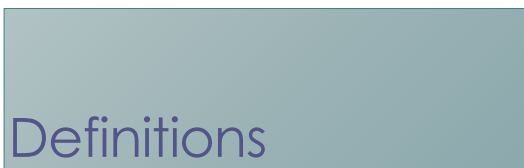


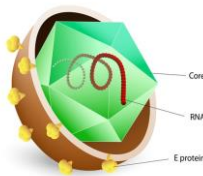
## Objectives

- 1) Describe the Hepatitis C virus (HCV), including transmission, disease progression, risk factors, and clinical significance.
- 2) Evaluate global and national HCV statistics.
- 3) Discuss HCV diagnostic testing procedures and treatment regimens.



## Hepatitis C (HCV) – the basics

### Hepatitis C virus



- Single stranded RNA virus
- Classified as "non-A, non-B" before 1989
- Seven different genotypes, G1-G7

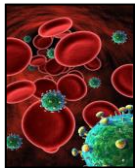
## HCV – transmission

- Exposure to contaminated blood and body fluids
  - IV drug use
  - Blood transfusion and organ transplant (before 1992)
  - Needlestick injury
  - Sexual contact
  - Perinatal
  - Unregulated body piercing and tattooing



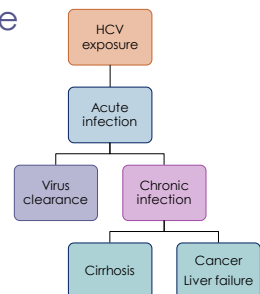
## HCV transmission

- **Cannot** be spread through
  - Breast milk
  - Food and water
  - Hugging, kissing
  - Sharing food or drinks with infected person



## HCV – the disease

- 15-40% clear virus w/out treatment
- 60-85% will develop chronic HCV
- Of those with chronic HCV, risk of cirrhosis is 15-30%

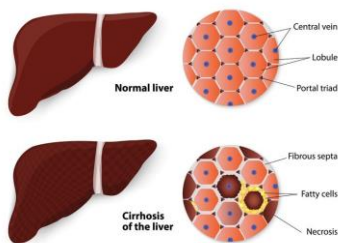


## HCV – acute phase

- Acute phase lasting @ 6 mths
  - Symptoms appear 6 – 7 weeks
  - HCV virus detectable in serum by 1 – 2 weeks
  - Antibodies to HCV detectable by 10 – 11 weeks
  - Liver enzymes spike, then return to normal
- Symptoms include:
    - Jaundice
    - Fatigue
    - Nausea
    - Fever
    - Muscle aches

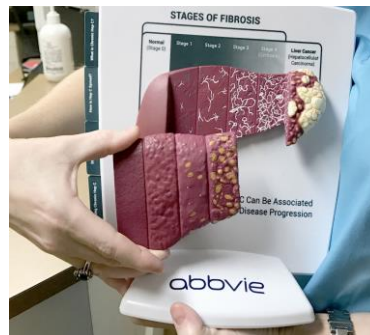
## HCV – chronic phase

- Viral infection for many years, long enough to damage the liver
  - HCV virus persistent in serum
  - Antibodies to HCV persistent in serum
  - Liver enzymes variable
- Symptoms include:
    - Fatigue
    - Jaundice, dark urine
    - Decreased appetite
    - Weight loss
    - Fluid buildup in abdomen (ascites)
    - Dermatological issues
    - Vasculitis
    - Rheumatoid issues
    - Multi-organ involvement



### Liver disease progression

- Fat deposits between hepatocytes, causing enlarged liver
- Inflammation results in scar tissue and fibrosis
- More connective tissue accumulates
- Necrosis of hepatocytes
- Blood flow is obstructed
- Carcinoma develops



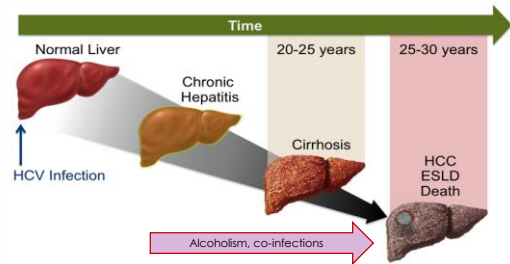
### Liver disease progression

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## HCV – disease progression



## HCV – disease progression



## Who is most at risk?

- Current or past injection or intranasal drug users
- Anyone who has had sexual contact with an HCV+ person
- Anyone born between 1945 – 1960
- Children born to HCV+ mothers
- Long-term hemodialysis patient
- Healthcare and emergency workers
- People exposed to unsanitary piercing or tattoo equipment
- Hemophiliacs treated with clotting factors before 1987
- Blood and organ recipients before 1992
- People with HIV
- People who are/were in jail or prison
- People who have shared personal care items with known HCV+ person
- Anyone with unexplained liver problems or inflammation, including abnormal liver tests



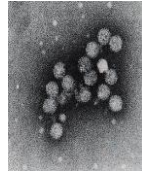
## HCV – clinical significance

- Most common bloodborne infection in US
- Most frequent cause of liver disease and liver cancer
- Leading indicator for liver transplant
- No vaccine available; research ongoing
- No marker to predict when/if acute becomes chronic
- Current epidemic correlated to injection drug use epidemic (opioid)

# Statistics

## HCV by the numbers, worldwide

- 71 million people infected
- 1.8 million new infections in 2015
- 339,000 deaths each year

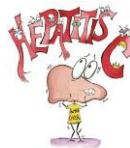


<http://www.who.int/mediacentre/factsheets/fs164/en/>



## HCV by the numbers, United States

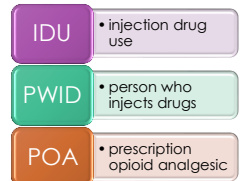
- 3.5 million people infected (chronic)
- 2436 new cases per year (reported)
- 33,900 new cases (estimated)
- 20,000 deaths each year



<https://www.cdc.gov/hepatitis/statistics/index.htm>

## Why do we have an HCV epidemic?

- Because we have an opioid epidemic
- IDU is primary risk factor for HCV transmission
- IDU is now the leading cause of HCV incidence in the US
- Virus can circulate quickly through networks of PWID
- POAs are major influence



Per CDC: <https://ajph.aphapublications.org/doi/pdf/10.2105/AJPH.2017.304132>

## What are opioids?

- Narcotic pain medication
- Bind opioid receptors in brain, spinal cord
- Interfere with pain message signaling to the brain
- Incurs tolerance, dependence, and addiction

Generic name	Brand name
Codeine	
Fentanyl	Actiq, Duragesic, Fentora
Hydrocodone	Hysingla ER, Zohydro ER
Hydrocodone/acetaminophen	Lortab, Norco, Vicodin
Hydromorphone	Dilaudid
Meperidine	Demerol
Methadone	Dolophine, Methadose
Morphine	Kadian, MS Contin
Oxycodone	OxyContin, Oxaydo
Oxycodone/acetaminophen	Percocet, Roxicet
Oxycodone/naloxone	Targin, Targiniq, Targinact

## The HCV/opioid epidemic

•Report published by CDC in *American Journal of Public Health (AJPH)*:

### HCV incidence

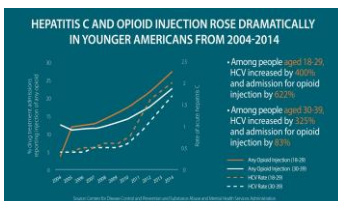
- ↑ 400% in persons aged 18 to 29
- ↑ 325% in persons aged 30 to 39

2004 – 2014

### Treatment admission for IDU, age 18 to 29

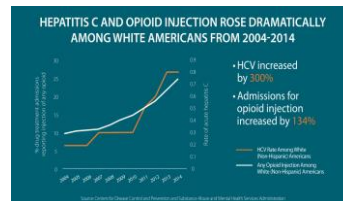
- ↑ 622% for any opioid injection
- ↑ 603% for heroin injection
- ↑ 817% for POA injection

<https://ajph.aphapublications.org/doi/pdf/10.2105/AJPH.2017.304132>



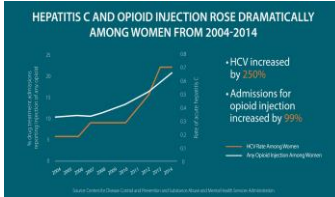
## The dual epidemic

Young Americans, age 18-29 age 30-39



## The dual epidemic

Non-Hispanic Whites represent largest increases

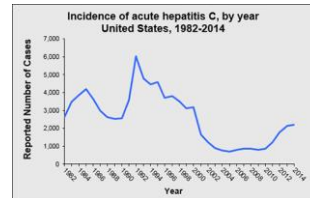


## The dual epidemic

Women,  
age 18-39

Infants born to  
HCV+ mothers  
↑ 68% from  
2011-2014

## HCV incidence, United States



# Diagnosis

## Liver profile

### Alanine aminotransferase (ALT)

- Enzyme found in cells of liver and kidney
- Converts alanine into pyruvate (required for cellular energy production)
- Released into blood when liver cells are damaged/dying
- Most specific to hepatitis
- Acute: sharp increase, gradual decrease
- Chronic: persistently increased

Test	Ref. range
ALT	7 – 55 U/L
AST	8 – 48 U/L
ALP	40 – 140 U/L
Total protein	6.3 – 7.9 g/dL
Bilirubin(total)	≤ 1.2 mg/dL
Albumin	3.5 – 5.0 g/dL
GGT	
Lactate dehydrogenase	
Prothrombin time (PT)	
Alpha-feto protein (AFP)	

## Hepatitis panel

May be ordered when:

- Patient has abnormal liver panel results
- Patient presents with symptoms of liver damage
- High risk patients
- Known exposure

Hepatitis A antibody, IgM
Hepatitis B core antibody, IgM
Hepatitis B surface antigen
Hepatitis C antibody

## HCV screening test

Anti-HCV

- EIA
- CLIA
- Rapid tests

### Antibodies to HCV

- Anti-HCV IgG
- Detectable 10 – 11 weeks after exposure
- Remain positive for lifetime
- Acts as a screen only
- Positives should be confirmed with molecular testing

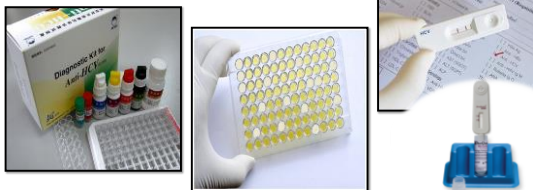
- **Reactive**
  - Current HCV infection
  - Past infection resolved
- **Nonreactive**
  - No infection

## HCV screening test

- Detect presence of antibodies to HCV

Anti-HCV

- EIA
- CLIA
- Rapid tests



## HCV molecular testing

HCV RNA

### Nucleic acid amplification test (NAT)

- per CDC guidelines if anti-HCV(+)
- RNA detectable within 1-2 weeks after exposure
- Remains positive for chronic infections
- **Detected**
  - current HCV infection
- **Not detected**
  - past HCV infection
  - false(+) Ab screen

### RT-PCR

- **Qualitative**
- **Quantitative**
  - Confirm (+)Ab screens
  - Detect suspected infection
  - Screen blood/organ donors
  - Detect perinatal transmission
  - Monitor viral load
  - Maintain therapeutic goals



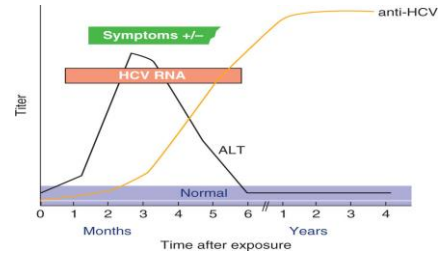
## HCV molecular testing

HCV RNA

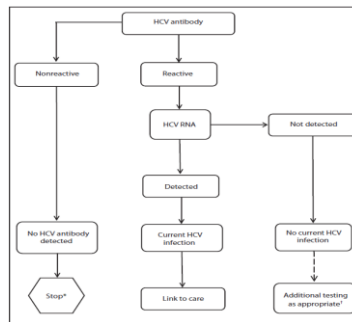
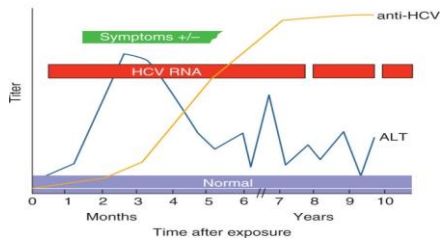
- Roche Diagnostics COBAS® TaqMan® Analyzer; Cobas® 4800 System
- Siemens ADVIA Centaur® Systems



## HCV serology – acute infection



## HCV serology – chronic infection



CDC  
Hepatitis C  
testing  
algorithm

<https://youtu.be/WyVQ6J0JUvI>

## HCV screening – much room for improvement

Current guidelines:

- One-time screen for persons born between 1945-1965
- Targeted screening for high risk patients

- Risk based practice may be limited and not include actual testing
- Screening disparities exist for women, African Americans, and Hispanics
- Linkage to care and treatment referral widely varies among providers
- Interest in screening still lacking in many age cohorts

## Vaccines and treatments

## HCV – vaccine research

- Began 25 years ago
- Progress is slow because:
  - Variability of genotype distribution
  - Virus can mutate rapidly within the host
  - Limited animal models



## HCV vaccine – clinical trials

- 1) Therapeutic vaccine trial
  - people who already have chronic hepatitis C
  - purpose is to determine whether each vaccine is safe and successful at reducing evidence of HCV RNA in participants' blood
  - 32 participants
  - Mayo Clinic (Florida, Minnesota), Temple University (Philadelphia), University of Puerto Rico
  - Completion of this trial is expected in 2020

ClinicalTrials.gov Identifier: NCT02772003

## HCV vaccine – clinical trials

- 2) Prophylactic (preventive) vaccine trial
- people at high risk of infection, i.e. PWID
  - purpose is to determine the safety of the two vaccines
  - find out whether participants receiving either vaccine are less likely to become infected with HCV
  - 548 participants
  - San Francisco, Maryland, New Mexico
  - Completion of this trial is expected in July 2018

ClinicalTrials.gov Identifier: NCT01436357

## HCV vaccine – clinical trials

- 3) Vaccine efficacy trial
- people with chronic HCV and healthy people
  - purpose is to investigate the effects of chronic HCV infection on the immune response to HBV vaccination
  - understand reasons for vaccine success vs failure
  - 130 participants
  - Rockefeller University Hospital, NY
  - Completion of this trial is expected in May 2019

ClinicalTrials.gov Identifier: NCT02429583

## HCV – treatment

Direct acting antiviral (DAA)

- Acute HCV infection: monitor and only consider for treatment if HCV RNA persists after 6 months
- Chronic HCV infection: new highly effective HCV protease inhibitors, oral dose for 8-12 weeks
  - Achieve sustained virologic response (SVR)
  - Absence of detectable virus 12 weeks after completion of treatment
  - 90% cure rate

## HCV – treatment

Direct acting antiviral (DAA)

### Mechanisms of action:

- Inhibit viral replication
- Interfere with protein synthesis
- Prevent virion assembly
- Enhance T-cell activity

- Oral pill/capsule forms and injections
- Many require combo therapy
- Cost prohibitive



Name	Action	Cost
Daclatasvir	Inhibits replication	\$63,000 (12 weeks)
Eltasvir-grazoprevir	Inhibits replication	\$54,600, \$72,800
Glecaprevir – pibrentasvir	Inhibits replication	\$26,400, \$36,400, \$52,600
Ledipasvir – sofosbuvir	Inhibits replication	\$64,000, \$94,500, \$189,000
Ombitasvir-paritaprevir-ritonavir	Inhibits replication	\$76,653 (12 weeks)
Peginterferon alfa-2a	Interferes with protein synthesis	\$9,250, \$18,500, \$37,000
Peginterferon alfa-2b	Interferes with protein synthesis	\$8,400, \$16,800, \$33,600
Ribavirin	Inhibits replication, protein synthesis, enhances T-cell activity	\$550 - \$850 (12 weeks) \$110 - \$1700 (48 weeks)
Simeprevir	Inhibits viral replication	\$66,360, \$85,000, \$150,000
Sofosbuvir	Terminates viral replication	\$84,000, \$168,000
Sofosbuvir – velpatasvir	Inhibits viral replication	\$74,760 (12 weeks)
Sofosbuvir – velpatasvir - voxilaprevir	Inhibits and terminates viral replication	\$74,760 (12 weeks)

FDA approved treatment options  
<https://www.hepatitisc.uw.edu/page/treatment/drugs>

## HCV – in summary

- Single-strand RNA virus, genotypes 1-3 prevalent in US
- Transmission via blood
- Leading cause of liver disease, liver cancer, and liver transplant
- Highest risk in PWID, baby boomers, children born to HCV+ mom
- Dual epidemic with opioid IV drug use
- Anti-HCV screen first, then molecular testing for HCV RNA

## HCV – in summary

- Vaccine research ongoing
- 3 current vaccine clinical trials in US
- Treatments available with 90-95% cure rate
- High cost and healthcare access prohibit many for receiving treatment
- Need for intensive testing plans nationwide, continued needle exchange programs, public health education

Thank you for listening!

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