



**Treatment**  
**Hepatitis C Virus (HCV)**  
**HIV / HCV Coinfection**

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# **HCV and HIV/HCV Natural History**

## **HCV Diagnostics**

- ♣ screening**
- ♣ monitoring**
- ♣ pre-treatment**

## **Who needs HCV Treatment?**

## **What is HCV Treatment?**

- ♣ side effects & management strategies**
- ♣ defining response**
- ♣ efficacy**
- ♣ HIV and HCV treatment issues**

# Hepatitis C Virus (HCV)

**HCV enters the bloodstream & infects liver cells**

**Can become a chronic (lifelong) infection for 55% to 85%**

**HCV can—but doesn't always—cause serious liver damage, over many years**

**The hepatitis C virus does not directly scar the liver, the body's immune response does when it walls off infected cells**

**HCV treatment, when successful, can halt liver damage, & sometimes reverse it**



# **HIV/HCV Coinfection**

## **HIV speeds up HCV progression**

Cirrhosis can develop in <10 years (versus 15 to 50 years in HIV-negative people)

## **HIV increases risk of serious liver damage**

Cirrhosis is 2 X more likely with HIV coinfection

## **Poorer survival after liver failure**

Both HIV & HCV-related

## **People with <200 CD4 cells at greatest risk**

Treating HIV may delay HCV progression by keeping the immune system healthy

# HCV Natural History

## Acute, chronic or cleared?

- Some people clear hepatitis C without treatment (15% to 45%) within a year: *spontaneous viral clearance*
- Young people, especially females, and Caucasians, are more likely to clear HCV
- HIV+ people are less likely to clear hepatitis C, although some do (5% to 20%)

# Acute to Chronic HCV



## 0 to 6 months

**Acute HCV:** usually no symptoms, some people (~20%) develop jaundice, fever, fatigue, appetite loss, nausea....thus, difficult to diagnose

HCV TX is *most effective* during acute infection



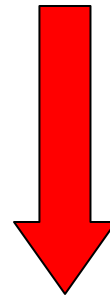
“Window” for HCV ab: 6 to 24 weeks

HCV RNA detectable within 1-- 2 weeks

Liver enzyme levels skyrocket

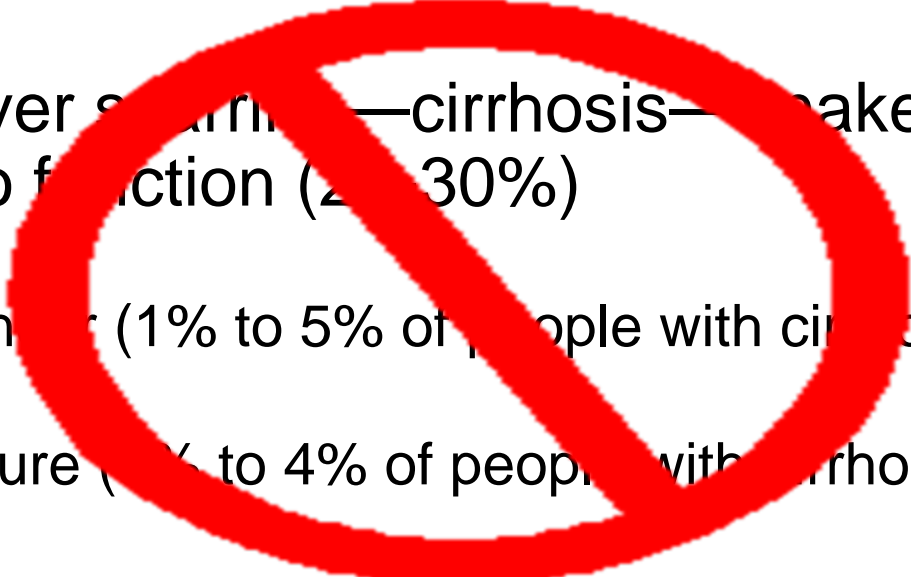
## 6 months on

**Chronic HCV:** Life-long infection unless cleared by treatment (this is called sustained virological response, or **SVR**)



**SVR** means that no hepatitis C virus is detectable in the blood six months after finishing HCV treatment--“cure”  
Significantly lowers risk of liver-related morbidity & mortality

# Chronic HCV: Range of Outcomes

- No symptoms, no liver damage
  - Symptoms (fatigue & depression) & some liver damage
  - Fat in the liver (steatosis)
  - Mild to moderate liver scarring (fibrosis)
  - Serious liver scarring — cirrhosis — makes it difficult for the liver to function (20-30%)
    - Liver cancer (1% to 5% of people with cirrhosis per year)
    - Liver failure (1% to 4% of people with cirrhosis per year)
- 

# HCV Progression: Cofactors

- HIV coinfection
- Age >40 at time of infection
- Insulin resistance, obesity, steatosis
- Aging/duration of HCV infection
- Chronic HBV co-infection
- Male

# Alcohol

Alcohol accelerates HCV progression, especially >50 grams/day

Safe amount?

Cutting down or quitting may be more important than HCV treatment for some people

Many physicians won't treat drinkers



# HCV Diagnostics: What Tests Are Necessary?

“My doctor says I have hepatitis...  
but not to worry about it.”

## **Signal:**

Liver Enzymes

## **Diagnose:**

Antibody testing

Hepatitis C viral load (HCV RNA)

## **Before treatment:**

HCV genotype

Liver biopsy (&/or alternatives)



# Liver Panel

## Blood tests, part of a routine physical exam

- Includes liver enzyme levels (ALT, AST)
- Liver enzymes can be elevated for many reasons
  - Liver enzymes enter the bloodstream when liver cells are damaged or dying
  - Abnormal liver enzyme levels do not mean that a person has HCV

Liver enzyme levels **DO NOT PREDICT** or **INDICATE SEVERITY** of liver damage in people with HCV

- Some people with persistently normal liver enzyme levels have serious liver damage

# HCV Diagnostics: Antibody & Viral Load

**Antibody testing:** a positive HCV antibody test result does not always mean chronic hepatitis C infection

**Viral load testing (HCV RNA):** Will confirm or rule out chronic hepatitis C infection, but:  
hepatitis C viral load is not related to amount of liver damage or rate of disease progression

- Hepatitis C RNA can be VERY high--in the tens of millions
- People with low HCV RNA (<400,000 IU/mL) are more likely to respond to HCV treatment

# Before Treatment: HCV Genotype

HCV has more than 6 different genotypes, numbered in order of discovery

Each HCV genotype has subtypes, lettered in order of discovery

HCV genotype can be determined by a blood test

HCV genotype is a determinant of HCV treatment duration, and the strongest prognostic factor for response to Treatment (2,3,4,1)

# Before Treatment:

## Liver Biopsy?

### PROs:

Only test that can grade (how much inflammation) and stage (how much scarring) liver tissue

Can identify other causes of liver disease

Can identify steatosis (fatty liver)

### CONs

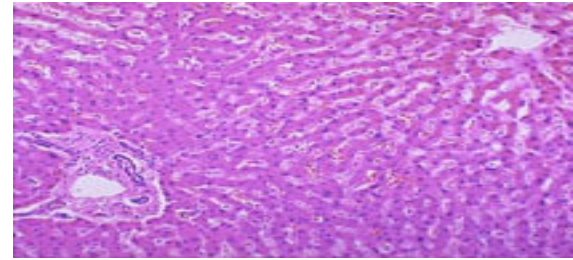
Expensive—access is limited

Invasive and painful—unpopular

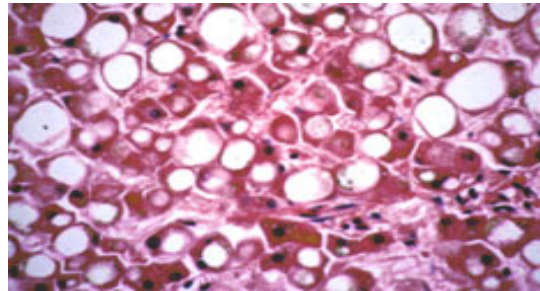
Risky—complications and very small risk of death

Not always accurate—depends on sample size & location, pathologist expertise

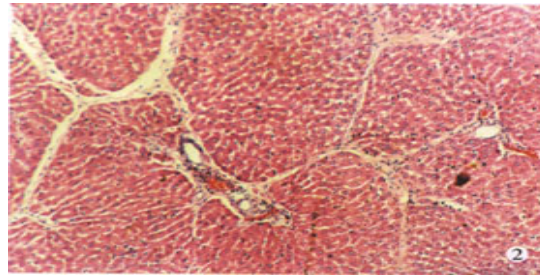
Normal Liver Tissue



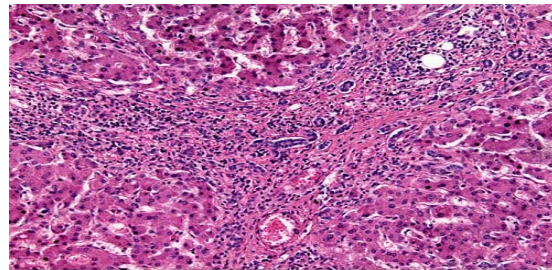
Steatosis



Fibrosis



Cirrhosis



# Biopsy Alternatives

Serum marker panels (Fibrotest, APRI, etc) can detect cirrhosis, but not mild-to-moderate liver damage—not ready for prime time (especially for HIV+ people)

FIBROSCAN uses sound waves to assess liver stiffness; not as good for inflammation

Useful tests, but not a substitute for biopsy

# Who To Treat?

The medical perspective:

“Patients with an increased risk of developing cirrhosis...”

**NIH, Consensus Statement 2002**

“Consider HCV treatment in *all* HIV/HCV coinfecting patients...”

**Veterans Administration 2005**

# HIV/HCV Coinfection

HCV-related end-stage liver disease is ***a leading*** cause of death among HIV-positive people in the US & western Europe

In fact, it is now ***the leading*** cause of non-AIDS related death

(Weber, et al; Arch Intern Med 2006)

# Treating HCV: A Complex & Individual Decision

Not always necessary

Not always effective--especially for coinfecting people

Not affordable

Side effects are intense

Newer therapies are in development, but they have not been studied in coinfecting people yet

Some people really need HCV treatment **now**, it may be a bridge until better drugs are available

# HCV Treatment

- Hepatitis C is treated with a combination of interferon and ribavirin
- They were not designed to treat HCV
- Duration of treatment: 12 to 72 weeks, depends on: early response to treatment, genotype, HCV viral load, & HIV status

# Interferon (IFN)

**Interferon** is a synthetic version of a chemical messenger made by the human body; it stimulates the immune system & fights viruses

**Pegylated Interferon (PEG-IFN)** is the standard of care

***Pegylation*** means that a small molecule has been attached to interferon to keep it in the body longer & increase efficacy

**Pegylated interferon** is injected 1 X per week

# Side Effects of IFN

## **Flu-like**

(fever, aches, nausea, appetite and weight loss, weakness, & fatigue)

## **Lab Abnormalities**

(anemia, neutropenia, thrombocytopenia)

## **Neuropsychiatric**

(suicidal ideation/suicide (rare), depression, insomnia, anxiety, irritability, mood swings, mania, psychosis)

## **Other**

(hair loss, optic nerve damage)

# Ribavirin (RBV)

- Pill or capsule, taken 2 X a day
- Same family (NRTI) as some HIV drugs but it does not work against HIV
- RBV dosing is usually based on weight
- There are interactions between RBV and some HIV drugs

# RBV Side Effects

Anemia: major, sometimes treatment-limiting side effect

Cardiac events

Shortness of breath, coughing

Itchy skin/rash

May also cause depression, irritability

# Managing Side Effects

**Flu-like symptoms** (evening/Friday night shot, low-dose Tylenol, anti-nausea medication, drinking lots of water)

**Appetite/weight loss** (many small, light meals, marinol)

**Fatigue** (exercise/napping)

**Anemia** (growth factor, dose reduction)

**Neutropenia** (growth factor, dose reduction)

**Thrombocytopenia** (severe: dose reduction or stop TX)

**Neuropsychiatric** (baseline psychiatric assessment; ongoing access to mental health care, peer support, and pre-emptive or as-needed medication)

# Will HCV TX Work?

**Crucial: education, support & effective management of side effects**

- HCV genotype (2,3,4,1)
- Race (White>African American)
- Viral load <400,000 IU/mL
- HIV status (not CD4 count or viral load)
- Amount of liver damage/steatosis
- Weight, insulin resistance, diabetes
- Adequate dose/duration of TX

# Response to HCV TX

**SVR: sustained virological response (6 months after finishing HCV treatment)** No detectable HCV RNA in the blood; many experts consider SVR a “cure”

**SVR-12:** No detectable HCV RNA in the blood 12 weeks after finishing HCV TX; not prospectively validated--used in HCV drug Development

**RVR: rapid virological response (4 weeks)** High likelihood of SVR if HCV RNA is undetectable; used mainly in research-but not accurate for early stopping rule

**EVR: early virological response (12 weeks)** If there is less than a 2 log (99%) drop, SVR is VERY unlikely--HCV TX usually discontinued

**ETR: end of treatment response** No detectable HCV RNA at completion of treatment

# HCV Treatment Efficacy

	SVR overall	SVR genotype 1	SVR genotypes 2 & 3
HCV alone	<b>56% to 61%</b>	<b>42% to 44%</b>	<b>70% to 82%</b>
HIV/HCV	<b>27% to 44%</b>	<b>14% to 38%</b>	<b>53% to 73%</b>

# Post-Treatment Response

**Histological Responder:** someone with an improvement in liver inflammation/scarring after HCV treatment; possible without SVR but less Likely

**Relapser:** undetectable during treatment, but virus returns after stopping; most likely to respond to re-treatment

**Breakthrough:** someone who became undetectable, but their virus came back during HCV treatment

**Non-responder:** someone who was never undetectable during HCV TX

**Null responder:** someone with little or no change in HCV viral load during treatment

# HIV Treatment Issues For Coinfected People

HIV treatment may delay HCV progression, but....

HCV coinfection triples the risk for liver toxicity from HIV meds--some drugs less liver friendly than others

Coinfected people more likely to d/c HIV TX for toxicity

HCV treatment reduces liver toxicity risk from HIV TX

SVR reduces risk of liver-related mortality

# HCV Treatment Issues For Coinfected People

Side effects are more severe; drop out rates from HCV treatment trials up to 40%

Drug-drug interactions/toxicity problematic:

**No AZT, ddl, d4T; abacavir ???**

CD4 count--but not percentage--can drop *dramatically* during HCV treatment even with use of stable antiretroviral therapy, although not associated with increased risk of OIs ; returns to baseline after HCV TX