Summary of Hepatitis C Virus (HCV) Care Model

Acute HCV Infection

Most patients with acute HCV-infection do not have an acute illness nor seek medical care. Symptoms: fatigue, anorexia, mild abdominal pain, low grade fever, nausea, vomitting. <25% develop jaundice; acute liver failure rare (<1%).

Defined as presenting within 6 months of exposure.

Transmitted through infected blood. Major risk factors:

- Injection drug use (IDU) - accounts for at least 60% acute HCV infections in US.
- Healthcare workers after needlestick or mucosal exposure to infected blood.
- HIV-infected men who have unprotected, high-risk sex with men.

See algorithm 1 for screening.

If acute HCV-infection:

- Also screen for HIV and HBV; coinfection may accelerate liver fibrosis. Vaccinate against HAV and HBV if susceptible.
- Avoid hepatotoxic insults (drugs such as acetaminophen and alcohol).
- Educate to lower risk of transmission to others and counsel about high risk behaviors.
- Spontaneous resolution of infection occurs in >20%.
- Majority of people who will clear the infection will do so by 6 months. Those who develop jaundice, elevated ALT, HBsAG positive, female, younger age, HCV genotype 1, and genetic polymorphisms are more likely to spontaneously clear HCV.

Acute HCV Treatment

Treatment decisions should be made with an HCV-specialist.

Only 20% people spontaneously clear the infection; 80% become chronic.

Individual previously cleared of HCV (spontaneously or by treatment) may become reinfected with new exposure: NOT immune to reinfection.

If decision made to initiate treatment during acute phase, monitor HCV-RNA for 12 - 16 weeks, to allow for spontaneous clearance.

Acute treatment has been based on PEG interferon, with or without ribavirin. However, current interferon-sparing treatments for chronic HCV have reduced need for aggressive treatment of acute disease.

AASLD recommendation: until data available showing safety and efficacy of newer treatment strategies for acute HCV infection, monitor for spontaneous clearance for minimum of 6 months. When decision made to treat, follow chronic HCV regimen.

If decision is to treat in acute phase: treatment with PEG interferon earlier (within 12 weeks of diagnosis) more effective than delayed treatment.

Chronic HCV: Screening and History

HCV most common bloodborne infection in US. Estimated 3 - 4 million US have chronic HCV; 50% unaware of infection.

Number of new infections decreased since 1980's (safe sex due to AIDS awareness and testing blood for transfusion).

Chronic HCV infection accounts for 15,000 deaths/yr in US.

One time testing for persons born between 1945 - 1965, regardless of risk factors. Cohort accounts for 3/4th all HCV-infection; prevalance 5x higher than other ages. Risk based screening fails to identify half of HCV infections.

Others screen based on risk factors. See algorithm 2 and table 1:

- Note: low risk of spread (<1%/yr) to heterosexual partner. May spread through tooth brush or razor (blood)
- Note: infection does not confer immunity. Screen periodically if ongoing risk of exposure even if previously cleared HCV.

H&P

- **History**
  - Risk factors for acquiring
  - Presence of significant comorbidities, including other viral infections or other causes liver disease
  - Psychiatric history and barriers to treatment: smoking, drug and alcohol history
  - Medication review (all)
  - History of prior treatment or assessment

Chronic HCV: Physical and Initial Management

H&P - continued

- **Physical**
  - May be normal
  - Stigmata of chronic liver disease: spider angiomata, palmar erythema, gynecomastia, testicular atrophy, hepato-splenomegaly, ascites, jaundice, altered mental status, Caput Medusae, asterixis

Management: as with acute infection:

- Screen for coinfection with HIV and HBV, vaccinate with HAV and HBV if susceptible. Pneumococcal, Flu vaccine and other routine vaccines per CDC guidelines.
- Counsel about reducing risk of transmission.
- Educate patient how to protect liver, including risks of OTC medications and supplements (e.g. iron, acetaminophen)
- Screen for alcohol use and support efforts at abstinence.
  - Strong evidence of deliterious effects of alcohol and progression of liver fibrosis and development of hepatocellular carcinoma (HCC). Also strong correlation between regular marijuana use and progression of fibrosis.
- Encourage weight loss in overweight and obese people with chronic HCV to reduce nonalcoholic fatty liver disease.

Chronic HCVInfection Testing and Natural History

Chronic disease: Anti-HCV positive and HCV-RNA positive.

Lab evaluation:

- Quantitative HCV-RNA test
- HCV genotype
- ALT, AST, albumin, bilirubin, Alk Phos, INR, CBC (with platelets)

Note: patient may have mixed infection (more than 1 genotype)

Determine severity of liver disease initially and serially. See table 2.

Natural History HCV Infection		
Acute HCV	20%	Clear
	80%	Chronic
Chronic HCV	70%	No cirrhosis
	30%	Cirrhosis
Cirrhosis	75%	Slowly progressive
	25%	HCC, Transplant, Death

Fibrosis is a scarring response to chronic inflammation. May progress to cirrhosis.

Typically, 20 - 30 years to develop cirrhosis. Patient usually asymptomatic during this time.

Risk for faster progression to cirrhosis: older age when acquire, coinfection with HIV and/or Hepatitis B, male, alcohol, marijuana, obesity, genetics.

Chronic HCV Infection: Cirrhosis

If cirrhosis present periodic assessment for complications:

- Esophogeal and gastric varicies (EGD)
- Hepatocellular carcinoma (HCC) [6th most common CA world wide and 3rd most common cause of cancer-related death.]
  - US q 6 mo. Accuracy limited by obesity and is technician dependent.
  - Consideration for CT-scan with triple phase protocol every 2 years.
  - More trials needed to determine best approach.

Compensated cirrhosis: do not have symptoms related to cirrhosis, but may have asymptomatic changes (varicies).

Decompensated cirrhosis: development of complications - variceal hemorrhage, ascites, encephalopathy, jaundice, hepatorenal syndrome, spontaneous bacterial peritonitis. Mortality increases with increasing severity.

Extrahepatic manifestations may include: mixed cryoglobulinemia, glomerulonephritis, porphyria cutanea tarda, lichen planus, Insulin resistance, B-cell non-Hodgkin lymphoma, others.

Child-Turcotte Pugh classification and Model for end-stage liver disease (MELD) score are predictors for mortality and prioritization for liver transplantation. See tables 3a and 3b.

Treatment of HCV

Decision to treat must be made through shared decision making, with an individual willing to commit to treatment.

Treatment choice and duration of therapy dependent on:

- Prior treatment experience
- Cirrhosis
- Genotype

HCV Genotype Distribution US*	
1	70%
(1a	40%)
(1b	30%)
2	16 %
3	12%
4	1%
5	< 1%
6	< 1%
*Ethnic, gender, age, regional variations	

See table 4 for treatment options. Unless indicated as alternative, multiple treatments listed are considered equivalent and in no particular order of preference.

Treatment discussion is for general information. Treatment decisions should be made with assistance of a specialist in HCV.

www.hep-druginteractions.org is a useful site to check for interactions with HCV drugs.

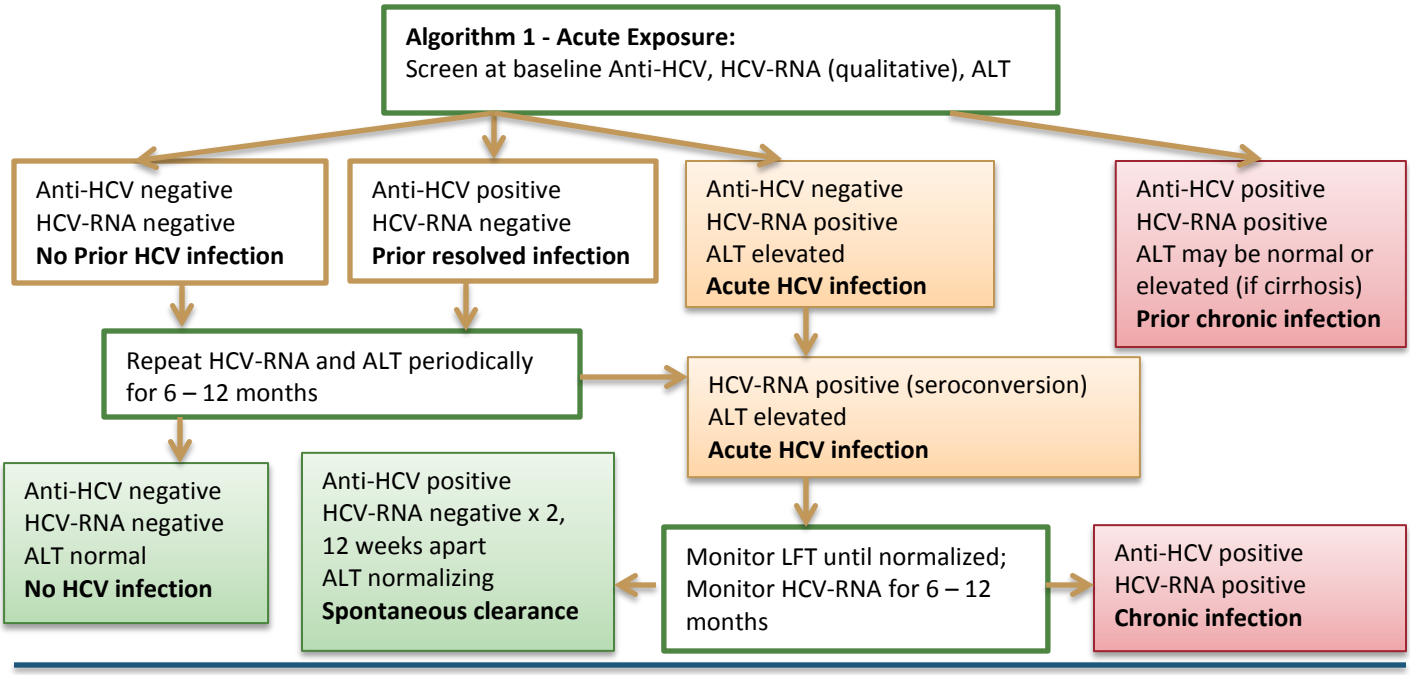
AASLD/IDSA /IAS-USA recommends therapy for all patients with chronic HCV. However, they recognize that the greatest benefit will be realized in those with highest risk. See table 5 for priority listing of patients for treatment.

Goals of HCV Treatment

1. **Cure**: Sustained Virologic Response (SVR) - undetectable HCV RNA 12 or 24 wks after treatment (SVR12 or SVR24). 90 - 100% who achieve SVR12 remain HCV RNA negative years later (unless new exposure).
   - Non (null) responder: minimal decrease viral load
   - Partial responder
   - Relapser: Was undetected viral load, now detected
2. **Reduce risk**: Pt with HCV and compensated cirrhosis who have HCV erradicated have markedly decreased risk of:
   - 10 yr all-cause and liver-related mortality
   - Liver inflammation and fibrosis
   - Liver transplantation
   - Hepatocellular carcinoma
   - Hepatic decompensation
3. **Tolerable treatment**: new direct-acting antivirals (DAA) have much more tolerated side effect profiles and are more convenient than previous therapies .

However, there is a very high cost. (Range $63,000 - $300,000 per treatment, dependent on type and duration.).

AASLD/IDSA/IAS–USA. Recommendations for testing, managing, and treating hepatitis C. http://www.hcvguidelines.org.



Algorithm 2 – Screening for Chronic HCV-infection*:
Screen with Anti-HCV

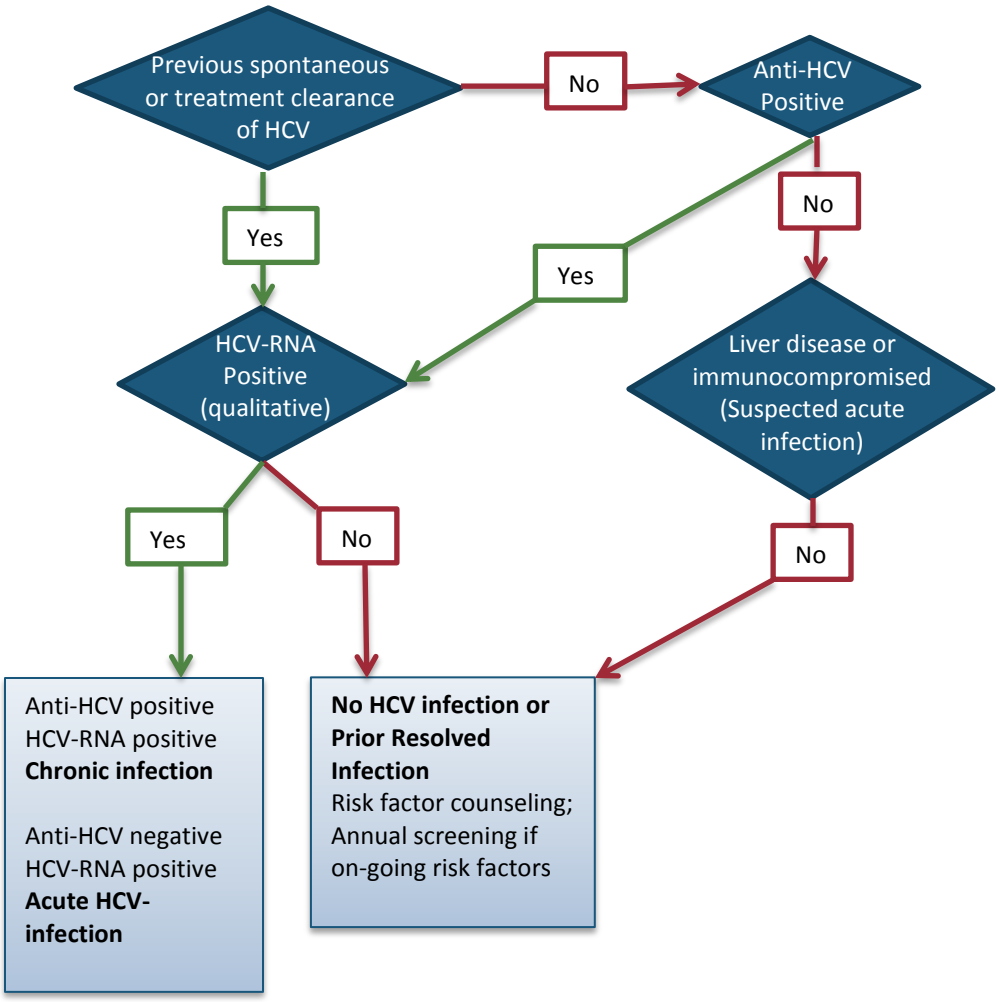


Table 1: *Screening Recommendations	
One time	Born between 1945 – 1965, regardless of risk
One time	Received transfusion before 1992
One time	Received clotting factor before 1987
Risk	Child born to HCV infected mother (7% risk transmission)
Risk	Ever incarcerated
Risk	Ever used IV drugs (60% transmission due to this)
Risk	Intranasal illicit drug use
Risk	Hemodialysis
Risk	Tattoo in unregulated setting
Risk	Healthcare workers exposed to infected blood (needle stick, mucosal) (<2% risk transmission
Risk	HIV positive
Risk	Men who have unprotected sex with men (MSM)
Risk	Unexplained chronic liver disease
Risk-based screening may occur after acute exposure or annually for high risk behaviors (IDU, HIV+ MSM)	

Table 2: Staging Liver Disease		
Test	Benefit	Limitation
History and Physical Exam	• Easy to perform	• Often normal until end stages
Routine Blood Tests Serial	• ALT, AST, albumin, bilirubin, Alk Phos, INR, CBC (with platelets)	• Sensitivity and specificity for chronic hepatitis C
Routine Blood Tests Initial	• Quantitative HCV-RNA, HCV genotype • Renal function, thyroid function, blood glucose, 1,25-OH vitamin D	
Indirect Markers of Cirrhosis	• APRI (AST to Platelet Ratio Index) • FIB-4 (calculated using AST, ALT and platelet count) • FibroIndex (AST, platelet count, gamma globulin) • FibroSure (alpha-2-macroglobulin, haptoglobulin, GGT, apolipoprotein A1, total bilirubin, ALT)	• Different sensitivities and specificities for fibrosis and cirrhosis • Not good for differentiating intermediate states of fibrosis
Direct Markers of Fibrosis	• FibroSpect II (hyaluronic acid, TIMP-1, alpha-2-macroglobulin	• Not good for differentiating intermediate states of fibrosis
Liver biopsy	• Considered Gold Standard • Amount and pattern of fibrosis. Commonly reported as Metavir or Ishak fibrosis score. • Severity of inflammation or steatosis • Exclude other causes liver injury	• Risk of procedure • Sampling artifact
Hepatic Ultrasound	• Non-invasive, loser cost • Evaluates nodularity, vascularity, HCC, spleen size (suggestive of portal hypertension)	• Operator skill
Abdominal CT	• Alternative to US	• Higher cost • Radiation risk
Transient Ultrasound Elastography	• ShearWave Elastography and FibroScan • Good, non-invasive alternative for determining presence or absence of cirrhosis	• Limited by ascites, elevated CVP or obesity
MR Elastography	• Alternative to US Elastography	• More expensive • Same limitations

Table 3a: Child-Turcotte-Pugh Score: http://www.mdcalc.com/child-pugh-score-for-cirrhosis-mortality/			
Clinical and Lab Criteria	**Points**		
	1	**2**	**3**
Encephalopathy	None	Mild – Moderate	Severe
Ascites	None	Mild – Moderate (diuretic responsive	Severe (diuretic refractory)
Bilirubin (mg/dl)	< 2	2 – 3	> 3
Albumin (g/dl)	> 3.5	2.8 – 3.5	< 2.8
Prothrombin time			
Seconds prolonged	< 4	4 – 6	> 6
INR	< 1.7	1.7 – 2.3	> 2.3
Child-Turcotte-Pugh class obtained by adding total points			
Class A	5 – 6 points	Lease severe liver disease	
Class B	7 – 9 points	Moderately severe liver disease	
Class C	10 – 15 points	Most severe liver disease	

Table 3b: Model for End Stage Liver Disease: http://www.mayoclinic.org/medical-professionals/model-end-stage-liver-disease/meld-model-unos-modification			
Complex calculation using serum bilirubin, INR, serum creatinine and a constant			
≥ 40	71% mortality	30 – 39	53% mortality
20 – 29	20% mortality	10 -19	6% mortality
< 9	2% mortality		
Refer to transplant center if MELD > 10			

Table 4: Treatment Guidelines AASLD/IDSA/IAS-USA† (Continued on next page)					
Geno-type	**Prior Treatment**	**Cirrhosis***	**Medication**	**Duration (Weeks)**	**Comments**
1a	Treatment Naïve	No	Harvoni[1]	12 ^	Brand : Generic Names [1] Harvoni : Ledipasvir + Sofosbuvir [2] Viekira Pak : Ombitasvir + Paritaprevir + Ritonavir + Dasabuvir [3] Sovaldi : Sofosbuvir [4] Olysio : Simeprevir
		Yes	Harvoni	12	
		No	Viekira Pak[2] + Ribavirin	12	
		Yes	Viekira Pak + Ribavirin	24	
		No	Sovaldi[3] + Olysio[4] ± Ribavirin	12	
		Yes	Sovaldi + Olysio ± Ribavirin	24	
	Retreat (had Peg + Ribavirin)	No	Harvoni	12	
		Yes	Harvoni	24	
		Yes	Harvoni + Ribavirin	12	† Not including people with decompensated cirrhosis, coinfection with HIV, renal impairment, acute HCV, post-transplant
		No	Viekira Pak + Ribavirin	12	
		Yes	Viekira Pak + Ribavirin	24	
		No	Sovaldi + Olysio ± Ribavirin	12	
		Yes	Sovaldi + Olysio ± Ribavirin	24	
**	Retreat (had Sovaldi)	No	Limited data, consider deferral		*Compensated Cirrhosis
		Yes	Harvoni ± Ribavirin	24	
	Retreat (had Triple therapy)	No	Harvoni	12	^May treat 8 weeks if low viral load (with caution)
		Yes	Harvoni	24	
		Yes	Harvoni + Ribavirin	12	
1b	Treatment Naïve	No	Harvoni	12 ^	††Limited data. Treatment recommended if advanced fibrosis
		Yes	Harvoni	12	
		No	Viekira Pak	12	
		Yes	Viekira Pak + Ribavirin	12	**Limited data
		No	Sovaldi + Olysio	12	
		Yes	Sovaldi + Olysio	24	^^ No differentiation made +/- cirrhosis
	Retreat (had Peg + Ribavirin)	No	Harvoni	12	
		Yes	Harvoni	24	▫(Viekira Pak without Dasabuvir
		Yes	Harvoni + Ribavirin	12	
		No	Viekira Pak	12	
		Yes	Viekira Pak + Ribavirin	12	
		No	Sovaldi + Olysio ± Ribavirin	12	
		Yes	Sovaldi + Olysio ± Ribavirin	24	
**	Retreat (had Sovaldi)	No	Limited data, consider deferral		
		Yes††	Harvoni ± Ribavirin	24	
	Retreat (had Triple therapy)	No	Harvoni	12	
		Yes	Harvoni	24	
		Yes	Harvoni + Ribavirin	12	
2	Treatment Naïve	No	Sovaldi + Ribavirin	12	
		Yes	Sovaldi + Ribavirin	16	
	Retreat (had Peg + Ribavirin)	No	Sovaldi + Ribavirin	12	
	Alternative	No	Sovaldi + Ribavirin + Peginterferon	12	
		Yes	Sovaldi + Ribavirin	16	
	Alternative	Yes	Sovaldi + Ribavirin + Peginterferon	16	
3	Treatment Naïve	No / Yes^^	Sovaldi + Ribavirin	24	
	Alternative	No / Yes^^	Sovaldi + Ribavirin + Peginterferon	12	
	Retreat (had Peg + Ribavirin)	No / Yes^^	Sovaldi + Ribavirin	24	
	Alternative	No / Yes^^	Sovaldi + Ribavirin + Peginterferon	12	

Table 4: Treatment Guidelines AASLD/IDSA/IAS-USA† (Continued from previous page)					
Geno-type	**Prior Treatment**	**Cirrhosis***	**Medication**	**Duration (Weeks)**	**Comments**
4**	Treatment Naïve	No / Yes^^	Harvoni	12	
		No / Yes^^	Sovaldi + Ribavirin	24	
	Alternative	No / Yes^^	Sovaldi + Ribavirin + Peginterferon	12	
	Alternative	No / Yes^^	Sovaldi + Olysio ± Ribavirin	12	
	Retreat (had Peg + Ribavirin)	No / Yes^^	Harvoni	12	
		No / Yes^^	Ombitasvir+Paritaprevir+Ritonavir + Ribavirin	12	
		No / Yes^^	Sovaldi + Ribavirin + Peginterferon	12	
		No / Yes^^	Sovaldi + Ribavirin	24	
5**	Treatment Naïve	No / Yes^^	Sovaldi + Ribavirin + Peginterferon	12	
	Alternative	No / Yes^^	Ribavirin + Peginterferon	48	
	Retreat	No / Yes^^	Sovaldi + Ribavirin + Peginterferon	12	
	Alternative	No / Yes^^	Ribavirin + Peginterferon	48	
6**	Treatment Naïve	No / Yes^^	Harvoni	12	
	Alternative	No / Yes^^	Sovaldi + Ribavirin + Peginterferon	12	
	Retreat	No / Yes^^	Harvoni	12	
	Alternative	No / Yes^^	Sovaldi + Ribavirin + Peginterferon	12	

Table 5: AASLD/IDSA/IAS-USA When and Whom to Initiate HCV Therapy
Highest Priority due to Highest Risk Severe Complications
Advanced fibrosis (Metavir F3) or compensated cirrhosis (Metavir F4)
Organ transplant
Type 2 or 3 essential mixed cryoglobulinemia with end-organ manifestations (vasculitis)
Proteinuria, nephrotic syndrome, or membranoproliferative glomerulonephritis
High Priority due to High Risk of Complications
Fibrosis (Metavir F2)
HIV coinfection
HBV coinfection
Other coexistent liver disease (NASH)
Debilitating fatigue
Type 2 DM
Porphyria cutanea tarda
Priority due to Elevated Risk of Transmission to Others
Men who have sex with men with high risk sexual practices
Active injection drug users
Persons on long term hemodialysis
Incarcerated persons
HCV-infected women of child-bearing potential wishing to get pregnant
Not Candidate
Severely limited lifespan