

In February 2009, at the 16th conference on Retroviruses and Opportunistic Infections in Montreal, Dr. Daniel Fierer from Mt. Sinai School of Medicine in New York City presented some alarming findings on rapid liver fibrosis (or scarring of the liver) in gay men co-infected with HIV and Hepatitis C (HCV).

On March 17, 2009 the Conant Foundation sponsored a Community Forum where Dr. Fierer presented his findings to a packed room at the LGBT Center in San Francisco. Dr. Fierer also discussed variables in treatment for HCV infection and new treatments coming down the research pipeline. His presentation was followed by a question and answer session with the audience. Dr. Fierer was joined in the Q&A by Dr. Brad Hare, M.D. and Dr. Marion Peters, M.D., who have tracked the growing number of patients co-infected with HIV and HCV at San Francisco General Hospital.

This forum was meant to raise awareness, and indeed alarm, about the medical consequences of HIV/HCV co-infection. The Conant Foundation believes HCV is a formidable foe, deserving of our community's attention and response. HIV and HCV co-infection doesn't mean sure death, but it *can* be fatal. Prevention, through condom use, is still key.

BACKGROUND ON HEPATITIS C

What is Hepatitis C?

Hepatitis C (HCV) is a virus spread by blood-to-blood contact, usually through the sharing of needles. Although less common, HCV can be sexually transmitted. This can occur if, for example, someone has an open wound or sore and comes in contact with the blood of an HCV infected partner during sex.

Hepatitis C attacks the liver. The virus can cause scarring to the liver (called fibrosis) or advanced scarring (called cirrhosis). Those with cirrhosis can develop liver failure or liver cancer.

How common is Hepatitis C?

Hepatitis C is much more prevalent than HIV. While there are 40 million people estimated to be infected with HIV worldwide, there are 270 million (or almost 7 times more) infected with Hepatitis C. In the U.S. alone, 1.2 million people are living with HIV, compared to 3.7 million infected with Hepatitis C.

How is Hepatitis C diagnosed and treated?

In the first six months of infection, Hepatitis C is called "acute." (In this case "acute" refers only to the duration of the infection, not its severity.) Patients with acute HCV often have no symptoms. There is no specific test to identify acute HCV. Rather, acute HCV infection is diagnosed if two of the following three are confirmed:

1. Seroconversion (this means that the body is producing HCV antibodies). This usually occurs 8 to 10 weeks after infection.
2. ALT tests are more than 5 to 10 times higher than normal. This usually occurs 2 to 8 weeks after infection. (ALT tests are used to detect liver damage by measuring levels of certain enzymes in the blood.)
3. HCV viral load fluctuates widely.

In 15-20% of cases the immune system is able to clear the virus from the body during the acute stage. This is called “spontaneous clearance.” No treatment is required. If 6 months after infection the virus is still present then it is referred to as “chronic” Hepatitis C.

The treatment for Hepatitis C is a combination of two medicines, interferon and ribavirin. Interferon is injected; ribavirin is taken orally. If treatment is started during the acute phase it is taken for six months. If begun after the infection is chronic then it must be taken for an entire year. Side effects from the treatment can include: flu-like symptoms, irritability, depression, concentration and memory problems, skin irritation, fatigue and insomnia, anemia, itchiness, nasal congestion, skin irritation, fatigue and birth defects.

Hepatitis C is considered “cured” if 6 months after the completion of treatment viral load is undetectable. This is called a sustained virological response, or SVR. We know that the likelihood of SVR is impacted by how early treatment begins. In general, treatment begun during the acute phase is twice as successful as treatment begun after the infection is chronic.

Other important factors include the genotype of the Hepatitis C virus and whether someone is also co-infected with HIV. (Genotype refers to the genetic characteristics of a cell or organism. Viruses can have multiple genotypes.) Genotype 1 (the most common genotype) and 4 are harder to treat than 2 and 3. On average, treatment cures about 50% of genotype 1 cases. However, this success rate drops to 25% if someone with genotype 1 HCV is also infected with HIV.

If treatment is unsuccessful those infected with Hepatitis C are at risk for liver damage and disease. It is estimated that 30-40% of HCV infections result in chronic liver disease, 15% progress to cirrhosis and 5% turn into liver cancer.

Can't I get vaccinated for Hepatitis C?

There is no vaccine for Hepatitis C.

There is, however, a vaccine for Hepatitis B, another infectious virus that attacks the liver. Those that contract Hepatitis B and C are at increased risk for developing liver cancer. *That's why it is very important to get vaccinated for Hepatitis B.* Dr. Conant noted that the AIDS community just lost a beloved member, Project Inform founding director Marty DeLaney, to liver cancer resulting from Hepatitis B infection.

Are there any new treatments in development for Hepatitis C?

Presidio Pharmaceuticals and Vertex Pharmaceuticals are working on developing new therapies for Hepatitis C. Vertex anticipates bringing a new drug to market some time next year. The clinical trial for the new drug is due to start shortly.

Has Hepatitis C infection always been prevalent amongst gay men?

No. The highest risk group for Hepatitis C infection was, and continues to be, injection drug users. Hepatitis C is highly contagious through blood-to-blood contact (and much more contagious than HIV).

There was very little evidence of sexual transmission of Hepatitis C amongst gay men in the 70s or 80s. Gay men who were not injection drug users were considered to have the same risk for Hepatitis C as the general population.

However, in 2004 sexual transmission of HCV in HIV positive gay men began to appear in the medical literature. This includes studies of acute HCV infection amongst HIV positive gay men in Paris, London, Switzerland and San Francisco.

DR. FIERER'S RESEARCH

Why is Dr. Fierer's research important?

Dr. Fierer's research adds to the growing body of evidence that sexually transmitted HCV infection is becoming more prevalent amongst HIV positive gay men. It also shows that HCV infection can be much more damaging in gay men already infected with HIV. More specifically, HIV and HCV co-infection appears to lead to more rapid and severe deterioration of the liver.

What inspired Dr. Fierer research into HIV/HCV co-infection?

Dr. Fierer presented the case of a 46 year old, HIV positive gay man. Initially, the patient had been diagnosed with asymptomatic HIV. His CD-4 count was 427 and his HIV viral load was low. He had also tested negative for Hepatitis C antibodies and had normal liver tests.

Three months after his negative Hepatitis C test, he returned for a follow-up visit during which he said he felt fine. He reported engaging in unprotected receptive anal intercourse with multiple men. He also reported using various drugs including crystal meth, cocaine and ecstasy. A second Hepatitis C antibody test came back positive. Results from a new set of liver tests were almost 20 times above normal.

During the next 2 months he was closely monitored by Dr. Fierer. As is common during the acute phase of infection, his Hepatitis C viral loads and his liver function tests

fluctuated widely. Ultimately, the patient was not one of the 15-20% whose immune system clears the infection.

At the end of two months, Dr. Fierer performed a liver biopsy to assess liver damage. The biopsy revealed the man was suffering from significant scarring to his liver. He was diagnosed with Stage 2 (of 4) liver fibrosis.

What was unique about this case?

Usually, Stage 2 fibrosis would occur in someone suffering from chronic Hepatitis C. It is very unusual to see that level of liver damage in someone who had been infected for such a short period of time (approximately 2 months). There were other factors that made this case stand out:

- The man was NOT an injection drug user.
- He likely contracted Hepatitis C through sex
- He was infected with HIV before he got Hepatitis C

This case inspired Dr. Fierer to do further research into Hepatitis C and HIV co-infection amongst gay men.

How did Dr. Fierer conduct his study?

Dr. Fierer identified 45 cases of HIV positive gay men who had Hepatitis C infection through the New York HCV referral network. The average age of the group was 40. Almost half (22) were white, 17 Hispanic, 5 African-American and 1 Asian. The duration of HIV infection ranged from 0 months (brand new) to 20 years. The median CD-4 count was 525 and almost a quarter had never been on anti-retrovirals.

His study was designed to answer the following questions:

What are the risk factors for contracting Hepatitis C amongst HIV positive gay men?

Of the 45 men identified, 21 were used to conduct a case control study on Hepatitis C risk factors. These 21 HIV positive gay men *with* Hepatitis C were compared to 21 HIV positive gay men *without* Hepatitis C (called the control group).

Other than their Hepatitis C status, the two groups were otherwise very similar in regards to their ethnicity, duration of HIV infection, CD-4 count and HIV viral load. The two groups were administered an extensive questionnaire about their sexual behavior, drug use, presence of other sexually transmitted infections, and other Hepatitis C risk factors over the prior 12 months.

Results showed that the following behaviors increased the risk for contracting Hepatitis C:

- Unprotected receptive anal intercourse (with or without ejaculation)
- Unprotected receptive oral sex with ejaculation
- Use of sex toys
- Sex while high
- Use of marijuana

How would study participants respond to treatment?

Of the 45 men in Dr. Fierer’s study group, 15 cases were diagnosed and able to begin treatment during the acute phase. Of those, 10 had completed treatment and were able to be assessed for SVR at the time of writing the study results. Of the 10, 8 were cured of their Hepatitis C infection. While the numbers are small, an 80% success rate is encouraging.

What is the level of liver damage amongst study participants?

Of the 45 men in the study group, 24 underwent a liver biopsy in December 2008. For 18 of the 24 men the biopsy occurred less than a year after their first elevated ALT test (a rough estimate for the time of infection). The remaining 6 men had the liver biopsy at least a year after their first abnormal ALT test.

In total, 18 (or 75%) of the 24 men had Stage 2 fibrosis. Of the 18 who had been infected for less than a year, 13 (or over 70%) already had Stage 2 fibrosis. Of the 6 that been infected for over a year, all 6 (or 100%) had Stage 2 or Stage 3 fibrosis. (See Chart 1)

Chart 1. Fibrosis during acute HCV infection in HIV + men			
Fibrosis (Stages 0 – 4)	All biopsies (total = 24)	Biopsies < 1 year (18) after first elevated ALT	Biopsies > 1 year (6) after first elevated ALT
Stage 0	2	2	0
Stage 1	3	3	0
Stage 2	18	13	5
Stage 3	1	0	1
Stage 4	0	0	0

The fact that all 6 of the men who had been infected for at least a year had as bad or worse liver damage than those who had been infected for less than a year shows that fibrosis is linear. In other words, it doesn’t go away or get better over time.

How do Dr. Fierer’s results compare to rates of fibrosis in people infected with acute Hepatitis C but *not* HIV?

When looking at research of Hepatitis C infection amongst people not infected with HIV, we see that those co-infected with acute Hepatitis C and HIV are at much higher risk for advanced liver fibrosis.

Dr. Fierer noted a study of 87 cases of acute Hepatitis C amongst HIV negative individuals. Results from that study showed that all 87 had Stage 0 fibrosis. Another study of 9 acute Hepatitis C infections in people not co-infected with HIV showed that 5 had Stage 0 and 4 had Stage 1 fibrosis. (See Chart 2)

Chart 2. Fibrosis during acute HCV: HIV + vs. HIV-			
Fibrosis (Stages 0 – 4)	HIV + MSM (18)	HIV – (87)¹	HIV – (9)²
Stage 0	2	87	4
Stage 1	3	0	5
Stage 2	13	0	0
Stage 3	0	0	0
Stage 4	0	0	0

This suggests that liver fibrosis is not a consequence of acute Hepatitis C infection alone. It is a property of acute Hepatitis C and HIV co-infection.

Could there be some other explanation for the advanced fibrosis observed in Dr. Fierer’s study?

The men in the study did not have many of the other typical risk factors that would lead to fibrosis:

- Most had normal ALT tests over last year
- Some has never taken anti-retrovirals (which can damage the liver, especially the d-drugs)
- Alcohol intake (which damages the liver) was low (<30 g/day)
- Some never used any recreational drugs
- Normal body mass index/fasting glucose
- Most had not been previously infected with Hepatitis B

Could it be that gay men with HIV are just at higher risk for fibrosis regardless if they are also infected with Hepatitis C?

Dr. Fierer cited a research study of 30 HIV positive men who were not co-infected with Hepatitis C but who had abnormal liver function tests (LFTs) because of other liver problems or liver disease. Few of these men had Stage 2 fibrosis or above. Dr. Fierer

¹ Kamal J. Hepatol ‘06

² Larghi Hepatol ‘02

argues that it is reasonable to assume that if this group had a very low rate of Stage 2 fibrosis then HIV positive men with normal LFTs probably have an even lower rate of fibrosis.

Again, this suggests that the accelerated liver fibrosis Dr. Fierer observed in his study was the result of HIV and acute HCV co-infection.

Why would HIV and acute HVC infection cause accelerated liver fibrosis?

This is still under investigation, but Dr. Fierer's hypothesis is that HIV infection, which weakens the immune system, may cause a lesion in the liver. If someone then also contracts acute HCV the preexisting lesion results in highly accelerated fibrosis.

What happened to the co-infected patient discussed earlier?

This patient is an example of what can happen when acute HCV is diagnosed and treated early. The patient began treatment with interferon and ribavirin 11 weeks after being infected. He continued treatment for 6 months. Six months after stopping treatment he had achieved a sustained virological response. His HCV viral load was undetectable. Another biopsy showed that the inflammation and fibrosis in his liver was almost all gone.

What are Dr. Fierer's key conclusions?

Dr. Fierer believes:

- Acute Hepatitis C infection amongst HIV positive gay men is a new (21st century) clinical syndrome.
- The route of transmission is related to sex.
- Resulting liver fibrosis is more rapid, occurring within weeks to months and does not regress in years.
- This could be an emerging epidemic in the U.S., Australia, Europe and possibly beyond.

What should medical providers be doing?

Enhanced surveillance of Hepatitis C infection amongst HIV positive gay men is needed to increase diagnosis and treatment during the acute phase to prevent further progression of liver damage. Liver function tests should be performed every 3 months and Hepatitis C antibody tests every 12 months amongst HIV positive gay men.

What do HIV+ gay men need to know?

- **Serosorting is probably contributing to the spread of Hepatitis C.** Even if two partners already have HIV they still need to practice safe sex to avoid getting other infections, like Hepatitis C.

- **The use of crystal meth is also probably contributing.** Men who have sex with men while high are at higher risk for contracting Hepatitis C – and other sexually transmitted infections.
- **Slamming (or injecting drugs) is incredibly risky.**
- **Condom use is still the best way to protect yourself.**

QUESTION AND ANSWER SESSION

I have been HIV+ for years. Last month I tested positive for Hepatitis C. Should I get a liver biopsy?

First, get on ribavirin and interferon right away.

Liver biopsies provide information about your liver that is helpful to know if that same information can't be obtained through other non-invasive tests. Given the evidence emerging, it may be a good idea for HIV+ men to start getting liver biopsies during the acute stage of Hepatitis C infection since we are starting to learn how much damage may already be occurring. Discuss this with your physician.

If I am HIV+, what's the best test to use for Hepatitis C: an antibody test or PCR test (for viral load)?

Antibody tests for Hepatitis C will work in those infected with HIV. However, an antibody test may not detect Hepatitis C if the infection is very new (the body may not be producing antibodies yet).

Viral load tests can be used, but they are more expensive and also tend to have more false positive results. Also, the Hepatitis C viral load will fluctuate widely in the first months of infection (at times it may even be close to zero). If the test is performed at a time when the viral load is very low, it may not pick it up.

During the acute phase of Hepatitis C the liver will become inflamed which shows up as high liver test results. If you get an abnormally high liver test at any time, be sure to find out why. Investigate further with your physician.

I am co-infected with HIV and Hepatitis C (genotype 1). My liver biopsy showed that I have Stage 0 fibrosis. Should I start taking ribavirin and interferon or should I wait for the new (improved) treatments?

Given the results of your liver biopsy, you may want to wait until the new treatment is available. However, be sure to monitor your liver functioning regularly.

We know that the existing treatment (ribavirin + interferon) works for only about 25% of patients with genotype 1 who are co-infected with HIV. We are hoping that the new treatment from Vertex Pharmaceuticals, anticipated to come out next year, will increase that rate to 75% to 80%.

While the new Vertex treatment will be taken orally, it is meant to be taken in addition to (not instead of) the current treatment. Unfortunately, that means patients will still have to deal with regular injections of interferon as well as the side effects from the ribavirin/interferon combination.

Some of the European studies you talked about earlier which showed increased rates of acute Hepatitis C infection amongst HIV positive gay men *didn't* show any fibrosis amongst study participants. Why?

In those studies fibrosis was assessed using a fibrometer, not a biopsy. A fibrometer doesn't work in the acute stage of infection.

There is not a lot of data available because it hasn't been standard practice to do a liver biopsy for cases of acute HCV. However, we do have other antidotal evidence of Stage 2 fibrosis amongst those co-infected with HIV and acute Hepatitis C.

There has been a rise in sexually transmitted infections (STIs) in the transgender community. Has there also been an increase in Hepatitis C?

When looking at the latest 30 new cases of Hepatitis C and HIV co-infection in San Francisco none have been transgendered. Does this mean the cases aren't there or are we just not looking? We aren't sure.

There is still a definite need to educate the transgender community about the risk of sexually transmitted Hepatitis C infection.

So am I right to say that Hepatitis C is sexually transmitted?

We know that it can be transmitted during sex if blood-to-blood contact occurs. Transmission through other bodily fluids, such as semen, is rare.

The amount of blood needed to transmit the virus is very small, perhaps not even noticeable. For example, if someone has a lesion from herpes that could provide an entry point for the virus. Condom use is the best protection from this kind of blood-to-blood contact during sex.

How big of a problem is acute Hepatitis C and HIV co-infection in the Bay Area?

To give you an idea, in 2007 there were no referrals for acute HCV and HIV co-infection at San Francisco General. Now we are seeing almost 2 cases a month.

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