

Using Hepatitis C Donor Organs in Adult Liver Transplant Candidates: Frequently Asked Questions

If you are a liver transplant candidate, you may be able to receive a Hepatitis C (HCV) donor organ. Doctors have begun using HCV donor organs for recipients without HCV infection to improve access to transplantation and reduce waitlist mortality (death). Continue reading to learn more about highly effective oral medications for HCV (DAA's), HCV testing, and receiving an HCV donor organ.

What is Hepatitis C?

Hepatitis C is a virus that infects the liver. If left untreated, it can lead to slowly progressing liver disease over 10 to 20 years.

Due to the large number of people infected with the **Hepatitis C Virus (HCV)** in the United States (about 4-5 million people), chronic (long-term) HCV has been a leading reason for liver transplantation. However, the number of people developing liver failure or liver cancer from HCV infection and needing a transplant has been decreasing recently due to the availability of highly effective medications called **Direct Acting Antivirals (DAA's)**.

Glossary:

HCV: Hepatitis C Virus

Direct Acting Antivirals (DAAs): highly effective Hepatitis C medications.

anti-HCV (+): HCV antibodies are present, indicating the person had HCV at some point.

NAT: Nucleic Acid Testing, searches for HCV genetic material (RNA) in the blood
HCV-RNA (the genetic material of the Hepatitis C Virus)

Anti-HCV (+) NAT (-) -: the person was infected with Hepatitis C, but the virus has now been cleared from the body

Anti-HCV (+) NAT (+) - person currently has the virus in their blood

Anti-HCV (-): Someone who does not have HCV antibodies in their blood, never infected.

How is Hepatitis C spread and diagnosed?

Hepatitis C is most commonly spread from one person to another through direct exposure to contaminated blood. Persons Who Inject Drugs (PWID) or use illicit drugs are at increased risk of acquiring and spreading HCV to others. The majority of people who get hepatitis C are unaware that they carry the virus because they do **not** develop symptoms like abdominal (belly) pain, fatigue, or jaundice during the acute infection.

The diagnosis of hepatitis C virus infection is made when an **antibody to the virus (anti-HCV)** is found in the blood. **Antibodies** are chemicals released into the bloodstream when someone gets infected. The antibody must turn positive within 2-4 weeks of exposure and remain detectable for prolonged periods of time for a reactive (positive) diagnosis to be made.

What do my HCV test results mean?

Non-reactive or a negative Hepatitis C Antibody Test result

- A non-reactive, or negative, antibody test means that a person does not have Hepatitis C.
- However, if a person has been recently exposed to the Hepatitis C virus, they will need to be tested again.

Reactive (positive) Hepatitis C Antibody Test result

- A **reactive (positive)** antibody test means the person has been infected with the Hepatitis C virus at some point in time.
- A reactive antibody test does not necessarily mean that the person **currently** has Hepatitis C.
- Once people have been infected, they will always have antibodies in their blood. This is true if they have cleared the virus or still have the virus in their blood.

- A reactive antibody test requires an additional, follow-up test to determine if a person is currently infected with Hepatitis C.

What to do if the Hepatitis C Antibody Test is reactive?

Nucleic Acid Testing (NAT) is the final step to determine if a person with a positive HCV antibody test has a current or past (resolved) HCV infection.

This blood test is very sensitive and looks for **HCV-RNA** (the genetic material of the Hepatitis C Virus).

- If the NAT follow-up test is negative - this means the person was infected with Hepatitis C, but the virus has now been cleared from the body.
- If the NAT follow-up test is positive- this means the person currently has the virus in their blood. If there is a reactive antibody test and a positive follow-up test, this means the person is HCV positive (+) and NAT positive (+) and the person needs to talk to a doctor experienced in diagnosing and treating Hepatitis C.
- Among the 4 million Americans exposed to HCV, nearly 20 out of 100 (20%) have **protective immunity** to the virus (anti-HCV + but NAT (-)) and are not infectious to others.
 - The remaining 80 out of 100 (80%) people with HCV + in the general population are NAT (+) and do have HCV that can be transmitted to others. HCV **genotypes refer to the strain of the virus that the person was exposed to when they were infected.** HCV genotypes 1, 2 and 3 account for over 95 out of 100 (95%) of the patients infected in the US.

Is Hepatitis C virus infection curable?

Yes. Oral medications for HCV (DAA's) have been very effective in curing infected HCV patients that are treated for 8 to 12 weeks. Currently, infected HCV patients have a 95-100% chance of achieving sustained virologic response at 12 weeks after completing treatment. **Virologic response** means that the hepatitis C virus is not detected in the blood during treatment. When the virus continues to be undetectable 12 weeks or more after completing treatment, this is a **“sustained” virologic response (SVR).**

Medications

Numerous DAA regimens have been approved for use in patients with chronic HCV infection by the US Food and Drug Administration (FDA).

- **Glecaprevir/ Pibrentenasvir (Mavyret or GP)** is one of the newly approved DAA regimens that works for people with HCV genotypes 1 to 6 and is also safe and effective in people with advanced kidney failure or on kidney dialysis.
- **Sofosbuvir/ Velpatasvir (Epclusa or SOF/ VEL)** is also approved for people with HCV genotypes 1 to 6 (pangenotypic) but **cannot** be given to people with advanced kidney disease or on dialysis.

How many organ donors have hepatitis C virus infection?

Deceased organ donors have a higher rate of carrying HCV infection compared to the general adult donor population.

- Deceased organ donors carrying HCV: 5 to 10 out of 100 (5-10%)
 - Among these, 70 to 80 out of 100 (70-80%) are **infectious** (i.e. NAT or HCV RNA positive) and capable of transmitting the virus during transplantation.
 - Of the estimated 10,000 annual deceased organ donors in the US, it is estimated that as many as 500 to 600 of them may have HCV infection.

In the past, HCV infected organs were directed to recipients with pre-existing HCV as the cause of their liver disease. This is no longer the case as the number of potential liver recipients with HCV has declined. Doctors have begun using anti-HCV + donor organs for recipients without HCV infection to improve access to transplantation and reduce waitlist mortality (death). Anti-HCV+ organs have HCV antibodies, meaning they had HCV at some point in the past, but this does not mean they still do.

How often are hepatitis C donor organs used in the United States?

Livers from organ donors with HCV infection have been used for over 20 years in the United States largely for recipients who already have HCV infection. Over 3,000 of these liver transplants have been completed to date.

Over the past 5 years, several transplant centers in the US have reported good outcomes when using anti-HCV + donor livers and kidneys into uninfected recipients. In this circumstance, the recipients provide written informed consent immediately before the transplant and they are carefully monitored for the appearance of detectable HCV RNA (HCV genetic material) in their blood for up to 12 months post- transplant.

What steps are taken if an uninfected recipient gets an anti-HCV+ liver and becomes infected?

If the recipients develop detectable HCV RNA, they are treated with potent DAA's for 12 weeks to rid the body and blood of detectable HCV RNA.

Although the numbers are small (less than 100) and the duration of follow-up is limited (less than 2 years in most), uninfected liver recipients of anti-HCV + donor livers have experienced excellent outcomes and survival.

Furthermore, use of a DAA regimen starting at 1 to 4 weeks after transplantation has been highly effective and well tolerated post transplant. To date, nearly **99 out of 100 (99%)** of patients receiving an infected donor organ are cured at 1-year post-transplantation after receiving a course of DAA therapy. At Michigan Medicine, we have transplanted over 20 anti-HCV + (infected) livers into anti- HCV + (infected) recipients and also transplanted anti-HCV + (infected) livers into a growing number of selected anti-HCV - (uninfected) recipients with good outcomes.

What is the risk of becoming infected with HCV if I receive an infected donor liver?

Donors with detectable HCV RNA at the time of transplantation have a nearly **100%** chance of spreading HCV infection to the recipient. Our protocol is to start DAA therapy in all recipients of a hepatitis C donor organ who become infected (HCV RNA +) after transplantation.

In contrast, donors who have had HCV but now have undetectable HCV RNA, spread active infection to only 5 to 20 out of 100 (5-20%) patients. If you receive one of these organs we would test you for HCV RNA at 1 week, 1 month, and monthly for the first year to see if you have acquired HCV infection and provide DAA therapy if HCV RNA is confirmed.

Why should I consider receiving an anti-HCV + donor organ if I currently don't have HCV infection?

Over the past 10 years, the number of deceased organ donors with HCV infection has been rapidly increasing. In 2010 there were an estimated 500 of these donors while in 2017 the number has increased to over 1000. Since many of these donors are young and otherwise healthy, these anti-HCV + donor livers function very well and there is only minimal or mild damage seen in the

liver at the time of transplantation. Remember, anti-HCV (+) means antibodies are present because the donor had HCV *at some point*, it is not certain whether there is a *current* infection.

Since there are more anti-HCV + livers compared to anti-HCV + recipients, liver transplant candidates without HCV infection who are willing to consider these organs can often get transplants more quickly. Therefore, potential advantages of receiving an anti-HCV + donor liver is a **shorter waiting** time to transplant and a lower likelihood of **dying** on the waitlist.

Potential downsides to accepting an anti-HCV + liver is that these recipients will **have to take a DAA regimen such as GP for 12 weeks after transplantation in case of a current infection.** People receiving GP are required to undergo additional blood test monitoring and be seen in clinic during and after treatment (Table 1, page 8). **Recipients of a hepatitis C donor liver must take all of the GP medication as prescribed.** The GP medication regimen has been well tolerated in liver and kidney transplant recipients so far. Nonetheless, there is a small (**less than 1%**) chance that the GP regimen may not be effective and the HCV RNA could remain detectable at 1-year post-transplant. In those circumstances, your Michigan Medicine liver doctor can prescribe other DAA drugs to you.

There is also a risk that an anti-HCV + donor liver could have pre-existing damage leading to lower long-term graft survival compared to a recipients of anti-HCV - donor liver. However, anti-HCV + livers are biopsied at time of donation and we only use livers with minimal to mild damage on biopsy. In our center, survival in recipients of anti-HCV + livers has been comparable to survival in recipients of anti-HCV - donor livers.

Am I at risk of acquiring other infections if I chose to receive an anti-HCV + donor organ?

All deceased organ donors undergo antibody and specialized testing for hepatitis C, hepatitis B, and HIV infection before they are used in transplantation. However, due to shared risk factors, hepatitis C donors are at greater risk of having hepatitis B or HIV infection but the overall likelihood of these viruses not being detected during organ donor screening is less than 1 in 100,000. Therefore, to maximize safety, all recipients of a hepatitis C donor liver will undergo testing for hepatitis B and HIV infection at 1, 3, 6 and 12 months after transplantation. If hepatitis B or HIV is transmitted, you would have a consultation with a Transplant Infectious Disease specialist and start antiviral therapy.

What direct acting oral antiviral agents are available to treat hepatitis C?

These are the DAA regimens that our center most commonly uses to treat patients with chronic HCV infection.

Type	Dose	Who can take it
Sofosbuvir/ Velpatasvir (SOF/ VEL)	Fixed dose combination given once a day in the morning with food	Effective in all HCV genotypes with an SVR in 95 to 99% of HCV patients. SOF/ VEL cannot be safely prescribed to patients with advanced kidney failure.
Glecaprevir/ Pibrentenasvir (GP)	Fixed dose combination of Glecaprevir and Pibrentenasvir.	Effective in all HCV genotypes with an SVR in HCV patients of 95 to

	<p>3 tabs taken together in the morning with food. The dose does not need to be reduced in patients with advanced kidney disease.</p>	<p>99%. GP is safe for patients with advanced kidney disease.</p>
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A note about GP: In transplant recipients, GP needs to be given for 12 weeks and daily doses should not be skipped since missing or delayed doses can lead to breakthrough infection and viral resistance. GP can be safely administered to transplant patients receiving tacrolimus, cyclosporine and everolimus. We will delay starting GP therapy until the person is stabilized and able to swallow pills and food and has been transferred out of the intensive care unit. We will also wait until the liver blood tests have improved. Our goal is to start GP in all recipients of anti-HCV + livers **before discharge** from their transplant admission and GP will be continued for a total of 12 weeks after initiation.

When will I receive antiviral medication for newly acquired HCV infection?

If you develop detectable HCV RNA, we will plan to start the medication during your transplant admission. Plans for further refills (to complete at a total of 12 weeks of treatment) will be made at the time of discharge. If you are discharged to a rehab facility, we will arrange to give you an adequate supply of GP.

If you do not develop evidence of active HCV infection with detectable HCV RNA by the time of discharge, you will continue to be monitored for late appearance of HCV RNA up to 1 year post-transplant. All recipients of anti-HCV + donor organs are required to undergo a series of blood tests and clinic visits as follows:

Table 1- Lab monitoring schedule during GP therapy in recipients of anti-HCV (+) livers

Testing	Day 1	Day 3	Day 7	Week 2	Week 4	Week 8	Week 12	Fu week 4	Fu week 12	Fu week 24	FU Week 48
HCV RNA	x	x	x	x	x	x	x	x	x	x	x
HCV Genotype	x										
Blood, chemistry, CSA/ Tacro	x		x		x	x	x		x	x	x
Clinic visit	x		x		x	x	x			x	x

Will my insurance company cover the costs of the antiviral medications for hepatitis C?

Most insurers will continue to provide DAA’s to recipients of a hepatitis C donor organ if it has been started during the transplant admission. Before transplantation, we will check your pharmacy benefits and determine if GP is a covered medication and what your anticipated co-pay will be. We will let you know if it is not a medication on the formulary of your prescription medication plan, and will not plan to use a hepatitis C donor organ unless a financial payment plan has been pre-arranged. The exact cost of GP treatment for 12 weeks is difficult to know with certainty but the average wholesale price in the US as of December 2018 is **\$45,000**.

If your insurance changes or if they refuse to provide the DAA regimen after receipt of a hepatitis C donor liver, the Michigan Medicine Transplant center will work with you and your insurance company to develop a plan to cover the costs of a course of GP or other effective DAA treatment for a maximum of 12 weeks.

Will any of the DAA medications interact with my other transplant medications?

DAA medications will not interact with the standard anti-rejection medications (tacrolimus, mycophenolate, steroids) and other medications to prevent bacterial, viral, and fungal infections. People who are on a statin medication for high cholesterol and other people receiving some anti-convulsants may have to have those medications held or temporarily discontinued during GP therapy. A list of medications to avoid or not use will be provided to you at the time of discharge from the hospital.

What if I develop recurrent hepatitis C infection despite taking these medications?

If you do not achieve SVR (are not cured) after a full course of GP for 12 weeks and remain HCV RNA +, you may have developed drug resistant infection. In that case, we will do specialized testing of your blood. Based upon that testing you will be offered treatment with an alternative DAA regimen that contains sofosbuvir.

Would I be eligible to receive a 2nd liver transplant if needed after I receive an anti-HCV + donor liver?

Yes. If you develop graft failure after your first transplant (which happens in less than 5% of all recipients), you would still be eligible to receive a second transplant based upon your medical and surgical status.

Will I be infectious to family members if I receive an anti-HCV + donor organ?

- Hepatitis C is not passed from person to person through casual contact (like hugging or shaking hands) or sharing things like utensils, glasses, or towels.

- Hepatitis C can be transmitted through infected blood (e.g., sharing needles). You should avoid activities such as sharing razors.
- Sexual transmission is low risk, but can occur. Condoms should be used until the virus is gone from your system.
- After the Hepatitis C is cured (by taking the medications), there is no risk of transmission to another person.

References

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