**Hepatitis C Human Challenge Study Overview**

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1Day Sooner is organizing healthy volunteers potentially willing to join human challenge studies for hepatitis C. In a human challenge study, participants are exposed to a disease in a controlled setting to study the efficacy of a vaccine or treatment, or to learn more about the disease itself. These studies are likely to be approved in Canada and/or the UK in 2024 and begin recruitment by early 2025. There are effective treatments for hepatitis C, but no vaccine, and it has been very difficult to run non-challenge studies to test hepatitis C vaccine candidates.

1. **In 2019, hepatitis C caused over half a million deaths by one estimate, a number that is projected to more than double by 2040.** Hepatitis C is a blood borne viral disease that causes damage to the liver over many years. Most people don’t have noticeable symptoms, so they may not know they have hepatitis C until their livers have already developed severe damage or cancer decades after infection. Even though there are now highly effective treatments, tens of millions still live with the disease, and access to treatments is not available for many of the world’s poorest. Vaccines could greatly accelerate the fight against the disease.

2. **Getting exposed to hepatitis C in controlled studies would be a concrete way for volunteers to help accelerate the development of vaccines.** Studies will be outpatient, so participants would not need to spend long periods of time in a hospital or clinic, though they should be prepared for frequent visits to monitor their health and the course of infection.
   a. Hepatitis C is highly treatable and long-term health effects are not expected to occur because of the short term of infection.
   b. Participation would be a minimal risk to others. As a bloodborne disease, hepatitis C is extremely difficult to spread through everyday contact or sex.

3. **There are no strong alternatives to challenge studies for vaccine testing.** This is the main reason leading researchers to call for human challenge studies in recent years.
   a. Testing on the only nonhuman animal that can naturally get hepatitis C, the chimpanzee, is functionally banned in North America and Europe.
   b. There have been only two preventative hepatitis C vaccine trials in humans. The most recent took six years to test an ultimately unsuccessful vaccine. A challenge study could take as little as a year, identifying vaccine candidates that do appear to work and ensuring further time and resources are only spent on them.
Extended Hepatitis C Q&A

So you’re thinking about getting hepatitis C! Congratulations. This fact sheet is to help answer questions you might have when considering joining a challenge study. 1Day Sooner is working with researchers — including on things like design of study protocol — but we do not conduct medical studies and do not officially represent them.

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Hepatitis C: The Basics

Hepatitis C is a liver disease caused by the hepatitis C virus (HCV). *Hepatitis* is the medical term for inflammation of the liver. Hepatitis C is *chronic* if it lasts for six or more months, and *acute* before that. Hepatitis C is curable, but can be deadly over the course of decades if left untreated.

**What does a hepatitis C infection do?**

The hepatitis C virus invades the liver, causing inflammation and damage over time. If left untreated for many years, hepatitis C can seriously harm the liver. The WHO estimates that between 15% to 30% of people with chronic hepatitis C will develop cirrhosis (severe scarring that causes the liver to fail) within 20 years (*WHO 2022*). A smaller number could develop liver cancer, which generally takes at least two decades of infection (*Andrade et al. 2009*). Damage to the liver in the short term (a few weeks or months) is considered minimal (*Liang et al. 2021; Barnes et al. 2022*).

**How does hepatitis C usually spread?**

Hepatitis C is mainly spread through contact with infected blood. It is not spread through the air or everyday contact with an infected person, so you wouldn’t be putting roommates, friends, or family at risk if you were infected as part of a challenge study.

In North America and Europe, people often contract it after reusing needles that have been used by others with the disease; people who inject drugs are at very high risk of getting hepatitis C. It could also spread if you shared, say, a toothbrush or nail clippers with someone who has it, because those might have microscopic amounts of blood on them (*CDC 2020*).

In the developing world, it is also spread through unclean medical equipment and blood transfusions, as blood supplies are often inadequately screened for diseases (*Roudot-Thoraval 2021; Martinello et al. 2018*). Transmission to infants during birth from mothers is possible but uncommon (*Liang et al. 2021*).

If someone is pregnant with hepatitis C, they could also transmit the virus to the baby if they give birth. Any human challenge study with hepatitis C will require people to use contraceptives to avoid becoming pregnant.
Can hepatitis C be spread through sex?
Transmission via sex is possible but rare. Analysis of several studies suggests there is minimal risk among monogamous heterosexual couples where one person is hepatitis C-positive. One review estimated that the chance that an instance of heterosexual sex between an infected and uninfected partner resulted in infection was roughly 1 in 10 million (Tohme & Holmberg 2010). A later study of a cohort of 500 heterosexual couples across several years estimated the risk as 1 per 190,000 sex acts (Terrault et al. 2013). Hepatitis C human challenge study participants will likely be required to use contraception to further decrease any risk.

Some, but not all, studies have found that transmission is more likely among men who have sex with men, but it is still fairly low (Tohme & Holmberg 2010).

How many people die of hepatitis C worldwide?
Even though effective treatments exist, an estimated 542,000 people died of hepatitis C-related causes in 2019 (Global Burden of Disease 2019). In general, people in poorer regions are harder hit by hepatitis C, but it is a problem worldwide (WHO 2021).

The WHO estimates that there were around 58 million people living with hepatitis C in 2019, with up to 1.8 million people infected that year (WHO 2021). By 2040, yearly deaths are projected to reach 1.2 million. At that point, hepatitis C would likely be killing more people per year than diseases like HIV/AIDS, malaria, or brain cancer (Foreman et al. 2018; Thomas 2019).

Is there a cure for hepatitis C?
Yes. Today, hepatitis C is curable in almost all cases with a class of drugs called direct-acting antivirals (DAAs), which have a success rate as high as 95–99% (Kish et al. 2017; Liang et al. 2021). Cure rates are especially high among people without existing liver problems and who have not had hepatitis C for a long time (Barnes et al. 2022) — the exact kind of person who would be accepted into a human challenge study.

Even if the first round of DAA treatment fails, a second round can be given, with a success rate about as high as first-round treatments (Sagnelli et al. 2018; Liang et al. 2021). One study, Martinello et al. 2023, examined 23 documented cases of retreatment for hepatitis C following failure of the first round of treatment. Of those 23 people that researchers were able to find complete information on, one was lost to followup (they stopped coming in for treatment). 100% of the remaining 22 were cured. Additional treatment failure is possible, however, and would warrant additional rounds of treatment.
Viral samples used for challenge studies will be tested for DAA resistance before being used to infect participants. If a sample showed any signs of resistance, it would be destroyed and never used in a participant.

**If there’s a cure, why do we need a vaccine for hepatitis C?**

The development of effective DAA treatments was a major breakthrough in the fight against hepatitis C, but treatments alone appear unable to bring the disease under control. In many countries, more people are infected with hepatitis C each year than are successfully treated for it (El-Sayed & Feld 2021; Thomas 2020). Infection does not necessarily grant immunity, so even if you are cured of hepatitis C, you can still catch and spread it again (Bailey, Barnes & Cox 2019).

The distribution and administration of treatments, which require regular adherence for several weeks or months, is also difficult. Currently, hepatitis C treatment reaches less than one in six people who need it globally, and in Africa, just 1% had received treatment by 2019 (WHO 2021). Treatments have fallen off since their peak in 2015, as the easy-to-reach patients have been reached already (Bailey, Barnes & Cox 2019; Cox 2020). Even in the United States, fully treating certain populations has proven extremely hard (Florko 2022). There is evidence that some strains of the hepatitis C virus are evolving resistance to DAAs as well, and that those strains can be transmitted to others, which may become increasingly common as DAAs are deployed more widely (Bailey, Barnes & Cox 2019; Chen et al. 2016; Cox 2020).

The WHO in 2016 proposed a plan for massive reductions in hepatitis C to eliminate it as an ongoing public health threat by 2030 without vaccines, but most countries are not meeting those targets five years in (Pedrana et al. 2021, Thomas 2019).

Ultimately, no infectious disease has ever been eliminated through treatment alone. For example, despite effective treatments that suppress HIV and prevent its spread to others, it still kills up to 1 million people per year (WHO 2022). An even more extreme example is syphilis, which can be cured by a single shot of antibiotics, but still caused an estimated 49.7 million infections in 2019 (CDC 2022; Global Burden of Disease 2019).
Can people fight off the infection without treatment?
Between 15% to 45% of people fight off the virus on their own, according to the WHO. For everyone else, the disease becomes chronic, remaining in the liver forever unless treated (Grebley et al. 2012; WHO 2022).

The Purpose of Hepatitis C Challenge Studies
The classic challenge study is used to test a vaccine, but before full vaccine efficacy challenge studies take place, a number of other steps must be taken. Information from this section is drawn from 1Day Sooner’s conversations with researchers, physicians, and other specialists and examination of hepatitis C challenge study grant application documents currently under review.

Where will the hepatitis C sample come from?
Researchers will obtain samples of major hepatitis C virus genotypes (different variants of the virus) from the blood of consenting individuals who already have hepatitis C. The samples will be tested for signs of any viral resistance to treatments and to make sure there are no other diseases present in the blood. The donors will then be treated, and only after they are successfully treated will the viral samples then be used in a challenge study.

What is a sentinel study?
The sentinel study (or sentinel trial) is a challenge study without a vaccine. It is the first challenge study that will occur. Researchers will infect participants with one of the hepatitis C virus genotype samples, monitor their health, and then administer treatment after a few months. This establishes the minimum amount of viral material needed to cause an infection and further confirms that the viral sample is not treatment resistant.

Why can’t vaccine developers just go straight into field trials?
They have tried! Field trials (where hundreds or more volunteers are given a vaccine, and then scientists track whether or not they are infected with a disease naturally) will likely be necessary after a successful challenge study. But field studies are extremely time-consuming and difficult. Challenge studies will ensure that the huge amount of time, effort, and resources are only spent on the most promising vaccine candidates. Right now, the cost and effort are so large that even though there are candidates that could be tested, there are no currently running vaccine efficacy field trials.
Why are field trials so difficult for hepatitis C? Some diseases (like Covid-19) spread so rapidly that there is enough circulating virus in a population to make field testing fairly easy. In other words, if you give an experimental vaccine to 1,000 people, you can reasonably expect that a decent number of those 1,000 people will be exposed to the Covid-19, providing enough data to analyze the vaccine’s efficacy.

That’s not really the case for hepatitis C, despite the tens of millions of people who live with it worldwide: because it is bloodborne, it spreads much slower than a respiratory disease like Covid-19 or the flu. In the industrialized world, studies must enroll people who inject drugs (PWIDs), the only major demographic group where the disease is relatively common (Lancet 2019; Barnes et al. 2022).

The most recent hepatitis C vaccine efficacy trial took six years and involved over 500 PWIDs. The vaccine candidate was ultimately ineffective (Page et al. 2021; Liang 2021). (Dr. Andrea Cox, who oversaw the study’s implementation, wrote an article about the difficulties she and her team faced and why it demonstrated the need for human challenge studies.) Such non-challenge studies present serious logistical and scientific challenges for researchers, as well as ethical concerns related to interacting with at-risk individuals (Cox, Sulkowski & Sugarman 2020). Indication of vaccine efficacy could be gathered in much less time, likely under a year, via human challenge studies.

**Why infect humans? Why not animals?**
Some animals like mice have been used to study aspects of hepatitis C, but in general, mice do not naturally contract hepatitis C. Testing a human vaccine in non-humans cannot provide definitive information on how effective the vaccine will be in humans, which would be necessary to license any vaccine for widespread use.

Humans and chimpanzees are the only two species known to naturally contract hepatitis C, and there are serious legal restrictions and moral concerns regarding use of chimpanzees (which are an endangered species) in medical research, with functional bans or moratoriums in many countries, including the U.S. (Berggren, Suzuki, & Ploss 2020; Cox, Sulkowski & Sugarman 2020; NIH 2015). While some other animals can be used as partial models, there are numerous practical obstacles to their scientific utility and ability to be used in vaccine testing, and chimpanzee infections still differ in several key ways from human infections (Burm, Collignon, Mesalam & Philip Meuleman 2018). The end of chimpanzee research seriously hindered hepatitis C vaccine development, and is one of the reasons many researchers are now advocating for human challenge studies (Liang et al. 2021).
What would happen after a vaccine efficacy challenge study?

Ultimately, candidates that perform well in challenge studies will likely advance to phase III field trials, as licensing based solely on challenge studies has been done only once before, for a cholera vaccine for adult travelers (McCarty 2021). Some researchers believe that a candidate previously tested in chimpanzees before the moratorium on primate experiments could also be approved based on challenge studies alone.

Regardless, the use of challenge studies will minimize time and resources devoted to running further trials for vaccines that are ineffective, thereby making research into vaccine candidates less risky. The ability for hepatitis C vaccine researchers globally to see results from other challenge studies can also enable them to optimize their own vaccine research strategies in response.

How do we know an experimental vaccine is safe?

Before a full dose of an experimental vaccine is given to anyone in a challenge study, researchers run safety studies. After studies in animals, the vaccine is given to groups of participants, usually starting with very small doses. The participants are monitored to make sure there are no serious reactions caused by the vaccine. Usually, about 20-100 people will have volunteered in this kind of study (FDA 2020). It is still possible that there are severe reactions to a vaccine, and study coordinators may ask you to monitor the injection site and be on the lookout for any serious symptoms just in case. (Initial hepatitis C challenge studies will not use vaccines, because they will be focused on developing the infectious sample of viral material needed for future vaccine studies.)

Being in a Hepatitis C Challenge Study

Recall that there are different types of challenge studies. In the next one to three years, we expect non-vaccine efficacy trials (namely, the sentinel study, see above) to begin recruiting. The primary difference as far as participant experience is concerned is that the sentinel study may have participants infected for a few months longer before receiving treatment, and there will be no vaccine used.

Where will these studies be?

Once the human challenge study model is established and standardized samples of the hepatitis C virus are made, they could be run anywhere in the world. For now, we anticipate the initial studies to be in Toronto, Canada, and Oxford, United Kingdom, and possibly somewhere in the United States East Coast. These will likely begin by early 2025.
What would a hepatitis C challenge study be like?
Details for specific studies will be made available to everybody before they consent to participation. In general, participants in the initial sentinel study/studies could expect:

- the screening process, which would include an examination of medical history, discussion of risks and the protocol for the specific study, and may also include things like blood tests;
- “challenge” day, when participants are exposed to the virus through a blood sample that has been screened and confirmed to be free of other diseases except hepatitis C;
- various visits throughout the duration of the trial to monitor infection and the health of the participant, which will include blood draws; and
- treatment in the form of daily DAA pills administered after two, three or six months, depending on the study, followed by occasional visits to ensure the participant remains healthy and has been totally cured of hepatitis C.

How often would I need to visit the study site?
This will depend on the individual trial. While trials will be outpatient, so participants won’t need to spend entire days or nights at a clinic, there will be a significant number of shorter visits to draw blood and otherwise monitor their health and the progression of the disease. The number of visits depends partially on an individual’s response to the disease and the specific study location, but a low estimate would be 20 visits over the course of about a year, but likely anywhere from 30-50 visits, which could mean up to 60 hours in a clinic over the course of a year. The first month or two would likely have a lot of visits, with fewer as time goes on.

How would participation in a human challenge study help develop a vaccine?
A candidate vaccine is an educated guess based on scientists’ knowledge of the immune system and hepatitis C. They will not know for certain if it will work until it is tested. Using a challenge study, researchers can determine whether the experimental vaccine looks like it helps protect against the disease in a controlled setting by tracking participants’ health directly.

What to Expect if You Get Hepatitis C
What are symptoms of acute hepatitis C like?
About 80% of people with hepatitis C have no symptoms before liver issues appear years or decades after infection (WHO 2022). For those who do experience symptoms, they usually start between 2 and 12 weeks after a new infection (CDC 2020). The symptoms are generally mild and intermittent (Tran 2012; Barnes et al. 2022).
Possible symptoms include: fever, fatigue/tiredness, nausea, vomiting, loss of appetite, dark urine and light stool (poop), abdominal pain, and jaundice (yellow-tinged skin and eyes).

Research into symptoms of acute (under 6 months) hepatitis C infection is far less extensive than chronic infection because acute infection usually goes undetected (Cox et al. 2008). Early studies noted that the symptoms could last from 2–12 weeks (Hoofnagle 1997). 1Day Sooner spoke with several scientists and physicians experienced in the study and treatment of hepatitis C, and the general consensus was that symptomatic acute infection was rarely serious enough to cause major problems in daily life and work for extended periods of time (on the scale of several weeks). There could still be several days or even more where you feel very unwell.

**What are short-term risks involved in getting hepatitis C for a few months?**

There are two main kinds of short-term risks to your health in a hepatitis C human challenge study. First, there is the risk that you get a symptomatic acute infection, and experience at least some of the symptoms described above, which are usually mild, but could affect your daily life.

Second, there is the very small risk of fulminant hepatitis — liver deterioration and failure that occurs very rapidly, within days or weeks. It may also be called fulminant hepatic failure or acute liver failure (Bernal & Wendon 2013). The risk of fulminant hepatitis due to acute hepatitis C infection is very low. A 2008 review in *Lancet* described hepatitis C as “almost never” causing it (Maheshwari, Ray & Thuluvath 2008). The most comprehensive study to date observed 2,332 patients with acute liver failure and 667 with acute liver injury (but not yet failure) in North America from 1998 to 2017, a total of 2,999 cases. Among these 2,999 cases of acute liver failure or injury, 62 patients had chronic hepatitis C, and just 3 had acute hepatitis C alone. Each of these three had a condition that increases the risk of hepatitis C complications and would exclude someone from participating in challenge study. Each of the three recovered with treatment (Rao et al. 2022).¹

Acute hepatitis C is thus very rarely the cause of liver failure, and it is likely an even rarer chance in otherwise healthy people who would be eligible for a challenge study.

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¹ The study did not specify when these cases occurred or what treatments were used. If they were before the mid-2010s, it’s likely they were treated with the previous generation of less effective antivirals. Two of the three cases in the North America study recovered after treatment. The third underwent a liver transplant before treatment (the hepatitis infection was not discovered until after the transplant, at which point treatment was successfully administered).
Finally, DAAs are another defense if there are signs the liver is starting to fail. In 2019, doctors in Japan published a case report of an elderly man with acute hepatitis C and rapidly deteriorating liver function that was at high risk for soon progressing into fulminant hepatitis. The man was treated with DAAs and fully recovered (Hatanaka et al. 2019).

**What are long-term risks involved in getting hepatitis C for a few months?**

Liver damage via hepatitis C occurs over many years of infection, usually decades, so there would likely be very little impact on someone who only has it for several months, as is the case in a human challenge study (Liang et al. 2021). Evidence from two cohorts of people in Germany and Ireland who were infected with hepatitis C accidentally after blood transfusions suggests that healthy people who recover from short-term infection are not at higher risk for liver cancer or cirrhosis (serious liver damage). These two cohorts consisted of hundreds of people who were infected with hepatitis C and cleared the virus naturally before their infections became chronic (long-term). Researchers followed up with them for decades afterwards, and none of them contracted liver cancer (Hsu et al. 2023).

There is some evidence that chronic hepatitis C infections change the organization of genes (epigenetic changes) that may increase the risk of liver cancer; evidence also suggests these changes are only in those who already have significant liver damage, which would not be the case for challenge study participants (Perez et al. 2019; Liang et al. 2021; Barnes et al. 2022).

There is no such thing as “long hepatitis C” as with diseases like Covid-19, and hepatitis C does not have any inactive, dormant phase where it is undetectable to modern testing (it may take a week or two to detect immediately after infection, however).

**What is treatment for hepatitis C like?**

Direct-acting antiviral (DAA) treatment involves tablets taken daily, usually for two or three months. Anyone in a hepatitis C challenge study will be given treatment for free. There are several different types of DAA. In general, they do not usually cause many side effects. The most common side effects of DAAs include headaches, nausea, and fatigue (Madeira et al. 2017; WHO 2022).

Here are the most common side effects of three common DAAs:

- Mayvret: headache (9% of people), nausea (6%), and diarrhea (5%). 98% of side effects were “mild or moderate” (Mayvret prescribing information).
- Epclusa: headache (22%), fatigue (15%), nausea (9%), asthenia (weakness, 5%), and insomnia (5%). Of those who experienced any side effects, 79% were grade 1 (mild) severity (Epclusa prescribing information).²
- Harvoni: headaches (14%), fatigue (13%), nausea (7%), insomnia (5%), and diarrhea (3%). The “majority” of these side effects were grade 1 (Harvoni prescribing information).

Note that the above numbers record if recipients felt the symptoms at any point during treatment, and do not necessarily mean recipients felt the symptoms for the entire time they were receiving treatment.

**Will I be able to donate blood in the future?**
Probably not. Past infection with hepatitis C, even if successfully treated, makes you ineligible for blood donation in many countries, including the United States and Canada (American Red Cross; Canadian Blood Services). Likewise, in the United Kingdom, hepatitis C virus antibodies are disqualifying (IPAC) — and most people who have hepatitis C develop antibodies (Martinello et al. 2018).

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² Grade 1 symptoms are generally mild, “causing no or minimal interference with usual social [and] functional activities” (NIH DAIDS 2017).