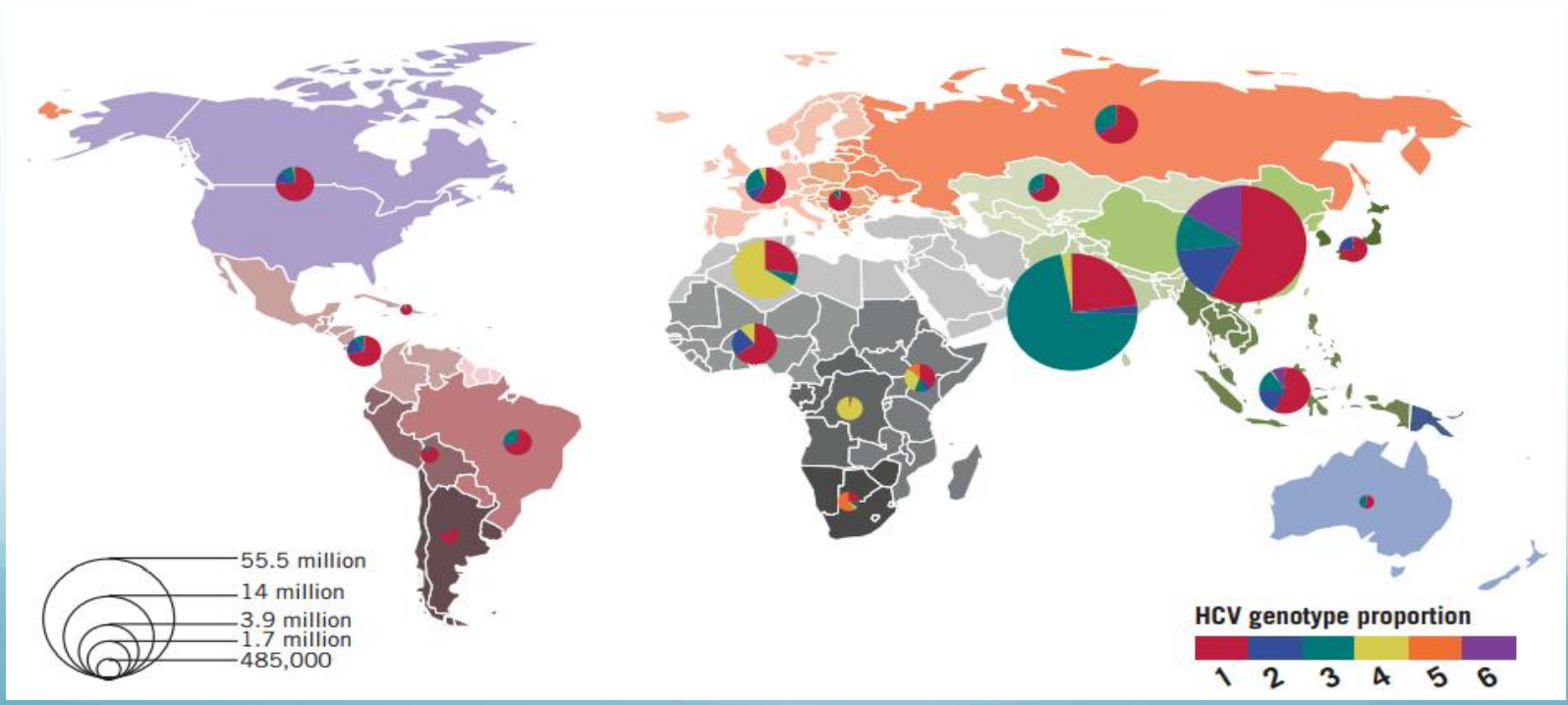
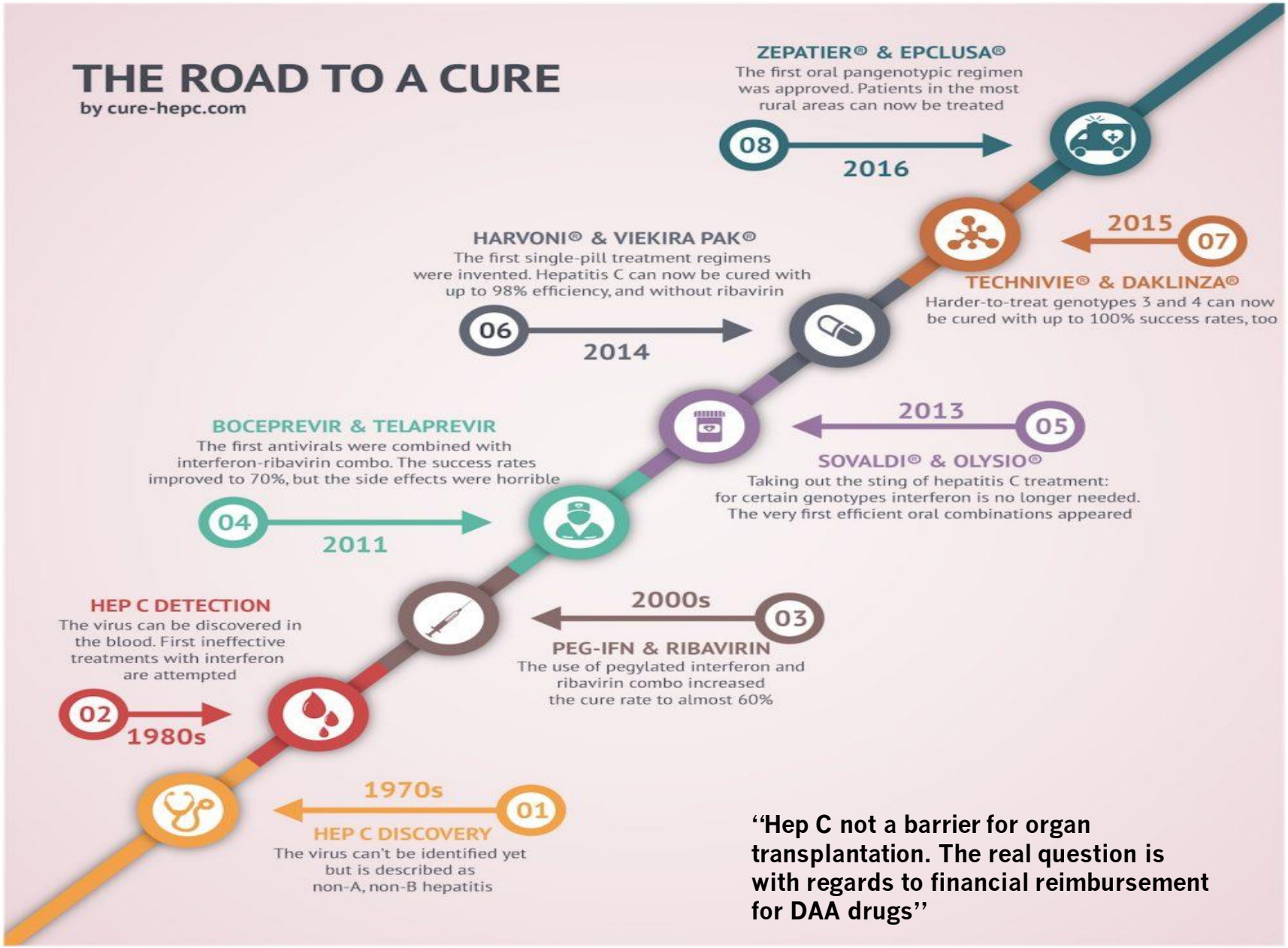
Kidney Transplantation from Hepatitis C positive donors – The Cardiff Experience

Dr. Sarah Browne
Cardiff Transplant Unit
28th January 2020

Epidemiology

- 160 million world wide – WHO – eliminate Hep C by 2030
- 12,000 in Wales – Welsh Assembly Government signed up to achieving WHO target





''Hep C not a barrier for organ transplantation. The real question is with regards to financial reimbursement for DAA drugs''

Transplanting kidneys from HCV positive donors in DAA era

Study	No. of Patients	HCV Status		SVR,%	Time DAA Initiated
		Donor	Recipient		
Sawinski *et al.*[8]	19	Positive	Positive	100	Median of 1123 d post-transplant
Bhamidimarri *et al.*[9]	25	Positive	Positive	96	Median of 125 d post-transplant
Goldberg *et al.*[10]	10	Positive	Negative	100	When viremia was detected (approximately 3 d)
Durand *et al.*[11]	8	Positive	Negative	100	Immediately pretransplant

Patient Advocacy

The Wall Street Journal: Leading Transplant Surgeon Accepts a Hepatitis C–Positive Heart for Himself

Transplant surgeon Dr. Robert Montgomery, a long-time advocate for the use of organs from high-risk

Why are we here?

UK Position Statement on the use of organs from Hepatitis C viraemic donors and increased infectious risk donors in Hepatitis C negative recipients

What next?

- Over to the UK transplant centres…
- For kidney transplant teams, increasing number of organs available for transplant is exciting (19 HCV positive donors offered on fast track in last year); (National Potential Donor Audit 2000 – 2015 identified 244 HCV Ab +ve donors)
- Moving from this exciting potential to the reality of a patient receiving a hepatitis C positive kidney will surely involve many steps/hurdles/barriers and a shedload of work?!
- Cardiff Transplant Unit decided to take on the challenge
  - Ball started rolling in April 2018
  - Identify stakeholders and see who is going to help and advise us

Stakeholders

- Transplant nephrologists
- Transplant surgeons
- Transplant nursing team
- N&T pharmacy team
- Infectious Diseases (consultants and pharmacists)
- Virology (consultants and labs)
- Radiology (Screening liver US)
- Referral units

- Leads identified for each area
  - Regular meetings and e-mail correspondence

- N&T directorate
- Welsh Renal Clinical Network (WRCN)
- Welsh Health Specialised Services Committee(WHSSC)
- Infectious Diseases service commissioners
- NHSBT
- Cardiff and Vale University Health Board
- Welsh Assembly Government (WAG)
- **Patients**

Patient engagement

- Discussed with patient representatives at transplant sector meeting
- Letter to all patients on the transplant waiting list
- n=42 currently willing to consider HCV kidney transplant offers, n =4 willing to consider SPK offers
- Patient information leaflets/booklet about Hep C (patients reviewed and commented on “user friendliness”)
- “Meet and discuss with transplant team” sessions arranged in Cardiff and Swansea
  - Full and open explanation about the plans for the new service and what it means for individual patients
  - Opportunity for patients to ask questions
- Patients asked to opt in or out
  - Consent form to sign
  - Can reverse decision at later date

Patient Information Booklet

Use of Hepatitis C Infected Organs in Hepatitis C Negative Recipients

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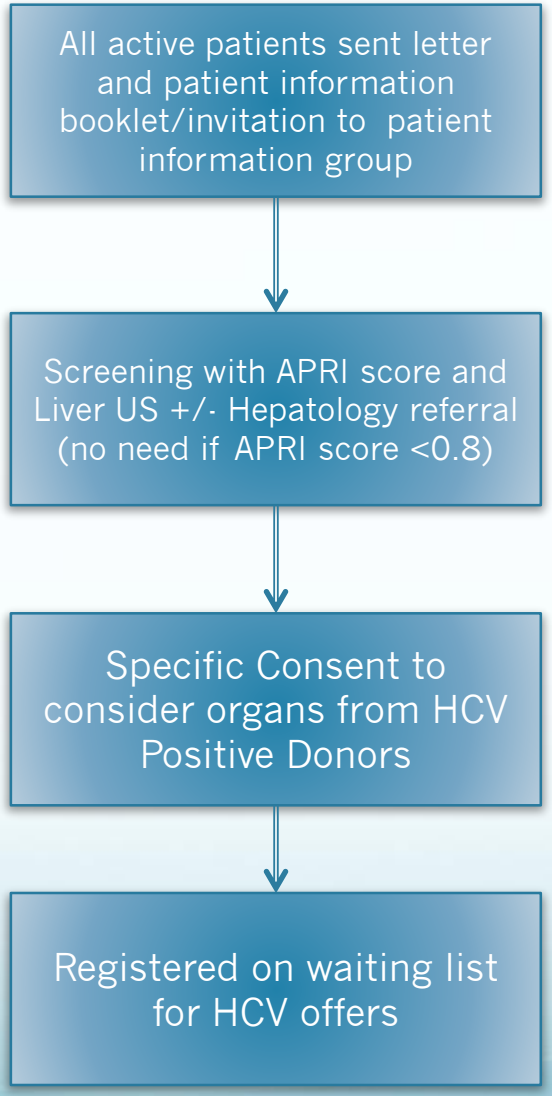
Pathway


All active patients sent letter and patient information booklet/invitation to patient information group
Screening with APRI score and Liver US +/- Hepatology referral (no need if APRI score <0.8)
Specific Consent to consider organs from HCV Positive Donors
Registered on waiting list for HCV offers

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

Patient Addressograph

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 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_____ Date_____

To be completed by the healthcare professional

Signed _____ Date_____

Print Name_____ Designation_____

Version 3: 20/09/19
Created by MS: 05/10/18

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Themes from patient and public feedback session (Credit; Dr. Leah Mc Laughlin WKRU)

- Recognition that attitude of potential recipients key to considering these transplants
- Participants concerned about “what else they might have if they had Hep C” “infecting family members e.g spouse/grandchildren”
- Concerns alleviated by information evenings with health professionals, feeling part of something “new”, high cure rate, health risks of not being transplanted
- Feedback from patients that professionals in dialysis unit more apprehensive than those in transplant unit

Developing the guideline

- Alongside the patient engagement, education and consenting process, a clinical guideline was drafted, redrafted and finally finalised by the MDT
- Cross speciality working with all clinical stakeholders proactive with support for the Hep C Transplant Programme
  - Writing the guideline
  - Structures to support the programme (eg ordering and reviewing virology blood tests)
  - Communication (eg e-mail group to ensure information is disseminated and followed up)
- N&T pharmacists and ID pharmacists working collaboratively
- Guideline launched at Cardiff and Vale UHB and shared with renal teams in Wales

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

Guidance prepared by Cardiff and Vale University Health Board

Dr Sarah Browne (Consultant Nephrologist)
Dr Brendan Healy (Consultant Microbiologist/Infectious Diseases)
Dr Rachel Jones (Consultant Virologist)
Dr Nicola Price (Consultant Virologist)
Rob Bradley (Consultant Pharmacist Nephrology/Transplantation)
Kymm O'Connor (Transplant Recipient Nurse Specialist)
Rachel Hart (Associate Transplant Nurse Specialist)
Dr Sian Griffin (Consultant Nephrologist)
Mr Michael Stephens (Consultant Transplant Surgeon)

Date of Approval

22nd November 2018

Date for Review

23rd May 2019

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Cardiff and Vale University Health Board

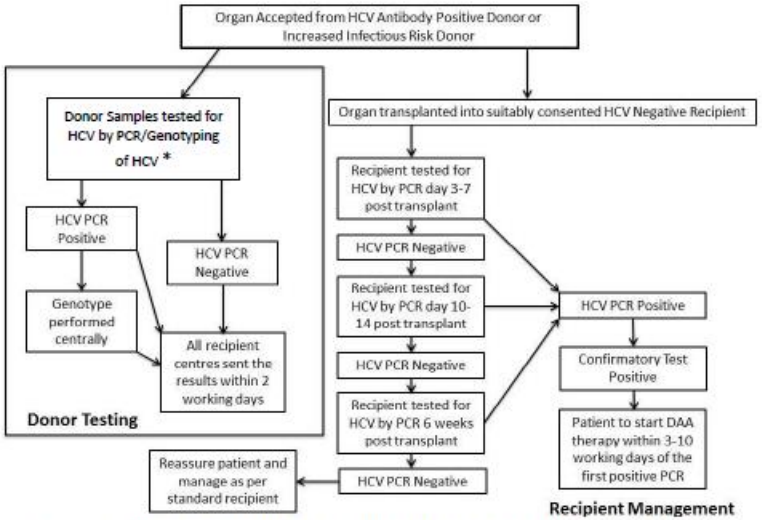
Patient and Unit Requirements Pre-Transplant

Pre- Transplant Patient Selection

All consenting patients will be screened pre-transplant using AST-to-Platelet Ratio Index (APRI) and with an ultrasound of the liver. Liver ultrasounds will be performed in advance of transplant by prior arrangement with the radiology department in the University Hospital of Wales. APRI scores are easily calculated using on line tools such as https://www.mdcalc.com/ast-platelet-ratio-index-apri.

If the APRI score is >0.8 or the ultrasound suggests significant or advanced liver disease, then an opinion from an infectious diseases and hepatologist (refer to Blood Borne Virus (BBV) clinic for fibroscan and opinion with onward referral to Hepatology if appropriate) should be sought before the patient is considered for a HCV D+ organ. Although the UK Position Statement felt that even cirrhotic patients could potentially receive HCV D+ organs safely, such patients will not be offered HCV D+ organs in the early stages of this new programme in Cardiff. If the APRI score is <0.8, there is no need for the patient to be seen by a hepatologist.

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 in Public Health Wales laboratory, University Hospital of Wales, Cardiff

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

Management of the Recipient of a HCV D+ Organ

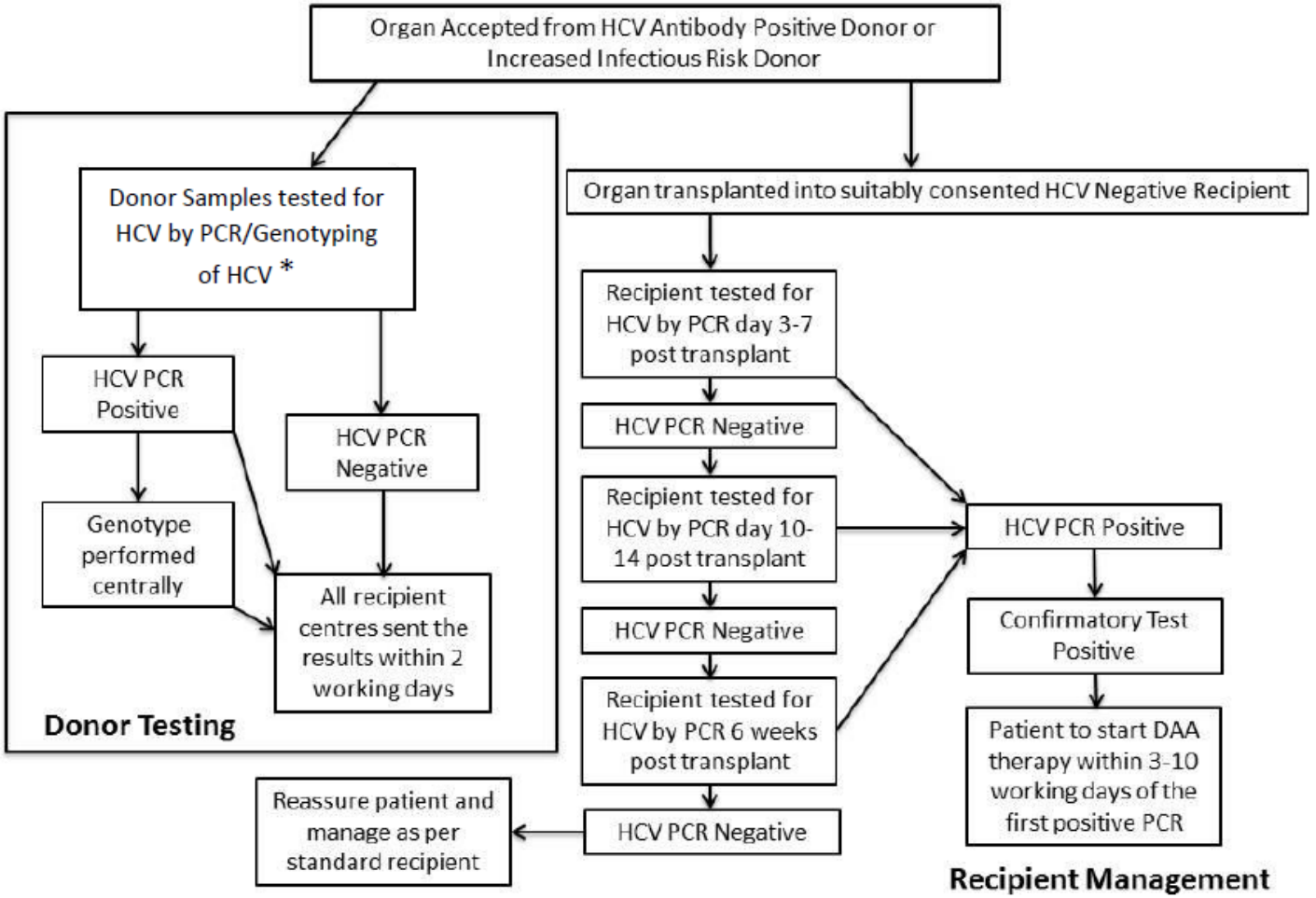


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Figure 1. Proposal for Testing of Donors and Management of All Recipients in the UK HCV D+/R- scheme

Pharmacological management

- Range of Direct Acting Antiviral (DAA) drugs available
- ID team kept things simple for us with 2 DAA options
  - Epclusa®
  - Maviret®
- Both agents are pangenotypic so treatment can commence without knowledge of the specific HCV genotype and subtype
- Hep C guidelines directs that DAA treatment starts within 3 to 10 working days of first positive Hep C PCR
  - For our new programme, aiming to start within 24 to 48 hours to provide added reassurance for patients and N&T team

Pharmacological management

Epclusa®

- Sofosbuvir 400mg plus Velpatasvir 100mg
- One tablet once a day for 12 weeks
- Can be taken with or without food

Maviret®

- Glecaprevir 100mg plus Pibrentasvir 40mg
- Three tablets once a day for 12 weeks
- Must be taken with food to maximise oral bioavailability

Story so far with the donor Hep C positive transplant programme in Cardiff

- Everything in place at mission control….NHS BT and national monitoring committee approval
- Ready for blast off….
- Debrief with transplant surgeons regarding donors considering acceptable under scheme (system of 2 surgeons on call with back up from virology/ID team) – checklist to avoid transmission of a drug resistant virus
- **26th May 2019 – first two kidney transplants performed in the UK from Hep C positive donor**

Prescribing and Supply of Antiviral Treatment

The first month of treatment will be supplied via the Kidney Transplant Ward or Outpatient Clinic. You will then be registered with the Antiviral Drug Homecare Service and the second and third month of treatment will be delivered directly to your home. Your General Practitioner will be kept informed but will not prescribe Hepatitis C treatment.

When attending the Transplant Clinic or if you need to be admitted to hospital for any reason, please take your antiviral drugs with you.

Starting New Medicines During Course Of Antiviral Treatment

Many common medicines can interfere with the antivirals. **In some cases these interactions can even stop the antiviral drugs from working effectively so it is very important to check with the Transplant Clinic Pharmacy Team before taking any new medication.** This includes medication prescribed by your General Practitioner, Hospital Doctor or Dentist or anything you buy from the Community Pharmacist or supermarket, including herbal remedies.

Your current medicines will also be reviewed when the course of treatment starts because adjustments may be required to avoid interactions with the antiviral drugs.

The table below can be used by you and the transplant team to record the dates and results of your HCV PCR blood tests.

HCV PCR testing (for diagnosis of viral infection)	Date	Result (positive or negative)
Day 3-7 post transplant		
Day 10-14 post transplant		
Week 6 post transplant		
If there is a positive HCV result treatment with antivirals will start **If all three blood tests are negative no antiviral treatment required**		
HCV PCR testing (during treatment of viral infection)	**Date**	**Result (amount of virus in the blood)**
Before starting treatment		
Week 4 post starting medication		
Week 12 post starting medication		
Week 24 post starting medication		
1 year post starting medication		
HCV PCR monitoring will then continue annually		

Please bring this leaflet when you attend Transplant Clinic and discuss with the Doctor or Nurse you see – this will help ensure the correct HCV blood tests are ordered for you.

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Hepatitis C Virus (HCV)

Information for Transplant Patients who have received a Hepatitis C Infected Kidney

Cardiff and Vale University Health Board
Nephrology and Transplant Directorate/Pharmacy Directorate

Clinic: 02921 846639
Pharmacy: 02921 841222
Specialist Nurses: 02921 844817
Transplant Ward: 02921 842228

Nephrology & Transplant
Nefroleg a Thrawsblannu

What is Hepatitis C (HCV)?

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, although on average it takes thirty 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.

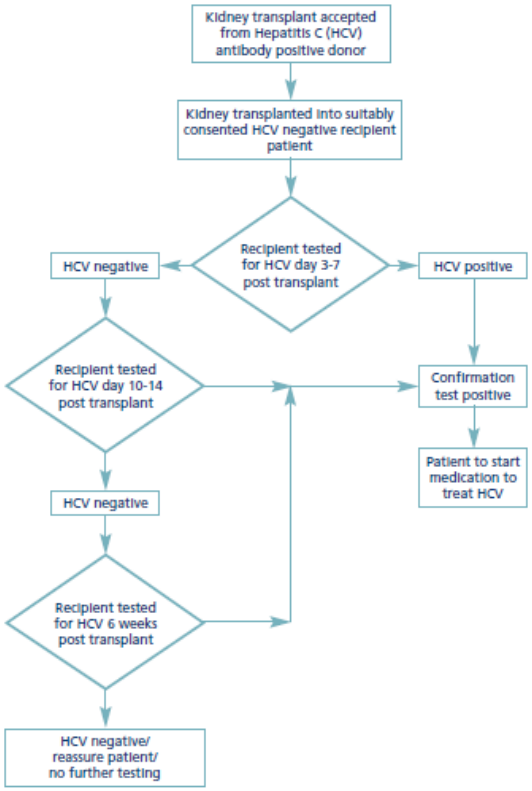
Treatments for Hepatitis C have changed greatly over recent years. There is a 1 in 2,500 chance that we will not be able to cure you of the virus. Treatment requires taking tablets for twelve weeks. Once the virus is cleared it does not come back and does not affect your long-term health.

Diagnosing HCV Infection

HCV is usually diagnosed by a blood test which checks for the presence of the virus in the blood stream (HCV PCR test).

We have a Protocol for checking for the HCV virus at various time points after the transplant (see chart below).

The first blood sample will be taken within the first seven days of your transplant, then again within the first fourteen days, and the last sample will be taken six weeks after your transplant. If the virus tests remain negative by that time, then your transplant organ has not passed on the infection to you and you will not require any further routine HCV blood tests.



Treatment and Monitoring

If any of these tests are positive for the Hepatitis C virus then the doctors looking after you will start you on highly effective antiviral treatment within 3-10 days of the result. We will aim to start the medication as soon as possible and continue for a total of three months.

During treatment you will have regular blood test at the Transplant Clinic to make sure that the treatment is working and that the virus is disappearing from your blood.

Once the treatment is finished you will have further blood tests to confirm that you have been cured of the virus.

These blood tests will be taken four weeks, twelve weeks, twenty-four weeks and one year after commencing treatment and will then be checked annually at the Transplant Clinic.

Close monitoring in the early stages after transplantation and rapid initiation of antiviral treatment if the virus is identified in your blood means that you are extremely unlikely to experience any symptoms of HCV. Successful treatment of HCV with antiviral drugs protects your liver and other organs in the short and long-term.

When the virus disappears from your blood and cannot be detected twelve weeks after the treatment has stopped then you have been cured. Unlike some other Hepatitis viruses, and the virus causing Chickenpox for example, Hepatitis C does not remain in the body in a dormant state which can potentially reactivate in the future.

For Patients Starting Antiviral Drugs

Name of Antiviral Drug: _____

Dose: _____

(tablets should be taken with food)

Date Treatment Started: _____

Duration of Treatment: _____

The antivirals are extremely effective at curing the viral infection but it is vital to take the tablets as advised and to complete the course. They are also very safe drugs and there are no particular side effects to watch out for but please report any problems to the Transplant Team.

Results so far

11 patients transplanted since programme commenced on 26th May 2019

Donor details

Donor number	Age	Sex	CoD	Creat	Genotype	Viraemic?
1	37	Male	Trauma	45	3a	yes
2	35	Male	Hypoxic Brain Injury	84	3a	yes
3	23	Male	ICH	57	3a	yes
4	42	Male	Trauma	39	1a	yes
5	50	Male	ICH	65	TBC	yes
6	36	Male	Hypoxic Brain Injury	52	1a	yes
7	63	Male	Hypoxic Brain Injury	42	TBC	no

Recipient Details

Patient	Age	Sex	Aetiology Renal Failure	Waiting time	Mode of dialysis	HLA mismatch	CIT (h:m)	Induction	Maintenance
1	63	m	FSGS	8m	HD	2:2:2	10:07	ATG	Tac/MMF/pred
2	74	f	FSGS	9m	PD	2:2:1	15:52	ATG	Tac/MMF/pred
3	70	m	DN	21m	PD	1:1:1	11:38	Campath	Tac/MMF
4	31	m	Unknown	4m	HD	1:2:1	10:51	Campath	Tac/MMF
5	33	m	Renal Dysplasia	1m	Failing Tx	1:2:0	14:53	Campath	Tac/MMF
6	77	m	Unknown	15m	Pre	2:2:2	12:33	ATG	Tac/MMF/pred
7	47	m	DN	16m	HD	1:2:1	8:27	Campath	Tac/MMF
8	70	m	Unknown	30m	Pre	0:2:2	13:12	Campath	Withdrawn
9	27	m	Renal Dysplasia	7m	APD	0:1:1	12	ATG	Tac/MMF
10	66	m	AKI	7m	HD	1:2:1	13	Basiliximab	Tac/MMF
11	72	f	Presumed GN	8m	PD	1:2:1	17	Basiliximab	Tac/MMF

Outcomes

Patient	First HCV +ve (days)	Max viral load	Renal function starting DAA	DAA regimen	Week 4 HCV PCR	Week 12 HCV PCR	Week 24 HCV PCR	Latest function
1	10-14	121176	Creat 281 eGFR 20	Maviret	<12	Not detected	Not detected	Creat 130 eGFR 48
2	10-14	89661	Creat 247 eGFR 21	Maviret	13	Not detected	Not detected	Creat 100 eGFR 47
3	3-7	5285	Creat 88 eGFR 74	Epclusa	Not detected	Not detected	Not detected	Creat 88 eGFR 76
4	10-14	104	Creat 138 eGFR 56	Epclusa	Not detected	Not detected	Pending 27/1/20	Creat 97 eGFR 66
5	10-14	1476	Creat 118 eGFR 61	Epclusa	Not detected	Not detected	Pending 27/1/20	Creat 121 eGFR 60
6	3-7	24191	Creat 288 eGFR 19	Maviret	<12	Not detected	Not detected	Creat 95 eGFR 79
7	3-7	240	Creat 190 eGFR 33	Epclusa	Not detected	Not detected	Pending 18/02/20	Creat 129 eGFR 47
8	3-7	59	Creat 178 eGFR 33	Epclusa	Not detected	Not detecte	Pending 14/02/	Tx Neph-rectomy

Results so far: Summary

- 6/7 HCV antibody positive donors have been viraemic; Confirmed genotypes 1a (n=2), 3a(n=2), TBC (n= 3)
- SVR 12; 4/11 have a documented SVR 12, 5 further results are pending in January 2020 (n=2), February 2020 (n=2) and April 2020 (n=1)
- 2 other patients transplanted on 13/1/2020 so just commenced testing algorithm

positive transplant programme in Cardiff

- DAAs well tolerated (some nausea and vomiting)
- Tacrolimus levels OK – usual variation expected for new transplant patients (interaction with Maviret doesn't appear to be strong)
- Switching DAA if renal function goes up or down?
  - Maviret to Epclusa if eGFR >30ml/min?
  - Epclusa to Maviret if eGFR <30ml/min?
  - No and no
- Interactions
  - 7 of the 8 patients on statins (all withheld for DAA course)
  - All 8 patients on PPIs or H2As (all stopped or switched to PRN)
- Clinic doctors told to check with pharmacist before prescribing anything new
- Patients told to tell any doctor they are seeing (primary or secondary care) about their DAAs

positive transplant programme in Cardiff

- 6/7 Hep C antibody positive donors have been viraemic
- The guideline development group, as the “experts” need to provide support, information and reassurance to
  - Patients
  - Transplant team on ward
  - Transplant team in clinic
- Keep reviewing processes (simple and complex)
  - Open discussions if any aspect not working well
  - Understand how other specialities work (eg virology, ID etc)

Media Interest

"When the team asked me would I consider a donor with hepatitis C, I didn't hesitate, I jumped at the chance. I felt I had nothing to lose." "Saying thank you isn't enough because what they have given me is simply my freedom."

Here is the 6.30pm national news

https://www.facebook.com/ITVWales/videos/2575295442533284?sfns=mo

Thank you

- **Colleagues and Collaborators**-
- Dr. Sian Griffin, Mr Michael Stephens, Dr. Brendan Healy, Dr. Rachel Jones, Dr. Nicola Price, Robert Bradley, Rhys Oakley, Kymm O'Connor, Sharon Warlow, Beth Travers, Dr. Leah Mc Laughlin, Dr. Ahmed Elsharkawy

- **Any questions**?

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