NATIONAL LGBT HEALTH EDUCATION CENTER
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NATIONAL CENTER FOR INNOVATION IN HIV CARE

New Era in HCV Management: Primary Care Innovations

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Continuing Medical Education Disclosure

- Program Faculty: Marwan Haddad MD, MPH, AAHIVS
- Current Position: Medical Director of HIV, HCV, and Buprenorphine Services
- Community Health Center, Inc., CT
- Disclosure: Speaker's Bureaus: Gilead, BMS, Merck (Spouse Only). Presentation contains recommendations for HCV treatment regimens that are not FDA approved.

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Learning Objectives

By the end of this webinar, learners will be able to

1. Summarize evidence-based recommendations for HCV screening.
2. Apply management recommendations for chronic HCV mono-infection and HIV-HCV co-infection in primary care.
3. Describe challenges of integrating HCV management in primary care.

Outline

- Epidemiology and Rationale
- Transmission
- Screening
- Management and Treatment
- Challenges of Integration in Primary Care

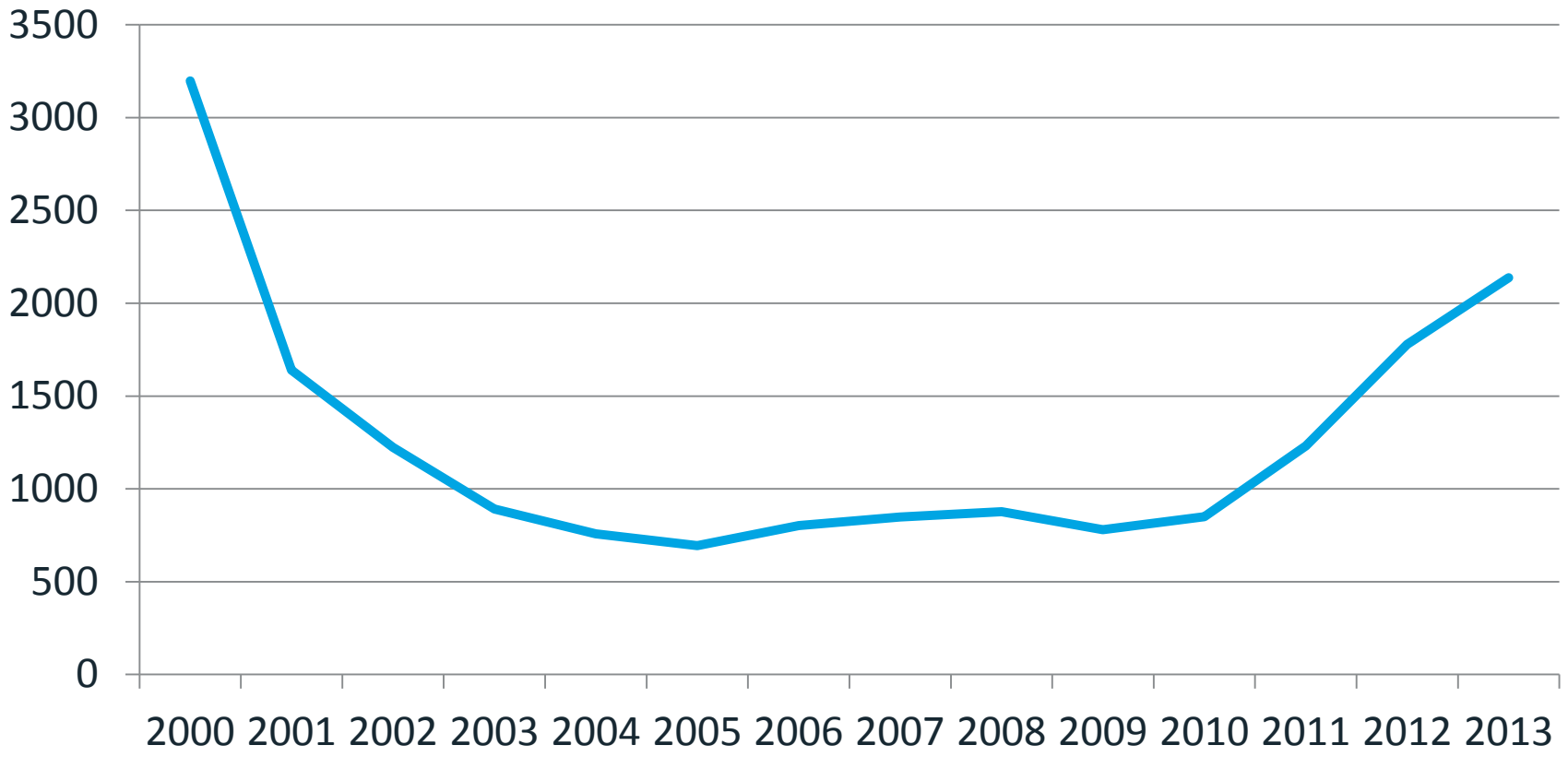
Epidemiology

- HCV is the most common chronic blood-borne infection.
- About 3.2 million people are chronically infected with HCV in the U.S.
- About half are not aware of their infection.
- Majority of HCV infections are among individuals born between 1945 and 1965.

Armstrong GL, et al. Ann Intern Med. 2006;144:705-14.; Denniston et al. *Hepatology.* 2012;55(6):1652-1661; MMWR 2012;61(No. RR-4)

HCV Incidence: CDC Estimates

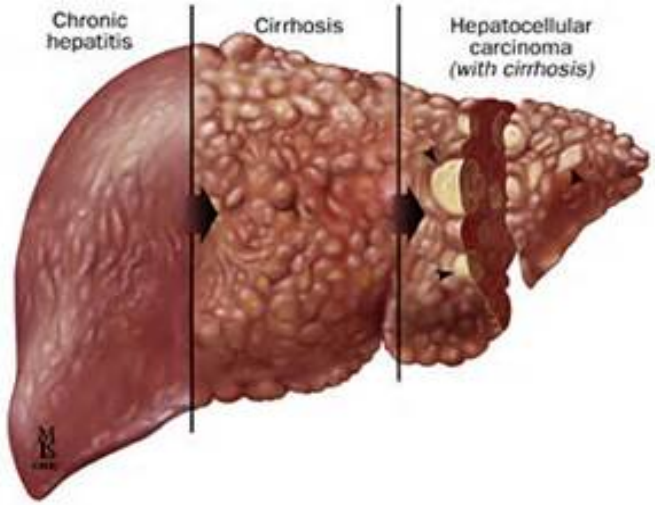
Reported Number of Acute Hepatitis C Cases: United States, 2000-2013



Source: National Notifiable Diseases Surveillance System (NNDSS)

Epidemiology

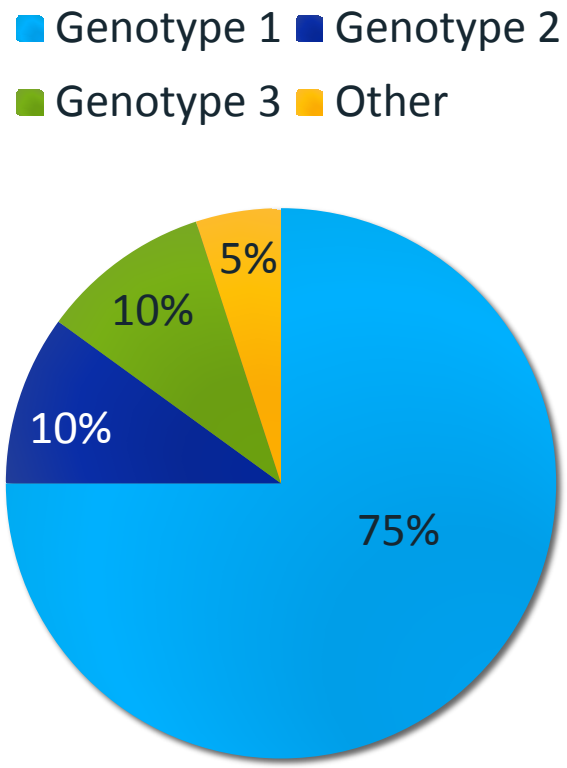
- 15,106 deaths (4.6 deaths per 100,000) estimated to be caused by HCV in 2007.
  - Increased to 4.8 deaths per 100,000 in 2011



CDC Website; Annals of Internal Medicine, 2012. 156 (4): p. 271-278

HCV Genotype Distribution

- 6 known genotypes.
- Little difference among them regarding transmission and natural history.
- Genotype 1 is most common in the United States.



Rationale for HCV Integration in 2015

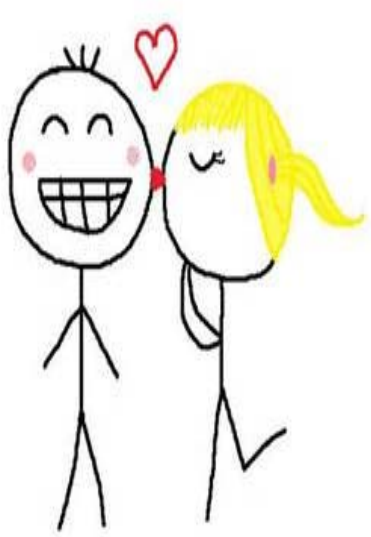
- All oral regimens available for all HCV genotypes.
  - Some as simple as one pill once a day
- Pegylated interferon seldom needed.
- Highly effective; well tolerated; short treatment duration.
- Consideration of HCV management in primary care essential to ensure every HCV patient has the opportunity to access curative therapy.

HCV Transmission

- Injection Drug Use
  - Most common means in U.S.
  - ~33% of IDUs aged 18-30 infected
  - ~70-90% of older IDUs infected

HCV Transmission

- Sex with HCV-infected persons
  - Heterosexual Risk



- Meta-analysis of several large prospective studies.
- Heterosexual discordant stable couples with 10 or more years of follow up.
- No increased risk of sexual transmission of HCV.
- Even after ~ 750,000 vaginal and anal contacts
- Probability of transmission less than 1 in 10 million sexual contacts

Tohme and Holmberg. Is Sexual Contact a Major Mode of Hepatitis C Virus Transmission? Hepatology 2010; 52: 1497-1505.

HCV Transmission

- Sex with HCV-infected persons
  - HIV-infected MSM
    - Studies limited, mainly in Europe; few in U.S., Australia.
    - Dutch study: increase from 0.08 cases/100 pys in ’84-’99 to 0.87 cases/100 pys in ‘00-’03.
    - UK study: incidence increased by 20% every year since ‘02.
    - French study: increase from 1.2/1000 pys before ‘03 to 8.3/1000 pys after ‘03.
    - Amsterdam study: HIV+ MSM 43 times more likely to get HCV infected than HIV- MSM.
    - Risk factors implicated but not consistent in studies:
      - condomless anal sex, fisting, group sex, multiple partners, other STIs, drug use, shared sex toys, HIV serosorting

Tohme and Holmberg. Is Sexual Contact a Major Mode of Hepatitis C Virus Transmission? Hepatology 2010; 52: 1497-1505.

Risk Factors for HCV Acquisition in HIV+ MSM

- MOSAIC study, case-control, in Netherlands
- N= 82 HIV+ MSM with acute HCV infection with 131 controls (median age 46; in 2009+)

Risk Factors	Odds Ratio
Injection Drug Use	>10
Ulcer-causing STIs (syphilis, genital herpes, LGV)	~ 5
Condomless receptive anal sex	~ 5
Sharing sex toys	~ 4
Sharing straws for drugs before or during sex	~ 3.5
Unprotected fisting	~ 3
Lower CD4 count at last visit before testing HCV +	~ 1.7 /cubic root lower

JW Vanhommerig, FALambers, J Schinkel, et al. Risk Factors for Transmission of HCV Among HIV-Infected MSM: A Case-Control Study. 2015 Conference on Retroviruses and Opportunistic Infections. Seattle, February 23-24, 2015. Abstract 674.

Risk Factors for HCV Acquisition in HIV+ MSM

- No association with having more sex partners, group sex, involvement at sex parties, anal rinsing or douching, or rectal bleeding in this analysis.
- Role of CD4 count unclear
  - Does a lower count facilitate acquisition or does acute infection cause a decrease in CD4 count or both?
  - Many HIV+ men with sexually transmitted HCV have high CD4 counts.

JW Vanhommerig, FALambers, J Schinkel, et al. Risk Factors for Transmission of HCV Among HIV-Infected MSM: A Case-Control Study. 2015 Conference on Retroviruses and Opportunistic Infections. Seattle, February 23-24, 2015. Abstract 674.

HCV Transmission

- Sex with HCV-infected persons
  - HIV-uninfected MSM
    - Variable study results and usually rare sexual transmission
    - Amsterdam study: 0 cases/100 pys
    - UK study: 1.5 cases/1000 pys
    - Studies in Canada, Argentina, Australia no association with sexual transmission
      - One Australian study showed an association but high rates of IDU confounding results
    - Omega Cohort Study
      - No increased risk, even with risky behavior e.g. multiple partners or unprotected anal sex
      - Pros: Large sample; controlled for all other risk factors
      - Cons: short observation time 1 year; few engaged in high risk behavior

Tohme and Holmberg. Is Sexual Contact a Major Mode of Hepatitis C Virus Transmission? Hepatology 2010; 52: 1497-1505.

Risk Factors for HCV Acquisition in HIV- MSM

- Retrospective study of acute HCV infection in HIV-MSM seen at sexual health clinics in London from 2010-2014.
- Only about 15% of 235,000 patients screened for HCV.
- 44 tested HCV positive
  - Rate of less than 1%
  - Median age 37; 67% white
  - 15 spontaneously cleared; 11 treated

K McFaul, A Maghlaoui, M Nzuruba, et al. Acute hepatitis C infection in HIV-negative men who have sex with men. *Journal of Viral Hepatitis* 22(6):535-538. June 2015.

Risk Factors for HCV Acquisition in HIV- MSM

- Risk factors identified:
  - Condomless anal sex, insertive and receptive
  - Group sex
  - Fisting
  - Intranasal drug use
  - Injection drug use
  - Sex while using drugs
  - Co-existing STIs

K McFaul, A Maghlaoui, M Nzuruba, et al. Acute hepatitis C infection in HIV-negative men who have sex with men. *Journal of Viral Hepatitis* 22(6):535-538. June 2015.

CDC's 2015 STD Treatment Guidelines

- Since HCV transmission has not been demonstrated between heterosexual partners, condom use might not be necessary.
- Heterosexuals and MSM with HCV infection and more than one partner, especially those with HIV co-infection, should use male latex condoms to protect their partners against HCV and HIV.

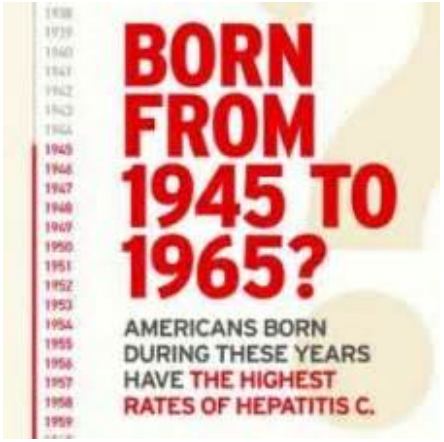
HCV Transmission

- Birth to HCV infected mothers
  - Around 3-5% transmission; higher in HIV co-infected
- Needle stick injuries in healthcare settings
  - About 1.8% transmission but reported as high as 10%
- Receipt of donated blood, blood products, and organs
  - About less than 1 chance per 2 million units transfused
- Sharing personal items contaminated with infectious blood, such as razors or toothbrushes
  - Considered an inefficient means

USPSTF Screening Recommendations

- US Preventive Services Task Force (USPSTF)* recommends:
  - Testing for HCV infection in patients at high-risk for infection. (B recommendation)
  - One-time testing in adults born between 1945 and 1965. (B recommendation)

*CDC, AASLD, IDSA, ACG have similar recommendations.



CDC Definition of High Risk

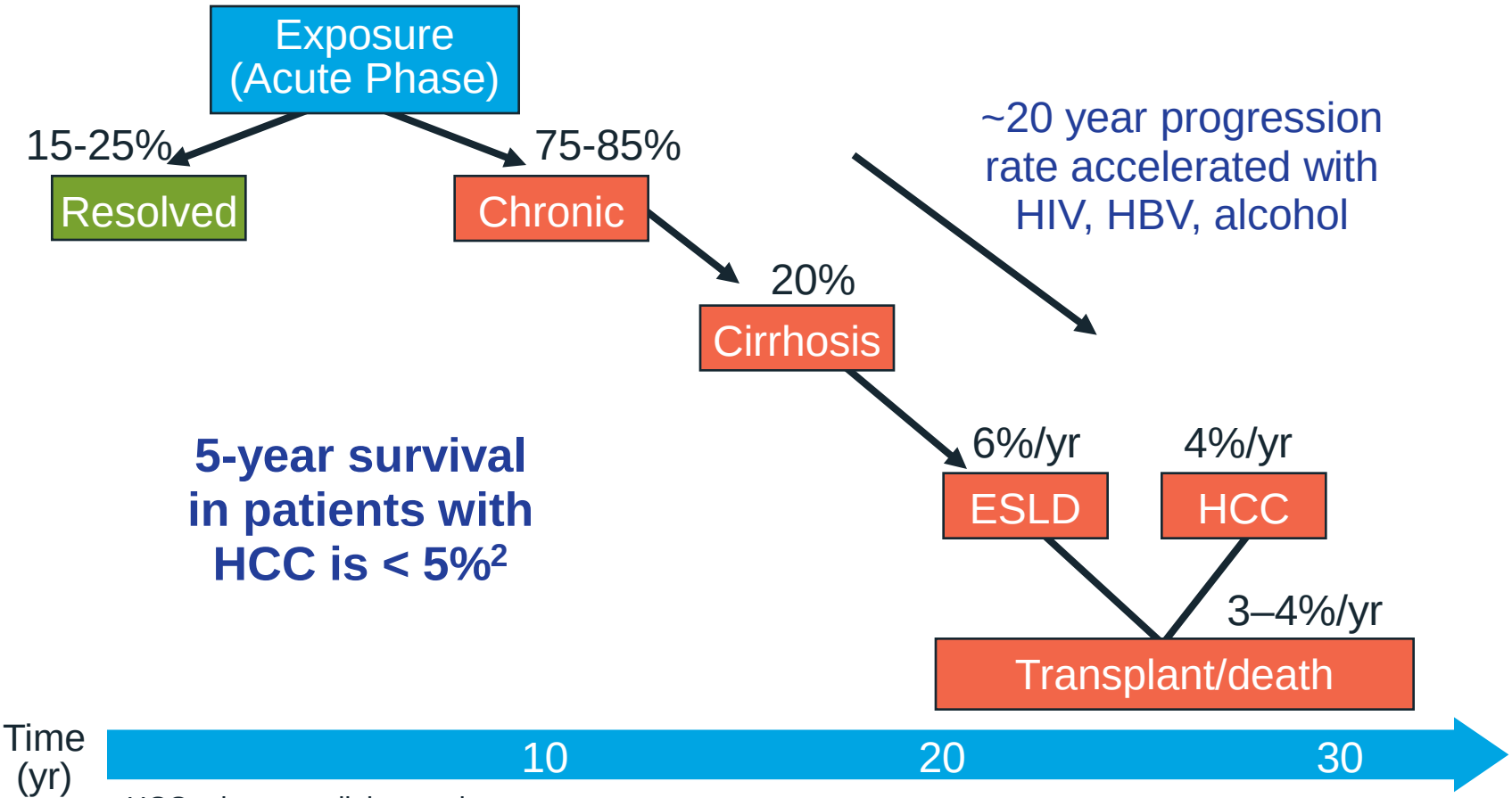
- Persons who have ever injected drugs, including only once
- Persons with HIV infection
- Persons with signs or symptoms of liver disease
  - e.g. persistently abnormal liver enzymes
- Persons with known exposures to HCV
  - e.g. HCWs after needle sticks, mucosal exposures to HCV-infected blood
- Children born to HCV-infected mothers
- Persons who were ever on chronic hemodialysis
- Recipients of blood transfusions and solid organ transplantations before July 1992
- Recipients of clotting factor concentrates before 1987

Other Risk Factors

- AASLD/IDSA/IAS-USA add as high risk:
  - Non-injecting illegal drug use
  - Tattooing
  - Incarceration
  - HIV infected MSM

- CDC lists as uncertain:
  - Non-injecting illegal drug use
  - Tattooing/body piercing
  - Multiple sex partners or STIs
  - Long term sex partners of HCV+ persons
  - Recipients of transplanted tissue (e.g. corneal, MSK, skin, ova, sperm)

Natural History of HCV Infection



HCC = hepatocellular carcinoma

ESLD = end-stage liver disease

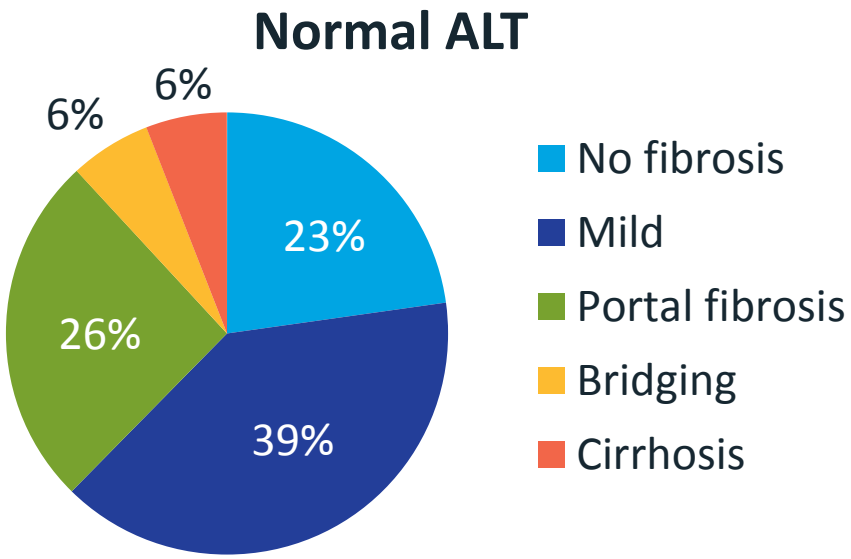
Hoofnagle J. *Hepatology*. 1997;26(suppl 1):15S-20S.

National Institutes of Health. *NIH Consens State Sci Statements*. 2002;19:1-46.

Progression of Hepatitis C Disease

- Related Factors
  - Heavy alcohol consumption
  - HIV infection
  - Hepatitis B infection
  - Immunosuppression
  - Male
  - Infection at > 40 years

- Factors Not Related
  - ALT
  - HCV RNA level
  - HCV Genotype
  - Mode of HCV transmission

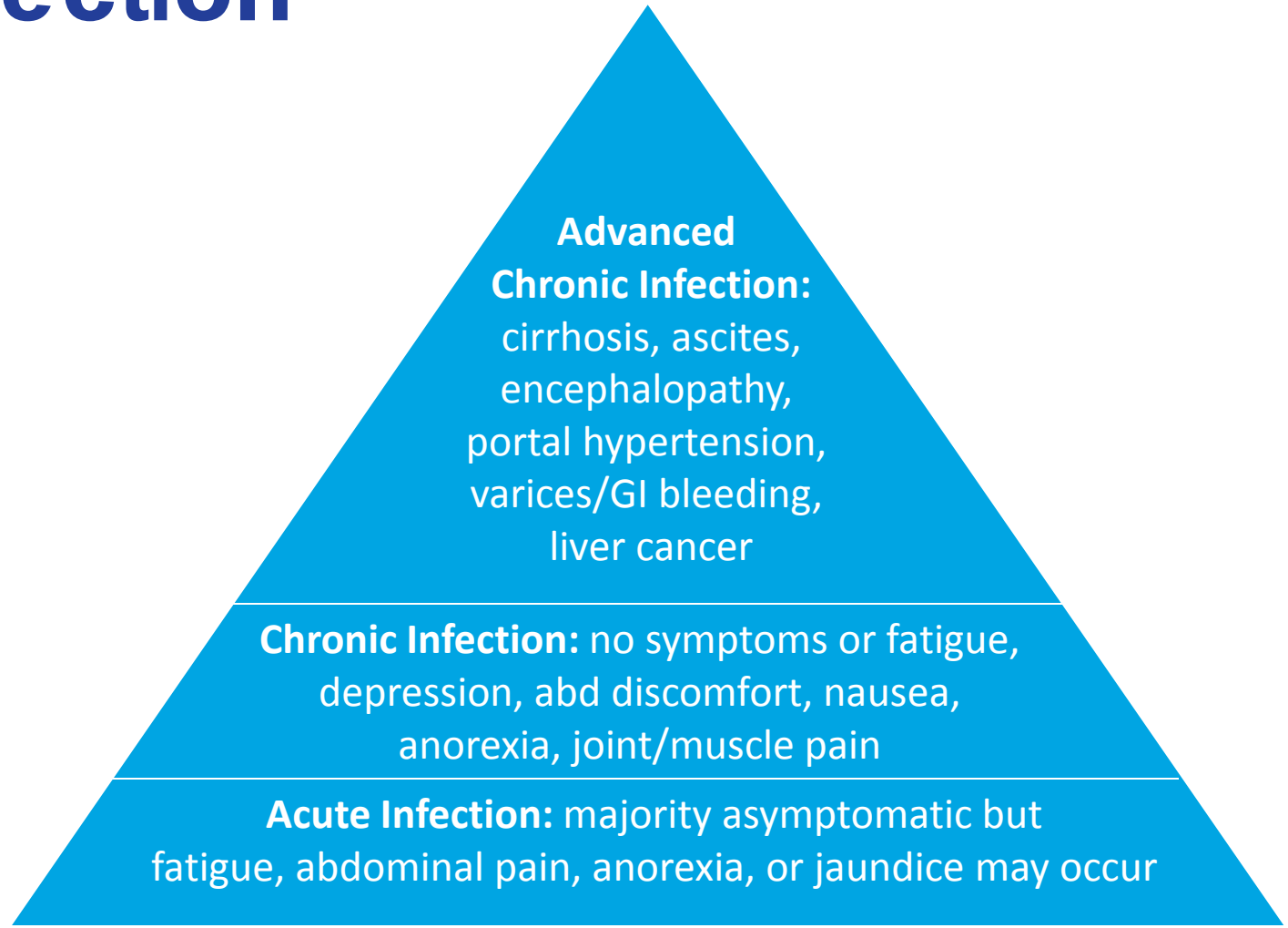


NIH Consensus Development Conference Statement, 2002

Poynard et al. Lancet 1997, 349: 825-832

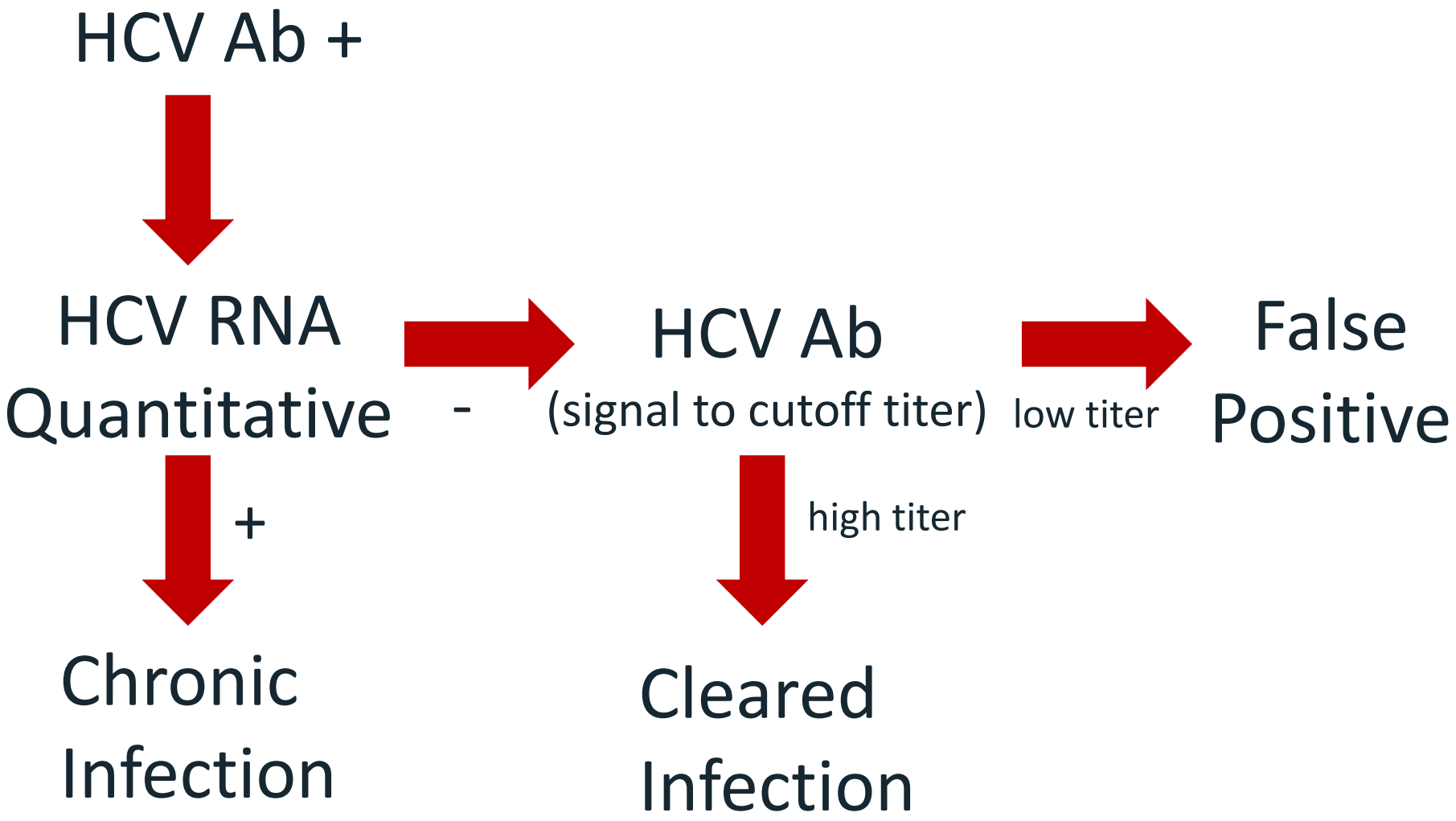
Shiffman et al J Infect Dis 2000, 182: 1595-1601

Stages and Symptoms of HCV Infection



CDC. *MMWR*. 1998;47(RR-19):1-38.

Sequence of HCV Screening and Confirmation

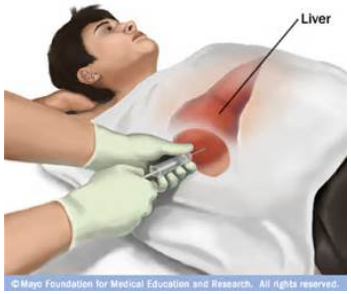


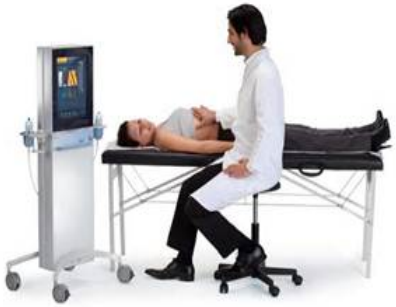
HCV Baseline Lab Investigations

- HCV RNA/Genotype
- CBC including platelets & diff
- Comprehensive Metabolic Panel including
  - Albumin
  - ALT/AST
  - Alkaline phosphatase
  - Creatinine
- PT/INR/PTT
- HIV
- Hepatitis A/B panel
  - HAV Ab total, HBV sAg, HBV sAb quantitative, HBV cAb total
- Liver Fibrosis Panel

Liver Imaging and Biopsy

- Abdominal U/S:
  - Assesses liver and spleen size and larger liver tumors (>3 cm)
  - Not good at assessing severity of liver disease
- CT scan or MRI of Abdomen
  - Better at assessment of liver tumors (<3 cm)
- Fibrosis Assessment
  - Liver biopsy
    - Invasive, expensive
  - Serum markers
    - E.g. FibroSure; Liver fibrosis panel
    - Blood test, cheap
  - Transient elastography
    - E.g. FibroScan
    - Noninvasive, availability issues





Current Available HCV Medications

- Pegylated Interferon
  - 180 mcg s/c injection
  - once a week
- Ribavirin (200mg, 400 mg, 600 mg)
  - Weight-based 1000 mg (<75 kg) or 1200 mg (>75 kg) daily in divided doses with food

Current Available HCV Medications

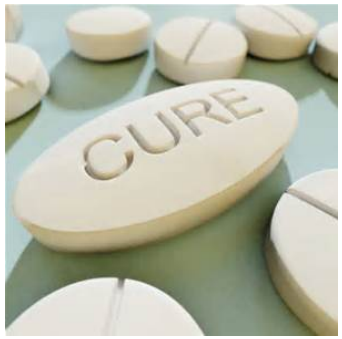
- Direct Acting Antivirals (DAAs)
  - Protease Inhibitors
    - First generation (not used anymore)
      - Telaprevir, Boceprevir
    - Second generation
      - Simeprevir (Olysio) 150 mg
      - one pill once a day with food
  - Polymerase Inhibitors
    - Sofosbuvir (Sovaldi) 400 mg
    - one pill once a day with/without food
  - NS5A Inhibitor
    - Daclatasvir (Daklinza) 60 mg
    - one pill once a day with/without food

Current Available HCV Medications

- Combination Direct Acting Antivirals (DAAs)
  - Harvoni
    - NS5A inhibitor/NS5B polymerase inhibitor
    - ledipasvir 90 mg /sofosbuvir 400mg
    - One tablet once a day
  - Viekira-Pak
    - NS3/4A protease inhibitor, NS5A inhibitor, NS5B polymerase inhibitor
    - paritaprevir 150 mg/ritonavir 100 mg/ombitasvir 25 mg once daily plus twice-daily dosed dasabuvir 250 mg
    - Three tablets in am and one tablet in pm

HCV Medication Cost

Is HCV Curable?



- Data from 9 randomized, multicenter trials
- 997 patients with a sustained virologic response (SVR24) defined as undetectable HCV RNA 24 wks post end of treatment.
  - 163 patients received pegylated interferon monotherapy
  - 741 patients received pegylated interferon and ribavirin
  - 93 HIV/HCV patients received pegylated interferon and ribavirin
- Overall, 99% of patients maintained undetectable HCV RNA at a mean of 4.1 years (0.4-7 years).
- 8 patients (0.8%) became HCV RNA positive a mean 2 years after finishing therapy. Unclear if this was due to relapse or re-infection.

Swain M et al. Presented at EASL 2007, April 11-15, Barcelona, Spain, Abstract 1

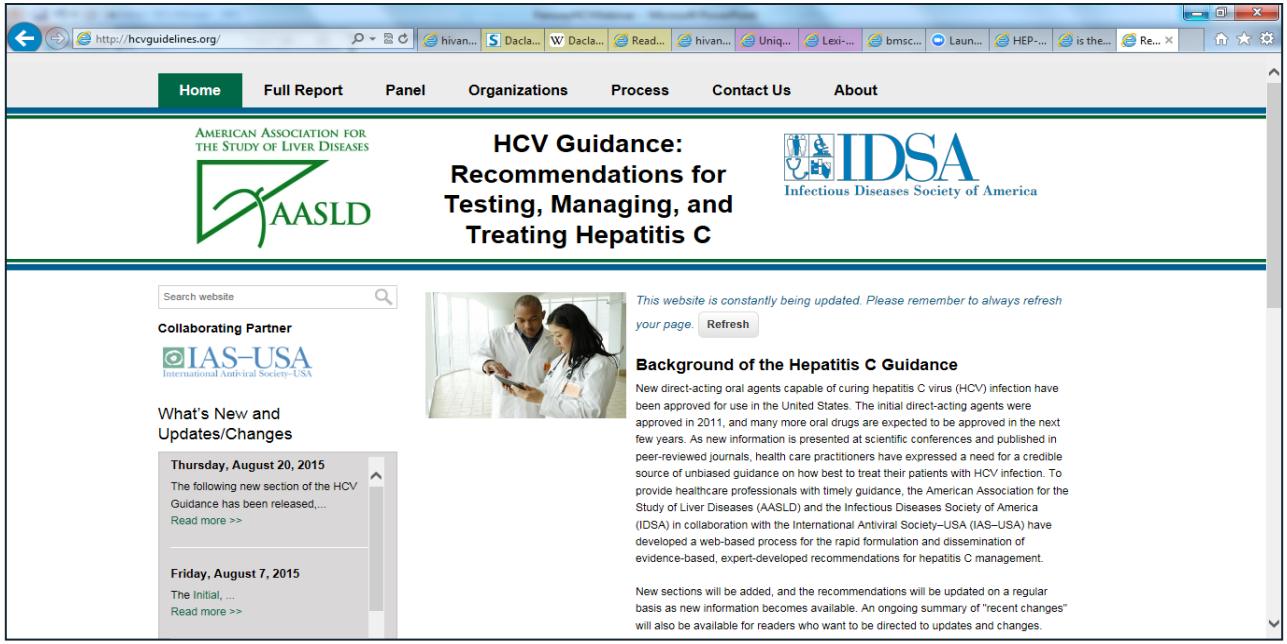
Is HCV Curable?

- SVR24 vs. SVR12
  - FDA has more recently determined SVR12 to be as valid as SVR24 as an efficacy endpoint based on high correlation.
  - Recent study finds >99% concordance between SVR12 and SVR24 with SOF-based regimens.
- With the advent of the Direct Acting Antiviral (DAA) medications, SVR12 rates have reached 80-100% in clinical trials, varying based on genotype, fibrosis stage, and prior treatment experience.

Yoshida EM et al. Concordance of sustained virological response 4, 12, and 24 weeks post-treatment with sofosbuvir-containing regimens for hepatitis C virus. Hepatology 2015 Jan; 61:41.

Treatment

- Treatment recommendations changing quickly.
- http://hcvguidelines.org/
  - AASLD/IDSA/IAS-USA living document



Initial Treatment Recommendations

Genotype 1	Genotype 2	Genotype 3	Genotype 4
SOF/LDV x 12 wk*	DCL+SOF x 12 wk	DCL+SOF x 12 wk +/-RBV x 24 wk if cirrhosis	SOF/LDV x 12 wk
DCL+SOF x 12 wk +/- RBV x 24 wks if cirrhosis	SOF+RBV x 12 wk	SOF+P/R x 12 wk	PTV/RTV/OBV+DSV +RBV x 12 wks
PTV/RTV/OBV+DSV+ RBV x 12 wks 1a: 24 wks if cirrhosis 1b: RBV if cirrhosis	X 16 wks if cirrhosis	SOF+RBV x 24 wk	SOF+P/R x 12 wk
SOF+SMV +/- RBV x 12 wk X 24 wks if cirrhosis			SOF+RBV x 24 wk

*x 8 wk if RNA < 6 million, Rx-naïve, no cirrhosis, HIV uninfected

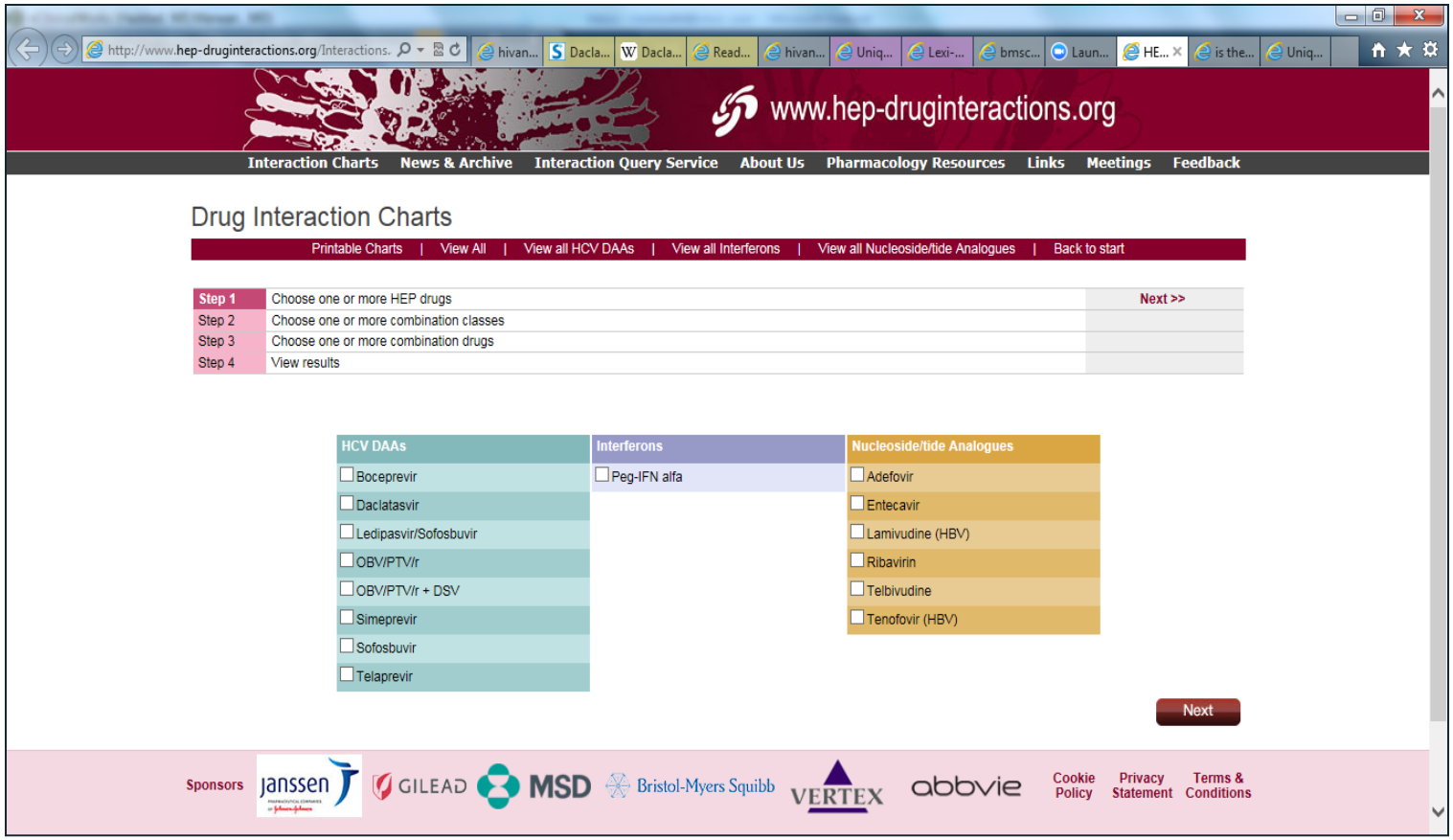
PTV =paritaprevir; RTV =ritonavir; OBV = ombitasvir; DSV = dasabuvir; RBV = ribavirin; SOF = sofosbuvir; LDV = ledipasvir; DCL = daclatasvir

HCV/HIV Co-infection

- Treatment and retreatment same as mono-infected.
- Main issue: drug interactions with ARVs.
- ARV regimen changes should be handled in collaboration with HIV practitioner.
  - Some examples:
    - DCL dose adjustment may be needed.
      - 30 mg with ATV/r and 90 mg with EFV and ETV.
    - LDV increases TFV levels
      - avoid if CrCL<60
      - avoid with PI/r
    - PTV/RTV/OBV+DSV can be used with ATV, DTG, FTC, 3TC, RTG, TFV.;
      - RTV dose may need to be adjusted.
      - Not use with DRV, EFV, LPV/r, RPV.
    - SOF/LDV not to be used with EVG/COBI/TDF/FTC.

HCV Drug Interactions

- http://www.hep-druginteractions.org/



Who Should Be Treated?

- Treatment is recommended for ALL patients except those with short life expectancy
- Prioritizing immediate treatment may be necessary
  - Advanced fibrosis/Cirrhosis
  - Liver transplant
  - Severe extrahepatic symptoms
- Other considerations:
  - Available resources
    - E.g. insurance coverage
  - Drug/alcohol use
  - Adherence
    - e.g. housing stability
  - Treatment should not be withheld simply on the basis of active substance use or cost.

Role of Primary Care

- HCV screening
  - Risk-based and one-time birth cohort screening with HCV Ab.
- Confirmation of HCV infection
  - HCV RNA testing required to confirm infection.
- Counseling
  - HCV transmission/prevention
  - Risks of alcohol use
- Screening in HCV-infected individuals
  - HIV/HAV/HBV
  - Alcohol and substance use disorders

Role of Primary Care

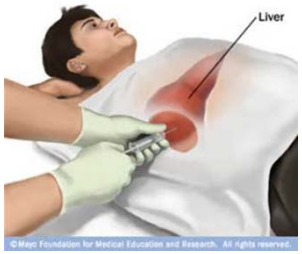
- Vaccination
  - Hep A and B
- Baseline liver assessment
  - CBC, INR, albumin, AST/ALT, bilirubin, alkaline phosphatase, GFR
- Treatment and Referral
  - Patients need to be informed of current effective, well tolerated treatments and referred to provider with HCV treatment expertise.

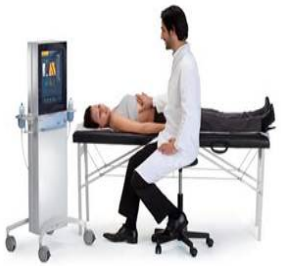
Key Challenges with Integration in Primary Care

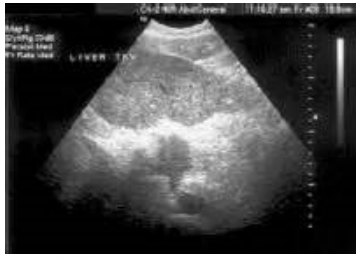
- HCV expertise
  - E.g. Project ECHO model of care delivery
- Potential costs /burden to health center
  - HCV medications
    - Coverage restrictions
    - Prior authorizations
    - Patient assistance programs
  - Lab tests, imaging, biopsies
    - Uninsured
    - Imaging/biopsies may not be needed
  - Medical visits
    - On average, about 3 visits during 12 week treatment

Key Challenges with Integration in Primary Care

- Liver fibrosis assessment
  - Interventional radiology
  - Non-invasive alternatives
    - serum markers, transient elastography
- Medication-related issues
  - Adherence
  - Drug-drug interactions
  - Side effects
- Ongoing alcohol and drug use
- Cirrhosis
  - Hepatocellular carcinoma screening
  - Referral to GI/transplant team







Summary

- HCV integration into primary care is essential to be able to manage the HCV epidemic in the U.S.
- Primary care centers can play an integral role in HCV management and treatment.
- Most management recommendations fall within the purview of primary care and can be easily adopted by health centers.
  - Screening (birth cohort and risk-based)
  - Prevention and transmission counseling
  - Lab tests
  - Vaccination
  - Drug and alcohol counseling
- Treatment of HCV has now become easier and can be managed in primary care with expert guidance, e.g. Project ECHO models of care delivery

Thank you!

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