to other Blood Borne Viruses (BBV)

Whilst this document deals primarily with hepatitis C infection transmission from HCV positive donors to HCV naive recipients, it is clear that in some cases, there may be a degree of concern regarding the possible concurrent transmission of other BBVs (namely HBV and HIV).

The estimated incidence of HBV infection among all potential deceased organ donors is 5.2/100,000. For HIV, the incidence is in the order of 2.6/100,000. This contrasts significantly with the estimated incidence for markers of HCV in the order of 36.9/100,000 donors (ref Davison et al 2018).

In donors who exhibit high risk behaviours, such as people who inject drugs (PWIDs), the risk of BBV transmission is higher. Approximately 50% PWIDs have ever been infected with **HCV** and around 25% of PWIDs are thought to suffer current active infection with only 50% estimated to be aware of the infection. Thus, the risk of HCV transmission from this at risk group to a recipient is **high**. In contrast, for **HBV**, the proportion of PWIDs ever infected with HBV is estimated to be relatively low at 16%, largely due to HBV vaccination, with around 75% PWIDs reporting having been vaccinated against the virus. Only 1 in 500 (0.2%) PWIDs are thought to suffer current active HBV infection. Thus, the risk of HBV transmission is **low**. Similarly, for **HIV**, infection amongst PWIDs is also **low** with around 1% PWIDs living with HIV (most are diagnosed and are being managed though that can be challenging). Regional variations in infection rates do exist, including due to outbreaks, emphasizing the importance of considering each individual offer on a case by case basis.

Thus, a number of scenarios could exist in this setting. When an offer is received from a high risk donor, it is possible that one or more positive BBV results are obtained. It is also possible that all retrieval BBV screening is negative, in which case it must be acknowledged that negative screening for BBVs at the time of retrieval has the potential to miss very recently acquired BBV infection in such high risk groups. The likelihood of a BBV screen being falsely negative depends on the test utilised for screening (direct detection based on antigen and nucleic acid testing has shorter window periods than testing based on antibody detection) and the likelihood that any individual has acquired the infection (incidence of infection in that population).

Thus, under the circumstance where initial screening for a given BBV is negative, the diagnosis and confirmation of transmission will then only be able to be made post transplantation. This document outlines how to effectively manage HCV transmission and

infection. As outlined above, for HBV and HIV, the risk of transmission is clearly very significantly lower than for HCV though the risk of transmission of infection from high risk donors is present nonetheless. Thus, the recipient should be counselled as such on a case by case basis, balancing the opportunity to obtain a good quality kidney transplant against the risks of BBV infection for which there are available highly effective treatments.

Testing for Patients with Potential Exposure to other BBV

In the setting of renal transplantation occurring using organs retrieved from at risk donors, the following BBV testing regimen will be followed:

Donor testing at retrieval	**HIV** (4th generation HIV Ab/Ag combo)
	HBV (HBsAg, HBcAb, HBsAb)
Recipient testing <u>fortnightly</u> weeks 0 – 12	**HIV** (4th generation HIV Ab/Ag combo)
	HBV (HBsAg)

By adopting this policy, it would therefore be anticipated that any BBV infection acquired by a donor immediately prior to donation and, thus, within the window period of exposure that might result in a negative screen at the time of retrieval, would become apparent in the post-transplantation screening.

Appendix 1

Consent to consider kidney offers from donors who are known or suspected to have hepatitis C

This form should only be completed after reading the "Patient Information Leaflet for the Use of Hepatitis C Infected Organs in Hepatitis C Negative Recipients" and discussing this with a member of the transplant team. If there is anything you do not understand, or if you need any additional information please ask. You may withdraw your consent at any time (even after signing this form). This form confirms you are willing to **consider** an organ offer from a donor who has hepatitis C. You will be provided with more information on the day of the transplant and still have the option to decline the offer at any time.

I confirm that I have received a copy of the patient information booklet relating to hepatitis C positive organ donors and have had the opportunity to discuss this with a member of the transplant team. .....

I confirm that the risks and benefits of accepting an organ offer from a hepatitis C positive donor have been explained to me. .....

I understand that, if I receive a transplant from a hepatitis C positive donor, then I will need to have several extra blood tests after the transplant to check whether the virus has been passed to me. .....

I understand that donors who have hepatitis C may also be at risk of having other viruses such as HIV and HBV. I understand that whilst the risk that these viruses will be transmitted to me is very low if the initial donor blood tests are negative, I may need further blood tests after my transplant to look for these viruses .....

I understand that if I develop hepatitis C as a result of receiving a transplant then I will need to have a course of tablet medication to treat this. The treatment is safe and highly effective but in a very small number of patients (less than 1 in 2000) this treatment may not work. .....

To be completed by the patient
Signed _____
Print Name_____

To be completed by the healthcare professional
Signed _____ Date_____

Appendix 2

Dear Mr/Mrs/Ms

We are writing to let you know about a new treatment that will make it possible to transplant kidneys from donors who have previously had infection with hepatitis C. Hepatitis C is a virus that usually causes no symptoms, but in the long term can lead to liver damage. If a kidney donor is infected with hepatitis C, then the virus can be passed to the recipient. Kidney donors have always been tested for hepatitis C infection, and if this was found to be present until now the kidneys have not been used in patients who do not have hepatitis C themselves.

However, there is now extremely effective treatment that can cure hepatitis C in the majority of patients.

This means that the kidneys from donors who test positive for hepatitis C can now be used for transplant. More often than not you will be offered a kidney from a donor who has not had hepatitis C, but we are asking you to consider whether or not you would accept a kidney transplant from a donor infected with hepatitis C, if it were offered to you.

It will be up to you whether you would accept one of these kidneys. If you do accept a kidney from a donor with hepatitis C, then if you become infected with this virus you will receive treatment for 12 weeks after the transplant.

The treatment is tablets, which have very few side effects. You will be started on treatment very quickly so there is minimal risk of liver disease. There is other treatment available in the unlikely event that the first course of tablets does not work. Once the virus is cured, it does not come back.

If you think you would accept a kidney from a donor who has had hepatitis C, we may need to arrange extra blood tests and ultrasound scans of your liver to make sure that you are suitable to have this type of kidney.

We are offering this option as it may mean that you receive a kidney transplant more quickly. Donors with hepatitis C are often younger than average, so we would expect the transplanted kidney to work well and last longer.

Please think about whether you would consider a transplant from a donor who has had hepatitis C and talk to your friends and family about it. There is further detailed information enclosed with the letter, which may help to answer any questions you have.

What happens next?

If you are not yet on the transplant waiting list, the possibility of considering a kidney from a donor with hepatitis C will be discussed with you further when you are seen in the transplant assessment clinic.

If you are already on the transplant waiting list and have a review appointment in the transplant or renal clinic in the near future, this can be discussed with you at the clinic appointment.

If you do not have a review appointment in the near future or you would like the opportunity to discuss this further, please contact any of the recipient transplant coordinators (*local coordinators*) who can arrange for you to come to the transplant clinic to discuss this further.

If you decide you do not want a kidney from a donor with hepatitis C, we will make a record of this, and you would not be offered these kidneys in the future.

Yours sincerely

Patient Information Leaflet for the Use of Hepatitis C Infected Organs in Hepatitis C Negative Recipients

Introduction

You are being asked to consider whether or not you would accept a kidney transplant from a hepatitis C virus infected donor. The information in this leaflet will help you decide whether or not you would accept a kidney transplant from a donor who has had hepatitis C.

What is hepatitis C?

Hepatitis C is a virus that is transmitted in infected blood and body fluids. It lives in the liver and blood of infected individuals and can cause inflammation and scarring of the liver. The scarring can be severe (this severe liver scarring is called "cirrhosis"), although on average it takes 30 years for the scarring to become life-threatening in non-transplant patients. Severe scarring may develop more rapidly in transplant patients taking drugs that suppress the immune system.

Treatments for hepatitis C have changed greatly over recent years. It is now possible to cure nearly all patients who are infected with the hepatitis C virus. Treatment requires taking tablets for 12 weeks. Once the virus is cleared it does not come back and does not affect your long term health.

Why am I being offered a hepatitis C infected kidney transplant?

There are not enough donated organs in the UK to transplant into all people who may need them.

Due to recent breakthroughs in hepatitis C virus treatment it is now possible to consider using organs from donors infected with hepatitis C virus for transplantation. These donors are generally younger than average and may be healthier, with lower blood pressure and less heart disease and other medical conditions. Hence their donated organs may be of higher quality than average.

What are the risks to me if I receive a hepatitis C infected kidney transplant?

The main risk of accepting a kidney transplant from a hepatitis C virus infected donor is that you become infected with the virus yourself. You will be offered treatment to cure you of the hepatitis C virus as soon as is has been confirmed that you have been infected. This will minimise the risk of any damage to you.

If hepatitis C virus infection is not treated you may become jaundiced (yellow) and may develop severe inflammation in the liver (called fulminant cholestatic hepatitis). In the case of untreated hepatitis C infection, in the longer term, this may result in kidney injury

There is a very small chance that the hepatitis C virus may not disappear after the 12 weeks of treatment (see below). The chances of this happening are less than 2 in 100 (2%). If this

were to happen, you would be offered a different course of tablets that has been shown to be highly effective in curing patients whose treatment has failed with other drugs. These drugs achieve 96 to 98% cure rates. This means that it is very unlikely (1 chance in 2000) that the transplant team will not be able to cure you of the virus if you are infected. Please discuss with your Transplant Doctor or Surgeon if you have any further questions regarding this small chance that you would not be cured by treatment with these tablets.

Whilst all donors are routinely screened for the presence of other blood borne infections in addition to hepatitis C, such as HIV or hepatitis B, the screening tests can very rarely miss infections with these viruses. There is therefore a very small possibility that these or other infections could also be transmitted at the time of transplantation even if the initial screening tests are negative. For this reason, all patients receiving a kidney from a patient with hepatitis C will also have blood tests taken every two weeks (taken at the same time as your other clinic blood tests) to look for these other infections. We will do this for the 12 weeks following your transplant. If your testing for these other viruses is negative, no further testing would be required as the negative tests will have shown that you have not been infected. If any of these blood tests come back with a positive result for another virus, these can be treated very effectively and your transplant team will discuss this with you further.

What has happened to other patients who have been infected with hepatitis C at the time of an organ transplant?

There have already been several studies looking at the results of transplanting kidneys from hepatitis C virus infected donors into patients who are not infected with hepatitis C virus. These have mainly taken place in the United States and patients have received treatment for hepatitis C within 4 weeks of the transplant. In these studies every recipient was cured of hepatitis C. Importantly, the transplanted kidneys then went on to work very well, and the overall outcomes were the same for the patients who received kidneys from hepatitis C virus infected donors as those for patients who received kidneys from hepatitis C virus negative donors.

How do I know that the kidney from the hepatitis C infected donor has not been damaged by the virus?

Hepatitis C can in rare cases, cause kidney damage. The health of kidneys from all donors that are offered for transplantation is carefully assessed by a series of blood and urine tests that are carried out on the donor before and after they die. Only kidneys with very little or no known pre-existing damage are used for transplantation. The same precautions will apply to kidneys from hepatitis C virus infected donors.

Are there any risks to my family if I receive a hepatitis C Infected kidney transplant?

The risks to your family are very small. Transmission of the virus is mainly through infected blood and body fluids. Until you are cured of hepatitis C virus, which should happen within the first 3 to 4 months after the transplant, we recommend that you do not share your

toothbrush and razor blades with anyone. The virus is not transmitted through kissing and saliva. The virus can be transmitted through sexual intercourse, although it is rare, so we recommend that you or your partner uses barrier contraception (condoms) until you are told that you have been cured of the virus. Because of some of the other drugs you may have been started on around the time of your transplant, some patients may need to use barrier contraception for a longer period of time after their transplant. If you are not sure whether this relates to you, please ask your transplant team doctor and they will be able to advise you.

How will I be treated if I receive a hepatitis C infected kidney transplant?

After your transplant you will have a specific and very sensitive blood test to look for the presence of hepatitis C virus in your blood.

The first blood sample will be taken within the first 7 days of your transplant, then again within the first 14 days and the last sample will be taken within the first 6 weeks of your transplant. If all the virus tests are negative then your transplant organ has not passed on the infection to you.

If any of these tests are positive for hepatitis C virus, then the doctors looking after you will start you on highly effective treatment very soon after we receive the result. This means that you will be prescribed some specific antiviral tablets that you will need to take for a total of 12 weeks. This will consist of either 1 extra tablet or 3 extra tablets a day. The exact number will depend on what treatment the doctors think is best suited to you. Once the treatment is finished you will have further blood tests to check that you have been cured of the virus. If the virus disappears from your blood and cannot be detected 12 weeks after the treatment has stopped then you have been cured. We predict that more than 95% of patients will be cured. If the first course of treatment does not work then a second 12 weeks course of treatment using a different combination of tablets will be used which cures more than 95% of patients whose first course of treatment has not worked. It is worth mentioning that these new drugs for hepatitis C have very few side effects in recent world experience and are generally very well tolerated by patients taking them.

What happens to me if I decide not to accept a hepatitis C infected kidney transplant?

It is your choice whether you choose to receive a kidney transplant from a hepatitis C virus infected donor. If you prefer not to accept an organ from such a donor you will remain on the transplant waiting list as now and you will continue to wait for a suitably matched organ.

Will I be entitled to compensation if I accept a hepatitis C infected kidney transplant?

No, you will not be entitled to compensation. Although there is a compensation scheme (Skipton Fund) for patients that have been unknowingly infected with hepatitis C, this would not be the case if you knowingly accept a hepatitis C infected kidney transplant.

Where can I find out more information?

Please speak first to your transplant doctor if you have any questions about the information contained in this leaflet.

Other sources of information are also available.

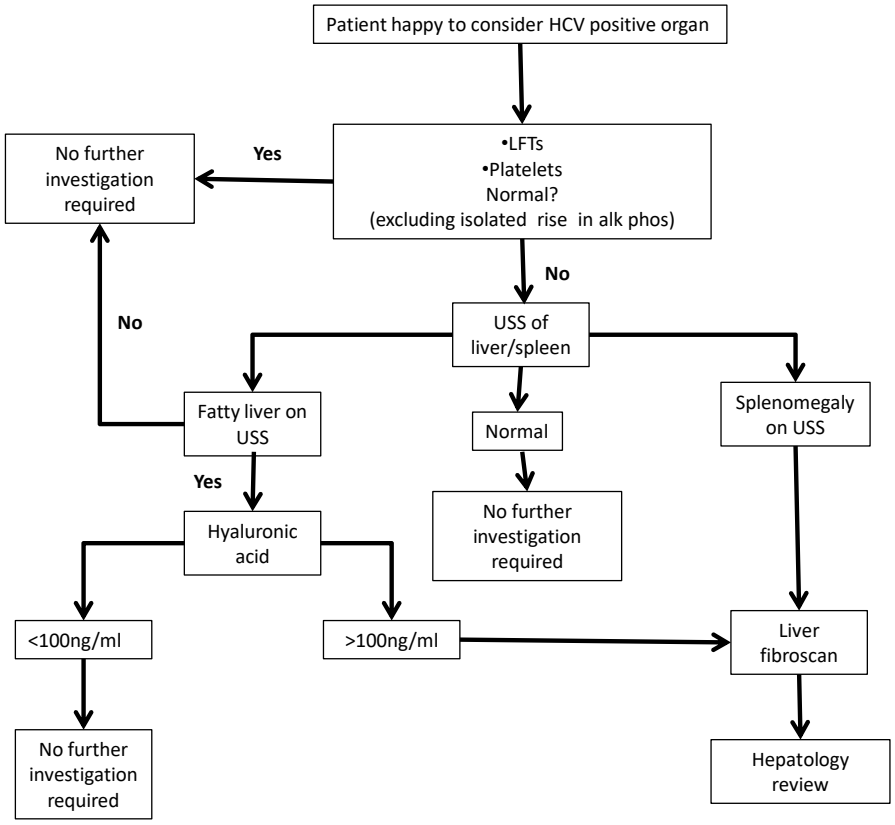
The Hepatitis C Trust is the national charity for people affected by hepatitis C and is patient-led. Staff on their confidential national helpline will be able to answer any questions you may have about hepatitis C and provide support and reassurance about the new treatments available – you can reach them on 0845 223 4424 or 020 79089 6221 and by email helpline@hepctrust.org.uk

There is also a lot of useful up-to-date general information on their website www.hepctrust.org.uk

The British Liver Trust has an excellent publication on hepatitis C that is free to access on the internet. The link to this is https://www.britishlivertrust.org.uk/wp-content/uploads/Hep-C-website.pdf.

Appendix 3

Pre-transplant patient selection algorithm



Appendix 4

Pharmacological treatment for Hepatitis C post kidney transplantation

Choice of Direct Acting Antiviral drug

There are a variety of oral Direct Acting Antiviral (DAA) drugs available for the treatment of Hepatitis C Virus (HCV). For the purpose of treating patients in receipt of organs from HCV viraemic donors or organs from increased HCV infectious risk donors there are currently two recommended as options for patients under the care of the Edinburgh Transplant Unit:

Sofosbuvir plus velpatasvir

- This is available as a fixed dose combined preparation called **Epclusa®**
- Contains 400mg sofosbuvir and 100mg velpatasvir

Glecaprevir plus pibrentasvir

- This is available as a fixed dose combined preparation called **Maviret®**
- Contains 100mg glecaprevir and 40mg pibrentasvir

Epclusa® and Maviret® are pangenotypic treatments, allowing treatment to commence without knowledge of the specific HCV genotype and subtype.

Discussion of the other antiviral drugs for treatment of HCV is beyond the scope of this document. Epclusa® or Maviret® will be appropriate DAAs for all transplant recipients and both are very well tolerated so use of alternative DAAs is extremely unlikely. Please speak to a transplant or HCV pharmacist about dosing in renal impairment and interactions if alternative DAAs are required.

Dose regimen and duration of therapy for DAAs

Epclusa®

- One tablet once a day for 12 weeks
- Can be taken with or without food

Maviret®

- Three tablets once a day for 12 weeks
- Must be taken with food to maximise oral bioavailability (significant increase in absorption compared to fasting state)

Prescribing DAAs in the presence of renal impairment

Epclusa®

Neither sofosbuvir or velpatasvir are predictable nephrotoxins.

Sofosbuvir is predominantly excreted through the kidneys (via filtration and active secretion) and 80% of a dose will be found in the urine – only 3.5% is unchanged drug with the remainder as a metabolite. Side effects of this metabolite have not yet been determined and it will undoubtedly accumulate in the presence of renal impairment but the consequences of this are unknown. In view of this uncertainty, prescribing advice can be summarised as:

- eGFR > 30ml/min – normal dose
- eGFR < 30ml/min – safety data is limited. If possible, as a precaution prescribe an alternative DAA regimen (Maviret®). Where no other suitable options are available, Eplcusa® can be used without dose adjustment. Velpatasvir is predominantly excreted via the biliary route so is not affected in renal impairment. It can therefore be prescribed in normal doses at all levels of renal function.

Maviret®

Neither glecaprevir or pibrentasvir are predictable nephrotoxins.

Glecaprevir and pibrentasvir are predominantly excreted via the biliary route so the same dose is used at all levels of renal function.

Adverse effects

Epclusa®

From clinical studies, 3.2% of Epclusa® treated patients experienced severe adverse events and 0.2% discontinued therapy due to side effects. Headache, fatigue and nausea were the most common adverse events. There are no specific additional biochemical or haematological monitoring requirements for patients taking Epclusa.

Maviret®

From clinical studies, 0.1% of Maviret® treated patients experienced severe adverse events and 0.1% discontinued therapy due to side effects. Headache and fatigue were the most common adverse events. There are no specific additional biochemical or haematological monitoring requirements for patients taking Maviret®.

Interactions – background and considerations

Understanding and avoiding clinically significant drug interactions is one of the most challenging aspects of prescribing antiviral therapy for HCV patients. The patient's medication must be reviewed by a specialist Transplant or HCV pharmacist before

commencing treatment to identify drugs that can reduce or increase exposure to DAAs. The former is particularly important because it can lead to HCV treatment failure. The medication review must also consider the potential impact of DAAs on the patient's existing medicines, especially their anti-rejection drugs eg:

- Tacrolimus (requires Therapeutic Drug Monitoring)
- Ciclosporin (requires Therapeutic Drug Monitoring)
- Sirolimus (requires Therapeutic Drug Monitoring)
- Mycophenolate Mofetil
- Mycophenolate Sodium
- Azathioprine
- Prednisolone

The narrow therapeutic window drugs are very susceptible to drug interactions leading to clinically significant disruption to serum drug levels. The vast majority of all new kidney transplant patients will be taking Tacrolimus, Mycophenolate Mofetil and Prednisolone so these are the agents to focus on when screening for interactions.

Many of the important drug – drug interactions for kidney transplant patients receiving treatment for HCV relate to the metabolism, absorption or excretion of drugs mediated by hepatic cytochrome P450 (CYP) enzymes (eg CYP3A group) and the transmembrane protein P-glycoprotein (P-gp). CYP enzymes are important in the metabolism of many drugs by the liver so other drugs that are strong inhibitors or inducers of these enzymes will, respectively, increase and decrease patient exposure to the drug. P-gp is found in various organ systems, for example the gut where it plays a key role in regulating the extent of oral drug absorption. Strong P-gp inhibitors lead to increased drug absorption whereas strong inducers cause reduced drug exposure as more drug is forced back out into the gut lumen to be excreted.

Drug – drug interactions frequently involve effects on both CYP enzymes and P-gp. There are other enzymes and transport proteins involved in the absorption, metabolism and excretion of DAAs and the list of potential drug interactions with DAAs is extremely long and beyond the scope of this document.

Also it is important to recognise that there is a wide spectrum of clinical significance when assessing the importance of specific drug – drug interactions for individual patients ranging from prescribing contraindication to prescribe cautiously with close monitoring to minor clinical relevance.

In summary, when a kidney transplant patient needs to commence DAA therapy, consideration must be given to the following questions:

Will the DAA reduce exposure of the drugs currently taken by the patient?

- For example, will serum tacrolimus levels be reduced to sub-therapeutic, increasing the risk of transplant rejection?

Will the DAA increase exposure of the drugs currently taken by the patient?

- For example, will serum tacrolimus levels be increased leading to higher risk of side effects such as nephrotoxicity and neurotoxicity?

Can any of the patient's current drugs reduce exposure to DAAs?

- If so, risk of treatment failure is increased.
- Clinically significant drug interactions of this nature must direct a review of treatment. The interacting drug must be stopped for the duration of antiviral treatment or, if this is not possible, an alternative DAA regimen with less interaction potential must be selected.

Can any of the patient's current drugs increase exposure to DAAs?

- If so, risk of DAA related side effects will be increased.
- As described above, DAAs are very well tolerated so these drug interactions are generally less clinically significant.

Patients must be asked to report any new medicines prescribed for them or that they buy themselves before taking them so that the pharmacist can check for interactions with DAAs.

Interactions

Interactions - Epclusa®

Both sofosbuvir and velpatasvir are substrates of P-gp. Velpatasvir is also a substrate for CYP3A enzymes. Potent inducers of P-gp or CYP3A enzymes (eg rifampicin and carbamezepine) will significantly reduce levels of both DAAs so prescribing with Epclusa® is contraindicated. Prescribing of moderate inducers of P-gp or CYP3A is not recommended.

Inhibitors of CYP3A enzymes and P-gp can increase levels of sofosbuvir and velpatasvir but in general such interactions are not regarded as clinically significant.

Velpatasvir itself is an inhibitor of P-gp so drugs that are substrates of P-gp can have levels increased by Epclusa®.

Interactions with anti-rejection drugs

- Tacrolimus and Epclusa®

    - Limited data (from single dose studies with sofosbuvir) show small increases in exposure to both drugs but this is not clinically significant and no dose adjustment is necessary.
    - Tacrolimus and velpatasvir has not been studied but significant interaction unlikely.
- Mycophenolate Mofetil and Epclusa®
    - No reported interactions
- Prednisolone and Epclusa®
    - No reported interactions

Interactions - Maviret®

Both glecaprevir and pibrentasvir are substrates of P-gp. Potent inducers of P-gp or CYP3A enzymes (eg rifampicin and carbamezepine) will significantly reduce levels of both DAAs so prescribing with Maviret® is contraindicated. Prescribing of moderate inducers of P-gp or CYP3A is not recommended.

Inhibitors of P-gp can increase levels of glecaprevir and pibrentasvir but in general such interactions are not regarded as clinically significant.

Glecaprevir and pibrentasvir are themselves inhibitors of P-gp and glecaprevir is a weak inhibitor of CYP3A so drugs that are substrates of P-gp and CYP3A can have levels increased by Maviret®.

Interactions with anti-rejection drugs

- Tacrolimus and glecaprevir/pibrentasvir
    - Tacrolimus levels may increase due to the inhibitory effect of the glecaprevir on CYP3A. The interaction is not sufficiently strong or predictable enough to direct a pre-emptive tacrolimus dose reduction. Serum tacrolimus levels will be checked on a regular basis in the post transplant period and this DDI should be kept in mind when reviewing results after commencing Maviret®. The tacrolimus dose may require adjustment in line with normal practice for the transplant team.
    - Tacrolimus is metabolised by CYP3A enzymes in the liver and gut wall and it is also a moderate inhibitor of CYP3A enzymes. Exposure to glecaprevir and pibrentasvir is not changed by tacrolimus.
- Mycophenolate Mofetil and Maviret®
    - No reported interactions
- Prednisolone and Maviret®

- No reported interactions

- Ciclosporin and Maviret®
    - The use of ciclosporin and Maviret® requires close monitoring as concentrations of glecaprevir/pibrentasvir may increase. It is not recommended to use this combination if using ciclosporin doses > 100mg daily

Interactions with non-immunosuppressant drugs– Epclusa® and Maviret®

Acid-suppression medicines

The solubility of DAAs reduces as gastric pH increases so acid suppression therapies may reduce drug absorption leading to an increased risk of antiviral treatment failure. However the significance of this varies for each DAA.

- Epclusa® -
    - Ranitidine must be prescribed with caution and PPIs (Proton Pump Inhibitors) such as omeprazole are not recommended.
    - If there is a strong clinical need for PPI treatment, patients must be advised to take Epclusa® with food and the PPI at least 4 hours later. The PPI dose should not exceed Omeprazole 20mg OD (or equivalent).
    - Administration of antacids should be separated by 4 hours from Epclusa®
- Maviret®
    - Although a decrease has been seen in single dose studies of acid suppression medicines and Maviret®, this is not thought to be clinically significant and no dose adjustment is required. However, there is no data available for doses greater than omeprazole 40mg daily and so doses above this should not be used

Lipid-lowering medicines

Epclusa® and Maviret® interact with lipid lowering therapies by increasing exposure to the statin or fibrate drugs, increasing the risk of side effects including myopathy. In some cases the interaction is predictable and strong enough to require discontinuation of the lipid lowering agent for the duration of the DAA course. See University of Liverpool website for details on individual agents.

Aspirin, co-trimoxazole, valganciclovir, isoniazid and lamivudine can be prescribed as prophylaxis post kidney transplant. There are no reported interactions with Epclusa® and Maviret®.

Further information about interactions can be found on the website managed by Liverpool University www.hep-druginteractions.org or advice sought from specialist pharmacist.

Prescribing and supply of DAAs

Transplant patients under regular surveillance for HCV will need to start treatment with DAAs if HCV PCR monitoring indicates the development of Hepatitis C viraemia. If treatment is initiated whilst the patient is an inpatient in the Renal Transplant Unit, it is anticipated that the first month of treatment will be provided by the Renal Transplant Unit in Edinburgh with subsequent treatment to be prescribed in conjunction with the local HCV pharmacist and treatment team.

DAA are not stocked by the hospital and will need to be ordered in on an individual patient basis. The lead time for both medicines is approximately 2 working days. Once confirmation of treatment is in place, the transplant pharmacist should be notified to allow an order to be placed. The transplant pharmacist should liaise with the HCV pharmacist from the home unit to ensure arrangements are in place for supply of month 2 and 3 of treatment.