

AASLD/IDSA Guidelines: Recommendations for Testing, Managing, and Treating Hepatitis C

Jay R. Kostman, MD

Clinical Professor of Medicine

Associate Director, Center for Viral Hepatitis

Perelman School of Medicine

Learning Objectives

Upon completion of this presentation, learners should be better able to:

- Review current recommendations for testing and linkage to care
- Describe current recommendations on HCV treatment prioritization
- State which regimens are recommended for HCV treatment by genotype, treatment experience, and stage of liver disease
- Describe recommendations for monitoring before and during treatment

Faculty and Planning Committee Disclosures

Please consult your program book.

Off-Label Disclosure

There will be no off-label/investigational uses discussed in this presentation.

AASLD/IDSA/IAS–USA Hepatitis C Guidance

- HCV Testing and Linkage to Care
- When and In Whom To Initiate Therapy
- Initial Treatment of HCV Infection
- Retreatment of Persons in Whom Prior Therapy has Failed
- Patient Monitoring Before, During or After Treatment
- Unique Patient Populations
 - HIV/HCV Coinfection
 - Decompensated Cirrhosis
 - Post-Transplant
 - Renal Failure

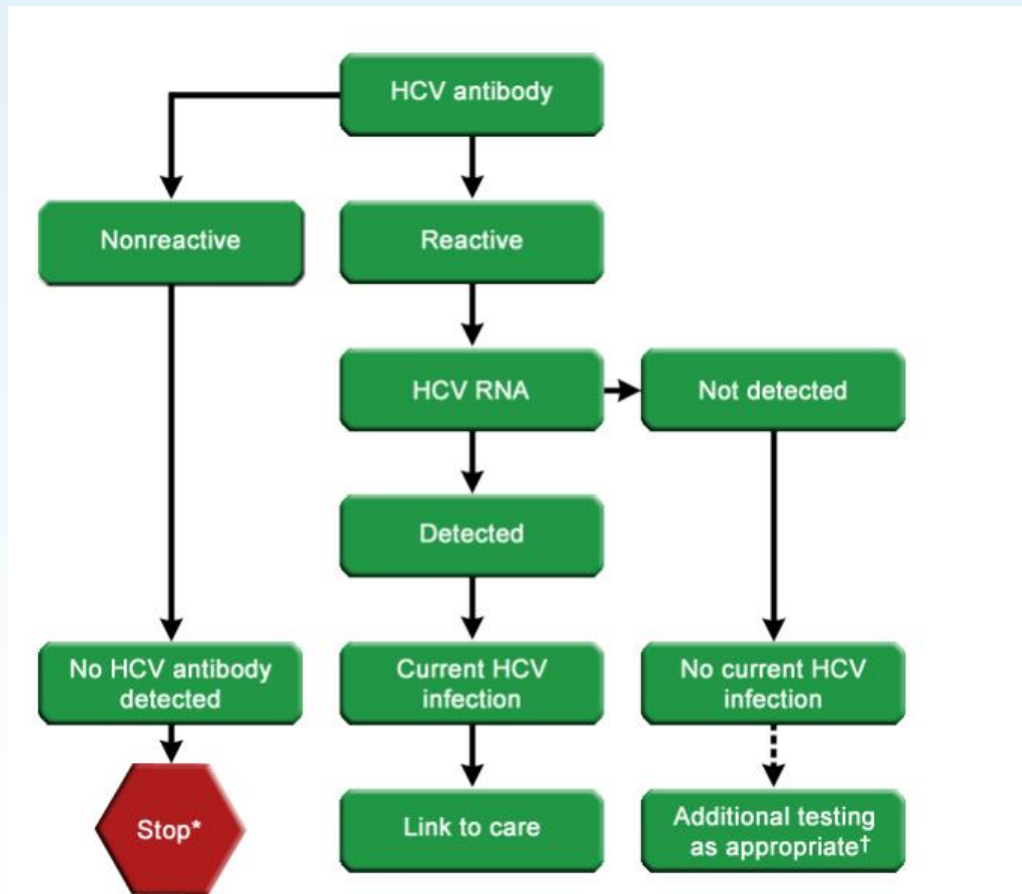
Grading System Used to Rate the Level of the Evidence and Strength of the Recommendation for Each Recommendation

Recommendations are based on scientific evidence and expert opinion. Each recommended statement includes a Roman numeral (I, II, or III) that represents the level of the evidence that supports the recommendation, and a letter (A, B, or C) that represents the strength of the recommendation.

Classification	Description
Class I	Conditions for which there is evidence and/or general agreement that a given diagnostic evaluation, procedure, or treatment is beneficial, useful, and effective
Class II	Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness and efficacy of a diagnostic evaluation, procedure, or treatment
Class IIa	Weight of evidence and/or opinion is in favor of usefulness and efficacy
Class IIb	Usefulness and efficacy are less well established by evidence and/or opinion
Class III	Conditions for which there is evidence and/or general agreement that a diagnostic evaluation, procedure, or treatment is not useful and effective or if it in some cases may be harmful

Level of Evidence	Description
Level A*	Data derived from multiple randomized clinical trials, meta-analyses, or equivalent
Level B*	Data derived from a single randomized trial, nonrandomized studies, or equivalent
Level C	Consensus opinion of experts, case studies, or standard of care

CDC Recommended Testing Sequence for Identifying Current HCV Infection



Common Barriers to HCV Treatment

- Contraindications to treatment (eg, comorbidities, substance abuse, and psychiatric disorders)
- Competing priority and loss to follow-up
- Long treatment duration and adverse effects
- Lack of access to treatment (high cost, lack of insurance, geographic distance, and lack of availability of specialists)
- Lack of practitioner expertise

Strategies for Overcoming Barriers

- Counseling and education
- Mental Health and substance use services
- Optimize treatment with simpler and less toxic regimens
- Engage case managers and patient navigators (HIV model) or co-localize services
- Collaboration with specialists (eg, via Project ECHO-like models and telemedicine)

When and in Whom to Initiate HCV Therapy –Highest Priority

- **Advanced fibrosis (Metavir F3) or compensated cirrhosis (Metavir F4)**
 - Rating: Class I, Level A
- **Organ transplant**
 - Rating: Class I, Level B
- **Type 2 or 3 essential mixed cryoglobulinemia with end-organ manifestations (eg, vasculitis)**
 - Rating: Class I, Level B
- **Proteinuria, nephrotic syndrome, or membranoproliferative glomerulonephritis**
 - Rating: Class IIa, Level B

High Priority for Treatment Owing to High Risk for Complications

- Fibrosis (Metavir F2)
 - Rating: Class I, level B
- HIV-1 coinfection
 - Rating: Class I, Level B
- Hepatitis B virus (HBV) coinfection
 - Rating: Class IIa, Level C
- Other coexistent liver disease (eg, [NASH])
 - Rating: Class IIa, Level C
- Debilitating fatigue
 - Rating: Class IIa, Level B
- Type 2 Diabetes mellitus (insulin resistant)
 - Rating: Class IIa, Level B
- Porphyria cutanea tarda
 - Rating: Class IIb, Level C

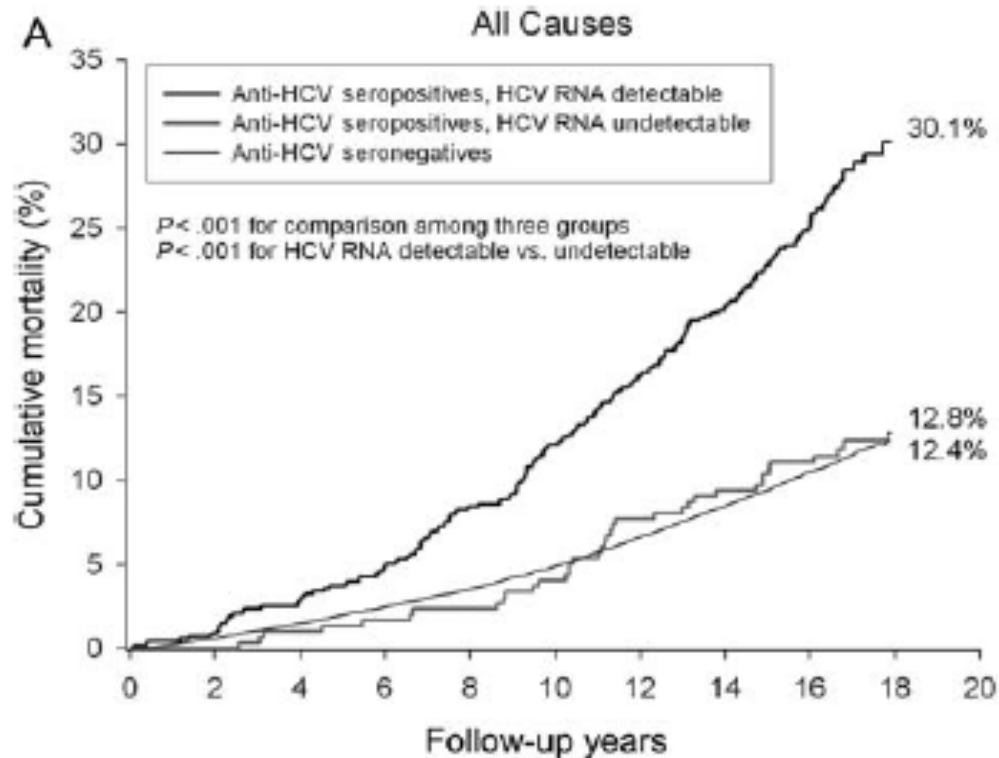
Persons At Elevated Risk of HCV Transmission and in Whom HCV Treatment May Yield Transmission Reduction Benefits

- Men who have sex with men (MSM) with high-risk sexual practices
- Active injection drug users
- Incarcerated persons
- Persons on long-term hemodialysis
- HCV-infected women of child-bearing potential wishing to get pregnant
- HCV-infected health care workers who perform exposure-prone procedures
 - Rating: Class IIa, Level C

Summary--Treatment Benefits All Pts

- AASLD/IDSA guidance emphasizes the potential benefits of—and recommends treatment for—all pts with HCV infection
- Urgent treatment initiation recommended for:
 - Advanced fibrosis (Metavir F3)
 - Compensated cirrhosis (Metavir F4)
 - Liver transplantation
 - Severe extrahepatic HCV
- Reduced HCV transmission expected with treatment of:
 - Women wishing to become pregnant
 - Long-term hemodialysis pts
 - MSM with high-risk sexual practices
 - Injection drug users
 - Incarcerated persons

HCV Viral Replication Increases All Cause Mortality

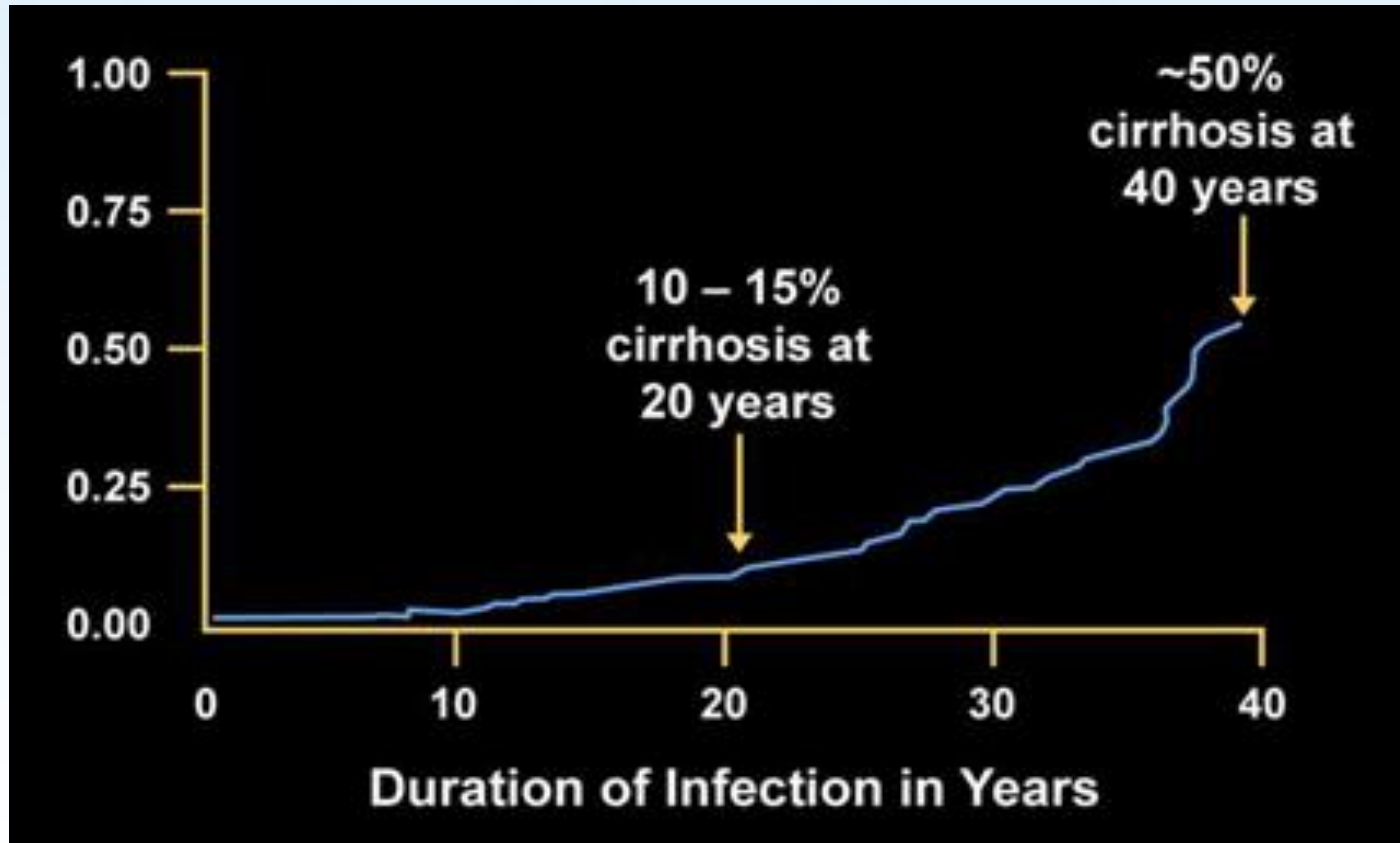


REVEAL HCV. Journal of Infectious Diseases 2012

Factors Associated with Accelerated Fibrosis Progression

- Host
 - Non-Modifiable
 - Fibrosis stage
 - Inflammation grade
 - Older age at time of infection
 - Male sex
 - Organ transplant
 - Modifiable
 - Alcohol consumption
 - Nonalcoholic fatty liver disease
 - Obesity
 - Insulin resistance
- Viral
 - Genotype 3
 - Coinfection with hepatitis B virus (HBV) or HIV

Progression is Probably Not Linear: Importance of Duration and Aging



Adapted from: Poynard T, et al. *J Hepatol.* 2001;34(5):730-739.

Recommended assessments prior to starting antiviral therapy

- Assessment of potential drug-drug interactions with concomitant medications
- The following laboratory tests are recommended within 12 weeks prior to starting antiviral therapy:
 - CBC and INR
 - albumin, total and direct bilirubin, alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase
 - Calculated glomerular filtration rate (GFR)
 - HCV genotype and subtype (at any time)
 - Quantitative HCV viral load, except in the circumstance that a quantitative viral load will influence duration of therapy (at any time)

AASLD/IDSA HCV Guidelines.

Recommended monitoring during antiviral therapy

- CBC, creatinine, liver panel at 4 weeks and as clinically indicated (ie-CBC on ribavirin)
- Monitor for adherence (clinic visits, telephone monitoring, etc)

AASLD/IDSA HCV Guidelines.

Recommended Regimens for GT1

- Options listed alphabetically, not by order of preference
- LDV/SOF (QD) ± RBV for 12-24 wks
- OMV/PTV/RTV (QD) + DSV (BID) ± RBV for 12-24 wks
 - Not recommended for pts with prior PI failure
- SMV (QD) + SOF (QD) ± RBV for 12-24 wks
 - Not recommended for pts with prior SOF or PI failure
- Regimens no longer recommended for GT1
 - SOF + RBV, pegIFN, boceprevir, telaprevir

Recommended Regimens for Treatment-Naive GT1 HCV Pts

Subtype	Noncirrhotic		Compensated Cirrhotic	
	Regimen	Duration, Wks	Regimen	Duration, Wks
GT1a or 1b	LDV/SOF	12*	LDV/SOF	12
GT1a	OMV/PTV/RTV + DSV + RBV	12	OMV/PTV/RTV + DSV + RBV	24
GT1b	OMV/PTV/RTV + DSV	12	OMV/PTV/RTV + DSV + RBV	12
GT1a	SMV + SOF ± RBV	12	SMV + SOF ± RBV	24
GT1b	SMV + SOF	12	SMV + SOF	24

*Shorter course can be considered in pts with pretreatment HCV RNA < 6 million IU/mL at provider's discretion but should be done with caution.

Recommended Regimens for Treatment-Experienced GT1 HCV Pts

Population	Noncirrhotic		Compensated Cirrhotic	
	Regimen	Duration, Wks	Regimen	Duration, Wks
Prior PegIFN/RBV				
▪ GT1a or 1b	LDV/SOF	12	LDV/SOF	24
▪ GT1a or 1b			LDV/SOF + RBV	12
▪ GT1a	OMV/PTV/RTV + DSV + RBV	12	OMV/PTV/RTV + DSV + RBV	24
▪ GT1b	OMV/PTV/RTV + DSV	12	OMV/PTV/RTV + DSV + RBV	12
▪ GT1a or 1b	SMV + SOF ± RBV	12	SMV + SOF ± RBV	24
Prior SOF				
▪ GT1a or 1b	Defer therapy*		LDV/SOF ± RBV	24
Prior PI				
▪ GT1a or 1b	LDV/SOF	12	LDV/SOF	24
▪ GT1a or 1b			LDV/SOF + RBV	12

*Based on limited available data, pts without advanced fibrosis and without an urgent need for HCV treatment should defer antiviral therapy pending additional data or consider clinical trial.

All-Oral Regimens for Other Populations

Population	Regimen	Duration
GT2	SOF + RBV ^[1]	12 wks
GT3	SOF + RBV ^[1]	24 wks
GT1/2/3/4 HCC pre-OLT	SOF + RBV ^[1]	48 wks*
GT1, post-OLT (Metavir \leq 2)	OMV/PTV/RTV + DSV + RBV ^[2]	24 wks
GT1/4 decompensated cirrhosis (CTP B or C)	SOF/LDV + RBV ^{†[3]}	12 wks [‡]
GT2/3 decompensated cirrhosis (CTP B or C)	SOF + RBV ^{†[3]}	Up to 48 wks

*Up to 48 wks or until transplantation, whichever occurs first. †Not FDA approved but recommended in AASLD/IDSA guidance. ‡24 wks of SOF/LDV if anemia or RBV intolerance; 24 wks of SOF/LDV + RBV (600 mg/day with increasing dose if tolerated) if prior SOF failure.

AASLD/IDSA HCV Guidelines.

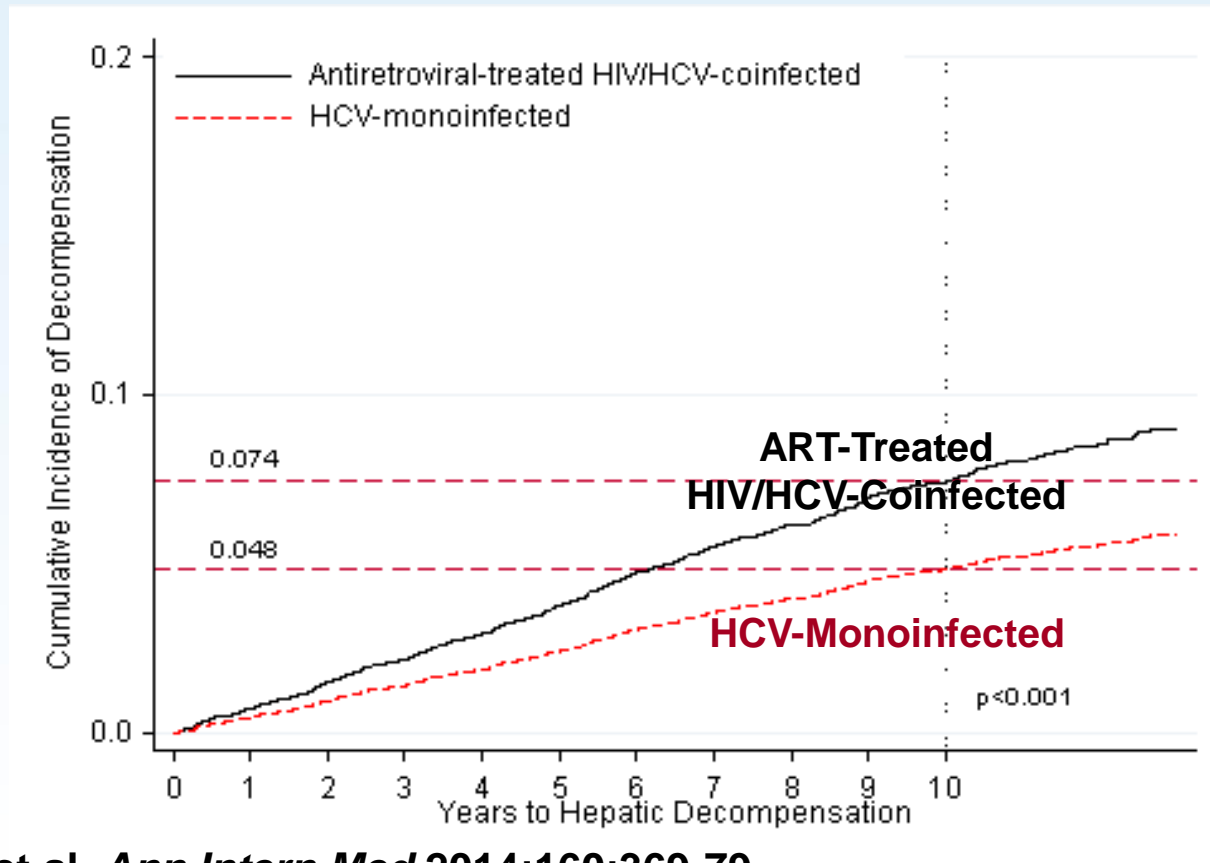
Recommended Regimens for GT4

- Recognizing that data are limited, AASLD/IDSA guidance makes these recommendations
 - LDV/SOF for 12 wks
 - OMV/PTV/RTV + RBV for 12 wks
 - SOF + RBV for 24 wks
 - Recommended in treatment-experienced and as alternative for treatment-naive pts: SOF + RBV + pegIFN for 12 wks
 - Alternative for treatment-naive pts: SOF + SMV ± RBV for 12 wks

Guidance for HCV/HIV Coinfection

- Same recommendations as in HCV-monoinfected pts
- Consider drug–drug interactions
 - Need to adjust or withhold RTV if receiving a boosted PI with OMV/PTV/RTV + DSV
 - Potential for LDV-mediated increase in tenofovir levels, especially if tenofovir used with RTV
 - Avoid LDV if CrCl < 60 mL/min or if receiving tenofovir with RTV-boosted PI
 - Do not interrupt antiretroviral therapy
 - Other interactions at aidsinfo.nih.gov/guidelines, hiv-druginteractions.org
- Do not use OMV/PTV/RTV ± DSV in coinfecting pts not taking antiretroviral therapy

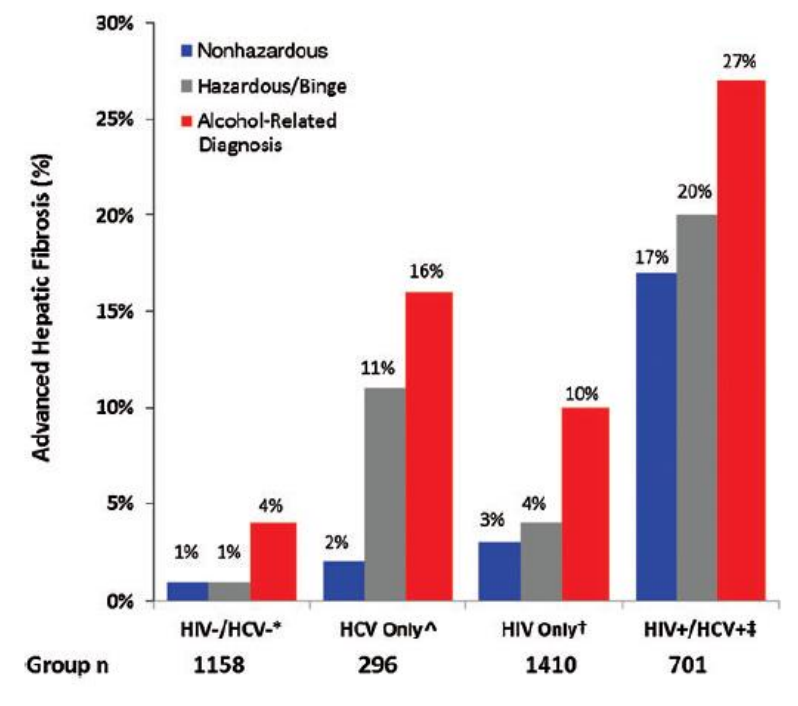
Liver Decompensation Rates are Higher in HIV/HCV vs. HCV Only Patients



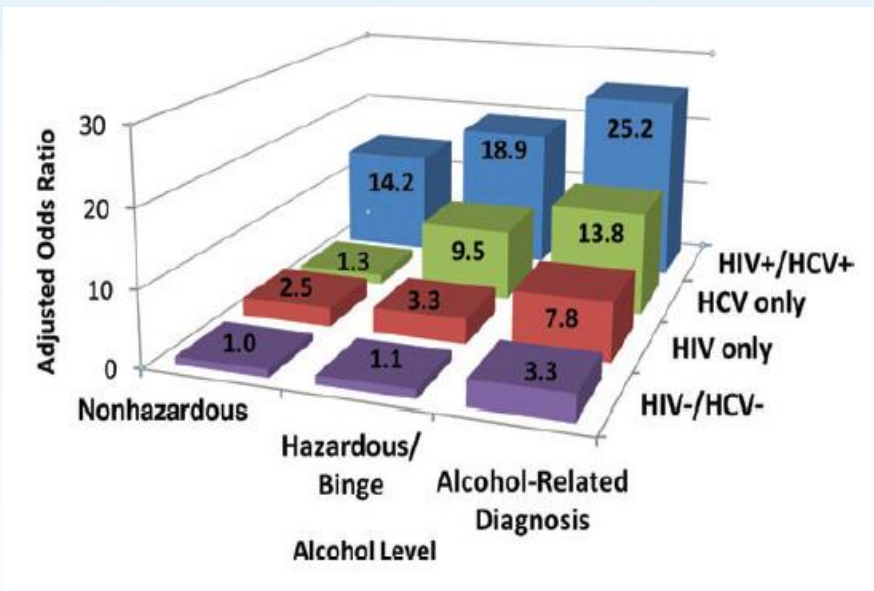
Lo Re V et al. *Ann Intern Med* 2014;160;369-79.

Advanced Liver Fibrosis (FIB-4>3.25), By Level of Alcohol Use and HIV/HCV

Prevalence of Advanced Fibrosis



Odds Ratio of Advanced Fibrosis



Lim JK et al. *Clin Infect Dis* 2014;58:1449-58.

Guidance for Renal Impairment

- If CrCl > 30 mL/min, no dosage adjustment needed with
 - LDV/SOF
 - OMV/PTV/RTV + DSV
 - SMV
 - SOF
- If CrCl < 30 mL/min, consult with expert—limited safety and efficacy data available

Guidance for Decompensated Cirrhotics

- Refer to experienced HCV practitioner (ideally liver transplant center)
- Avoid IFN, TVR, BOC, SMV, OMV/PTV/RTV + DSV
- GT1/4 HCV infection
 - LDV/SOF + RBV* for 12 wks
 - Consider 24 wks for prior SOF failure
 - LDV/SOF for 24 wks in pts with anemia or RBV intolerance
- GT2/3 HCV infection
 - SOF + RBV[†] for up to 48 wks

Initial dose of 600 mg daily, increased as tolerated.

[†]1000-1200 mg daily based on weight, with consideration for pt's CrCl and hemoglobin.

AASLD/IDSA HCV Guidelines.

Guidance for Recurrent HCV Post Liver Transplantation

- For pts with GT1 infection
 - Recommended
 - LDV/SOF + RBV for 12 wks
 - Alternative
 - SOF + SMV ± RBV for 12 wks
 - For F0-F2: OMV/PTV/RTV + DSV + RBV for 24 wks
 - For treatment naive: LDV/SOF for 24 wks

AASLD/IDSA HCV Guidelines.

Management of Acute HCV Infection

- If treatment delay acceptable, monitor for spontaneous clearance for 6-12 mos
 - Monitor HCV RNA every 4-8 wks
- If treatment initiated during acute infection phase
 - Monitor for spontaneous clearance at least 12-16 wks before treatment
 - Recommended regimens are the same as for chronic HCV infection
 - Alternative regimen for IFN eligible acute HCV: pegIFN ± RBV for 16 wks (GT2 or 3 with rapid viral response) to 24 wks (GT1)

Key Monitoring Guidance

- Before treatment
 - Degree of hepatic fibrosis by noninvasive testing or by biopsy
 - Potential drug–drug interactions (hep-druginteractions.org)
- After treatment
 - If pretreatment Metavir \geq F3, ultrasound for HCC every 6 mos
- Before and during treatment
 - HCV RNA before treatment and at Wk 4
 - If detectable at Wk 4, assess again at Wk 6 only
 - ALT before treatment and at Wk 4
 - If elevated at Wk 4, assess again at Wk 6 and Wk 8

Summary

- PegIFN no longer recommended for first-line therapy of any pt
- 3 FDA-approved pegIFN-free regimens for GT1
- No differences in treatment recommendations for HCV monoinfected vs HCV/HIV-coinfected pts
 - Consider drug–drug interactions

A 45 year old HIV/HCV-coinfected man has F3 fibrosis by fibroscan.

He is on Tenofovir/Emtricitabine/Efavirenz (Atripla) for his HIV infection with a CD4 cell count of 450 and an HIV VL < 20. Treatment options for his GT 1 HCV infection would include:

1. Sofosbuvir plus ribavirin
2. Sofosbuvir plus simeprevir
3. Change HIV regimen to Raltegravir/Truvada, then Viekira
4. Pegylated Interferon/ribavirin/Sofosbuvir

**According to AASLD/IDSA Guidelines,
the highest priority for HCV treatment
includes patients with all of the
following except:**

1. Advanced fibrosis
2. Severe extrahepatic complications
3. High risk for HCV transmission
4. Organ transplantation



ACTHIV 2015: A State-of-the-Science Conference for Frontline Health Professionals

Activity Code FA663