Hepatitis C in HIV Infected Patients 101

ETAC Project Team

Initial HCV screening is best performed by?

1. HCV enzyme immunoassay (EIA)
2. Recombinant immunoblot assay (RIBA)
3. EIA and if positive followed by RIBA
4. Qualitative HCV RNA
5. 2 and 4

Initial HCV screening is best performed by?

1. HCV enzyme immunoassay (EIA)

- RIBA is no longer recommended
- Qualitative HCV RNA is not recommended

Confirming a positive HCV antibody test should be done by ordering?

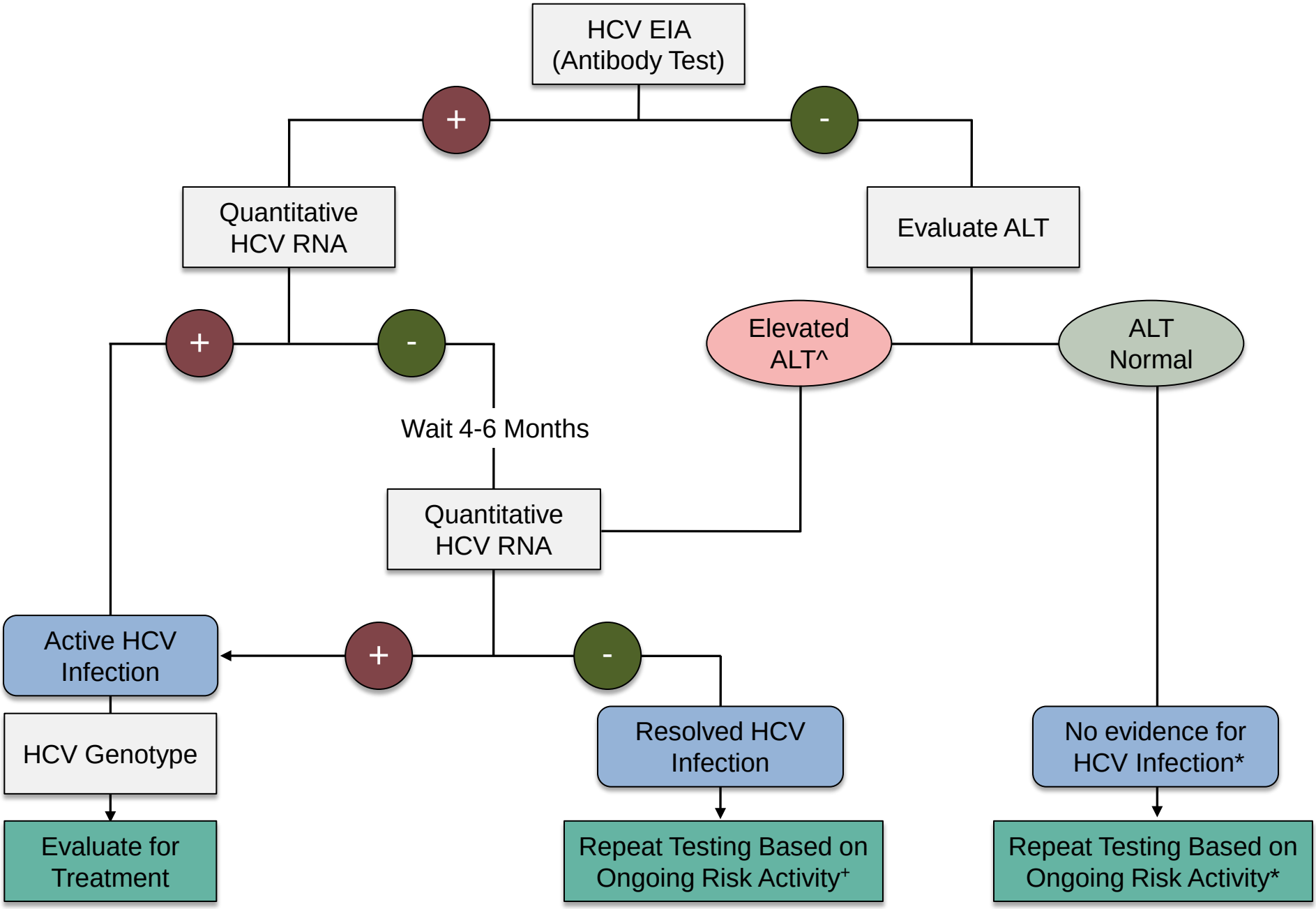
1. Recombinant immunoblot assay (RIBA)
2. Quantitative HCV RNA
3. Qualitative HCV RNA
4. 1&2 above
5. 1&3 above

Confirming a positive HCV antibody test should be done by ordering?

2. Quantitative HCV RNA

- Patients with positive HCV EIA should undergo quantitative HCV RNA testing to determine whether they have active or resolved HCV infection.

Figure 1. HCV Testing Algorithm



Indications for HCV RNA Testing in HCV-Seronegative Patients

- Persistently elevated ALT levels
- Acute HCV infection is suspected
- Suspect false-negative EIA HCV antibody tests
  - severe immunodeficiency (CD4 count < 100 cells/mm^3)
  - dialysis.
- Suspect“window period”
- If HCV RNA testing is negative in this setting repeat HCV EIA annually if has ongoing risk

Baseline Studies in Persons with Established Chronic HCV

- Routine Laboratory Studies.
- HCV Genotype.
- Quantitative HCV RNA.
- IL-28B Testing.
- Screening for Other Causes of Liver Disease

Disease Severity

- Similar to HBV, but 80% go on to chronic disease (rather than 5% in adults)
- 15-30 years, 20% cirrhosis, ESLD or CA in 5% or more
- In US, most common reason for liver transplantation
- Course accelerated by *ANY* alcohol consumption, HIV

Figure 2. Child-Pugh Classification for Severity of Cirrhosis

Clinical and Lab Criteria	Points*		
	1	2	3
Encephalopathy	None	Mild to moderate (grade 1 or 2)	Severe (grade 3 or 4)
Ascites	None	Mild to moderate (diuretic responsive)	Large or refractory to diuretics
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
International normalized ratio	<1.7	1.7-2.3	>2.3

***Point System and Classification**
-Class A (5 to 6 points): least severe liver disease
-Class B (7 to 9 points): moderately severe liver disease
-Class C (10 to 15 points): most severe liver disease

Signs and symptoms of cryoglobulinemia include:

1. Peripheral neuropathy
2. Palpable purpura &/or arthralgias
3. Renal disease
4. 2 & 3
5. All the above

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HCV Genotyping

- 6 major HCV genotypes
- US, approximately 75% genotype 1, 90% in AA
- Genotype 1 or 4 : poor response to treatment
- Genotypes 2 or 3 and: better response to treatment
- Genotype determine ribavirin dose
- Limited data exist with HCV genotypes 5 and 6.

HCV Treatment Medications and Doses

Medication	Recommended Dose
Treatment for HCV Genotypes 1 and 4	
Peginterferon alfa-2a *plus* Ribavirin	180 µg SQ once/week ≤ 75 kg: 1000 mg/d >75 kg: 1200 mg/d
Peginterferon alfa-2b *plus* Ribavirin	1.5 µg/kg SQ once/week ≤ 65 kg: 800 mg/d 66-80 kg: 1,000 mg/d 81-105 kg: 1,200 mg/d >105kg: 1,400 mg/d
Treatment for HCV Genotypes 2 and 3	
Peginterferon alfa-2a *plus* Ribavirin	180 µg SQ once/week 800 mg/d
Peginterferon alfa-2b *plus* Ribavirin	1.5 µg/kg SQ once/week 800 mg/d

Liver biopsy should be considered, but not required, to evaluate the stage of liver disease prior to initiating HCV therapy?

1. True
2. False

Liver biopsy should be considered, but not required, to evaluate the stage of liver disease prior to initiating HCV therapy?

1. True

Liver Biopsy

- Helpful in patients in whom treatment is less desirable i.e. genotypes 1 or 4 and a HCV RNA level greater than 400,000 IU/ml, risk of drug toxicities
- Not be routinely performed for patients in whom HCV treatment is planned regardless of results
- Not indicated in persons with acute HCV infection.

Non-invasive tests for estimating liver fibrosis:

1. Are not recommended for routine use
2. Are best in differentiating minimal from advanced fibrosis
3. Must be ordered if a patient refuses or cannot undergo a liver biopsy
4. 1 & 2 are true
5. All the above are true

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Non-invasive tests determining fibrosis

- Best in differentiating minimal fibrosis from advanced fibrosis (cirrhosis)
- Should be considered in patients who refuse or are unable to undergo liver biopsy.
- Currently available:
  - HCV FiboSURE™, ALT, AST, platelet count, AST-Platelet Ratio Index (APRI), and FIB-4.
  - Transient elastography (FibroScan®) used in combination with serum markers.

Management of HCV/HIV Patients

- Baseline evaluation
- Modify risk factors for liver decompensation
- Assessment and management of ETOH and Polysubstance abuse
- Monitor for cirrhosis and HCC, referral if needed
- Assessment for treatment readiness

Patients with chronic HCV who have not been treated and do not plan to be treated should have an annual HCV RNA test?

1. True
2. False

Patients with chronic HCV who have not been treated and do not plan to be treated should have an annual HCV RNA test?

2.False

If Therapy is Not Initiated

- Monitor for liver disease complications
- Abstain from alcohol use
- Limit acetaminophen to less than 2 grams/day
- Avoid NSAIDS
- Avoid raw seafood
- Maintain a normal body mass index (< 25 kg/m^2),
- Avoid iron supplements
- Reevaluate yearly for HCV treatment and assist for treatment readiness.
- If HCV therapy due to minimal liver disease, repeat fibrosis staging Q 2-4 year.

Hepatitis A and Hepatitis B Immunization

- Screen all HCV-infected persons with total HAV antibody, hepatitis B surface antibody (HBsAb), and HBsAg.
- Vaccinate all patients without immunity.
- If CD4 <200 cells/mm^3 , follow up titers 4-6 weeks after completion of the vaccine series
- Non-responders should repeat the entire vaccine series.
- If CD4 cell <200 cells/mm^3, defer the repeat vaccination series until the CD4 >200 cells/mm^3.

Why treat HCV?

- Treatment of HCV has the potential to result in cure
- ↓risk of developing cirrhosis and end-stage liver disease, HCC
- ↓ risk of ART-induced hepatitis
- ↓extrahepatic complications
- ↓transmission of HCV to others.

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Indications for HCV Therapy

- Patient willing and motivated to treat
- Acute HCV infection
- A biopsy showing chronic hepatitis with significant fibrosis (greater than portal fibrosis)
- Cryoglobulinemic vasculitis
- Cryoglobulinemic membranoproliferative glomerulonephritis
- Stable HIV infection
- Compensated liver disease
- Acceptable hematologic parameters
- Serum creatinine < 1.5 mg/dl

Absolute Contraindications for HCV Therapy

- Uncontrolled active major psychiatric illness
- Hepatic decompensation
- Uncontrolled HIV with advanced immunosuppression (CD4 < 100 cells/mm^3)
- Known allergy or severe adverse reaction to interferon and/or ribavirin
- Severe concurrent medical disease
- Untreated thyroid disease
- Patients concurrently receiving didanosine
- Women who are pregnant, nursing, or not able to practice contraception
- Men who have pregnant partners
- Sarcoidosis
- Active, untreated autoimmune disease
- Hemoglobinopathies

Relative Contraindications for HCV Therapy

- Significant hematologic abnormality: hemoglobin < 10.0 g/dl, absolute neutrophil count < 1,000/µl, or platelet count < 50,000/µl
- CD4 <200 cells/mm^3
- Patients on dialysis or CCr<60 mL/min
- Uncontrolled DM
- Patients concurrently receiving AZT
- Autoimmune disorders
- Ongoing heavy alcohol use
- Active substance use if interference with adherence is anticipated
- Untreated mental health disorder
- Solid organ transplantation patients

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Recommended Monitoring During Treatment with Peginterferon plus Ribavirin

	Treatment Week											Post-Treatment Week		
	0	**2**	**4**	**8**	**12**	**18**	**24**	**30**	**36**	**42**	**48**	**4**	**12**	**24**
CBC	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CMP	X	X	X	X	X	X	X	X	X	X	X	X	X	X
TSH	X				X		X		X		X			X
HCV RNA	X		X		X		X		X		X			X
CD4 Cell Count	X				X		X		X		X		X	X
HIV RNA	X				X		X		X		X		X	X
Depression Screen	X		X		X		X		X		X	X		
Clinician Visit	X		X	X	X	X	X	X	X	X	X	X		X

Virologic Response

- Rapid Virologic Response (RVR)
- Early Virologic Response (EVR)
  - lack of EVR=“ Stopping Rule”
- End-of-Treatment Response (ETR)
- Sustained Virologic Response (SVR)
- Relapse
- Breakthrough

In which situation should an end of treatment viral load be assessed to determine if durable HCV eradication has occurred?

- 1. Week 4 viral load – undetectable
- 2. Week 12 viral load - 1 log reduction
- 3. Week 24 viral load – 3 log reduction – 3000 copies
- 4. Week 48 viral load – 12,000 copies/mL

In which situation should an end of treatment viral load be assessed to determine if durable HCV eradication has occurred?

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Evaluation of treatment response:

- **Treatment Week 4** provides an early assessment regarding the likelihood of SVR
- **Treatment Week 12.** HCV treatment should be discontinued in patients who fail to have ≥2 $\log_{10}$ reduction in HCV RNA level at week 12 compared to baseline HCV RNA level (EVR)
- **Treatment Week 24.** Patients with partial EVR at week 12. Should discontinue treatment if still detectable at week 24.
- **End of Treatment**. (ETR)

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Side Effects of the Therapy

- HIV: ↑ side effects
- The most common initial flu-like symptoms
- Common Side effects N/V, fatigue, weight loss, rash and neuropsychiatric effects
- Peginterferon: autoimmune thryoiditis, cytopenias, ↓CD4(not CD4%), retinal hemorrhage
- Ribavirin: anemia, teratogenic

Influenza-like Symptoms

- Usually seen 4 to 6 hours after the peginterferon ,may persist over several days.
- Self-limited
- Prophylaxix with NSAIDS or acetaminophen (< 2000 mg/day)
-

Fatigue

- Up to 90%
- Muli-factorial
- Neurovegetative symptoms may be treated with antidepressant agents
- Exercise regimen can reduce fatigue

Which of the following is true regarding management of depression during HIV/HCV treatment?

- 1. Mild depression must be co-managed with a mental health professional
- 2. Interferon dose reduction should be performed for the onset of any depressive symptoms during treatment
- 3. Moderate to severe depression can be managed with mental health counseling and antidepressant therapy without interferon dose adjustment
- 4. Antidepressant therapy, if initiated, should be continued for 2-3 months after HCV treatment discontinuation

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Depression

- **Monitoring for Depression During Treatment:** Centers for Epidemiologic Study Depression Scale (CES-D), the 9-item patient health questionnaire (PHQ-9), Beck's Depression Inventory (BDI), or the Zung depression scale (Z-SDS)
- **Management of Mild Depression**.
- **Management of Moderate to Severe Depression** evaluation by a mental health professional and dose reduction of peginterferon:
  - reduce peginterferon alfa-2a from 180 to 135 mcg and peginterferon alfa-2b from 1.5 to 1.0 mcg/kg.
  - in person evaluations at least every 2 weeks
  - Evaluate for suicidal ideation

- **Duration of Antidepressant Therapy.**
  - antidepressants should be continued for the total duration of HCV treatment and for 2 to 3 months after treatment cessation

Management of Cytopenias

- Stepwise dose reduction of peginterferon or ribavirin dose
- Colony stimulating factor
- Temporary hold or discontinue the therapy

Post Treatment Monitoring

- Follow up for resolution of adverse events at 4, 12 and 24 week
  - Cytopenias usually resolve within 4–8 weeks
  - Depression, may take longer follow for at least 3 months post treatment.
- Monitor HCV RNA PCR at 4, 12, and 24 weeks after therapy.
- SVR =HCV RNA undetectable at post-treatment week 24
-

Future Drug Classes.

- Target specific functions of the hepatitis C virus
  - HCV NS5B polymerase
  - NS3 serine protease
  - NS5A region.

Which of the following new HCV drug classes is furthest along in development?

- 1. Novel interferon compounds
- 2. NS3 serine protease inhibitors
- 3. NS5B polymerase inhibitors
- 4. ribavirin analogues

Which of the following new HCV drug classes is furthest along in development?

- 2. NS3 serine protease inhibitors
- Both Telaprevir and Boceprevir are serine protease inhibitors

Telaprevir, Incivek(Vertex)

- The serine protease inhibitor
- treatment discontinuation rate due severe, treatment-limiting rash in up to 7% of patients
- gastrointestinal side effects
- Anemia
- viral breakthrough and relapse with HCV variants resistant to telaprevir was observed in most patients who did not achieve SVR

Boceprevir, Victrelis(Merck)

- serine protease inhibitor
- significant anemia
- No rash has been reported
- Similar to telaprevir, patients with viral breakthrough and viral relapse were found to have HCV variants resistant to boceprevir

Conclusion

- Properly staged and a thoughtful decision should be made regarding HCV treatment
- If patient is no a treatment candidate, closely monitor and modify factors for liver decompensation
- Aggressive monitoring and treatment of HIV/HCV-infected persons
- Liver transplantation is an option for HIV/HCV-coinfected