

Hepatitis C
QUIKFAQS



REFERENCE guide

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TRANSMISSION

- ▶ Efficiently transmitted via blood
 - Viral titers often in the millions
 - Durable ex-vivo – up to 4 days
- ▶ Injection drug users at high risk
 - ~50% in 1st year
 - ~70% after 5 years
- ▶ Small risk via non-injection drug use
 - Drug straws and crack pipes may contain blood
 - Behavioral risk with stimulant use
- ▶ Many infected via blood transfusion ≤ 1992
- ▶ Sexual transmission possible but uncommon
 - ~2% of long term monogamous relationships
 - Risk confined to first year
 - Multiple partners/STD/HIV increase risk
 - NOT by casual contact: hugging, kissing, eating and cooking utensils
- ▶ Breast feeding is safe
- ▶ Vertical transmission risk low, 5-6%
 - C-section is not protective
- ▶ Lack of protective immunity: reinfection may occur
- ▶ Bleach kills HCV
 - Difficult and impractical to decontaminate syringes
 - Use only new equipment – needle exchanges, etc.

NATURAL HISTORY

- ▶ Benign in the majority of cases
 - Only ~15% cirrhosis risk after 20 years
- ▶ Fibrosis risk increased by
 - Alcohol
 - Nicotine and cannabis, to a small extent
 - Coinfections: HIV, HBV
- ▶ African-Americans less likely on average vs. Caucasians to develop cirrhosis
- ▶ Fibrosis progression dictated by host immune response
 - HCV virus is not apoptotic
 - Progression NOT related to viral load or genotype
 - No need to perform serial viral loads
- ▶ ~25% clear virus spontaneously – it is GONE, not dormant
 - Occurs within 6 months of initial exposure, if at all
 - No risk for transmission to others
- ▶ ~75% develop chronic infection
 - Presence of viremia \geq 6 months after initial exposure
 - Progression generally, but not always, slow

HCV TESTING

- ▶ **ALT/liver enzymes**: often normal
 - Screen based on risk factors and age, not labs
- ▶ **EIA screening test**: detects antibodies to HCV
 - Indicates prior exposure, NOT current infection
 - Screen all persons born between 1945-1965
 - Stays positive even after spontaneous clearance or treatment-related cure
 - Should be followed by reflex viral testing
- ▶ **RIBA**: outmoded and rarely needed
 - Differentiate false + Ab vs. spontaneous clearance
- ▶ **Viral testing**: required to diagnose current infection
 - Quantitative PCR: numbers typically in millions, or
 - Qualitative PCR/TMA: most sensitive assay, or
 - Genotype: 1-6, most common in U.S. is G1
 - Determines treatment duration, regimen, and success rate but NOT fibrosis progression
- ▶ **Liver imaging**: Ultrasound/CT of limited utility
 - Insensitive to fibrosis
- ▶ **Noninvasive fibrosis tests**: eg, Fibrosure, Fibroscan
 - Not FDA approved, less accurate than biopsy
 - Predict fibrosis via blood test panel or liver elasticity
- ▶ **Liver biopsy**: gold standard fibrosis quantification
 - Metavir stages 0-4, S4 = cirrhosis
 - Ischak stages 0-6, S6 = cirrhosis
- ▶ **IL28B genotype**: helps predicts treatment response
 - CC highly responsive vs. CT or TT

HCV TREATMENT-GENERAL CONSIDERATIONS

- ▶ Treatment algorithms are evolving rapidly and should be verified prior to initiating medications.
- ▶ The backbone of HCV treatment is pegylated interferon (PEG) and ribavirin (R) for all genotypes.
- ▶ Triple therapy with PEG/R and an HCV protease inhibitor (PI) is used for patients with genotype 1.
- ▶ Treatment duration is 24-48 weeks.
- ▶ The main determinant of treatment duration, regimen, and outcomes is the HCV genotype.
- ▶ **Genotype 1**: most common genotype in U.S. (75%) and least sensitive to interferon therapy. About 70% of patients treated for 24-48 weeks with PEG/R/PI triple therapy will have SVR.
- ▶ **Genotype 2**: the most interferon-sensitive genotype. About 85% SVR with 24 wks of PEG and ribavirin 400 mg bid.
- ▶ **Genotype 3**: less interferon sensitive than genotype 2. About 75% SVR with 24 wk PEG and ribavirin 400 bid. Consider 48 wk and ↑riba if no RVR.
- ▶ **Genotypes 4-6**: intermediate sensitivity. Treat for 48 wks with PEG/R.

TREATMENT CANDIDACY

► Considerations:

- Risk of progression to severe liver disease
- Probability of response
- Risk of adverse events
- Patient motivation

► Indications:

- Advancing/advanced fibrosis
- Compensated cirrhosis/bridging fibrosis
- Accelerated fibrosis: HIV/HCV or HBV/HCV coinfection
- Severe symptoms
- Extrahepatic disease; e.g., cryoglobulinemia
- Acute HCV

► Contraindications:

- Absolute:
 - Pregnancy
- Strong:
 - Hepatic decompensation
 - Solid organ transplant (except liver)
 - Severe heart/lung disease
- Relative
 - Autoimmune diseases
 - Unstable psychiatric disorder
 - Active alcohol/drug use

TREATMENT MEDICATIONS

▶ **Pegylated interferon**

- Currently the backbone of all treatment regimens
- Enhances innate immune response to HCV virus
- ▶ PEG= **P**oly**E**thylene **G**lycol, long chain carbohydrate that prolongs IFN half-life
- ▶ SQ injection once weekly
- ▶ Cytopenias, flu-like symptoms, fatigue, depression are major side effects

▶ **Ribavirin**

- Improves efficacy of interferon
- Oral agent
- No efficacy as monotherapy
- Can cause hemolytic anemia that may be severe

▶ **Protease inhibitors: Genotype 1 only**

- Telaprevir and boceprevir currently approved
- Used in combination with interferon and ribavirin
- High potential for resistance if not taken correctly
- Improve genotype 1 treatment outcomes by ~50%
- Boceprevir: fatigue, anemia, nausea, headache, dysgeusia
- Telaprevir: rash, itch, anemia, nausea, hemorrhoids, diarrhea, anorectal pain/itch, dysgeusia, fatigue, vomiting

HCV TREATMENT ABBREVIATIONS

| | Term | Definition |
|-------|--------------------------------------|--|
| RVR | Rapid virologic response | Undetectable HCV RNA at treatment week 4 |
| EVR | Early virologic response | 100-fold reduction or undetectable viral load at treatment week 12 |
| cEVR | Complete early virologic response | Undetectable HCV PCR at treatment weeks 4 and 12 |
| eRVR | Extended rapid virologic response | Undetectable HCV PCR at treatment weeks 4 and 12 |
| ETR | End of treatment response | HCV PCR undetectable at end of treatment |
| SVR12 | Sustained virologic response week 12 | HCV PCR undetectable 12 weeks after end of treatment |
| SVR24 | Sustained virologic response week 24 | HCV PCR undetectable 24 weeks after end of treatment |

HCV RESPONSE TERMS

| Term | Defintion |
|------------------|---|
| Breakthrough | Reappearance of HCV RNA while on therapy |
| Non-response | Failure to clear HCV RNA by week 24 |
| Null response | <100-fold drop in HCV RNA by week 12 |
| Partial response | >100-fold drop in HCV RNA by week 12, but virus still detectable at week 24 |
| Relapse | HCV PCR undetectable during treatment but positive afterward |

HCV MEDICATION DOSING

► Pegylated Interferons

- **PEG IFN alfa-2a (Pegasys®)**: 180 mcg SQ/wk
- **PEG IFN alfa-2b (Peg-Intron®)**: dosed by weight:

| Weight (in lbs) | Strength | Volume (cc/wk) |
|-----------------|----------------|----------------|
| < 88# | 50 mcg/0.5 cc | 0.5 cc |
| 88-111# | 80 mcg/0.5 cc | 0.4 cc |
| 112-133# | | 0.5 cc |
| 134-166# | 120 mcg/0.5 cc | 0.4 cc |
| 167-186# | | 0.5 cc |
| 188# and ↑ | 150 mcg/0.5cc | 0.5 cc |

HCV Medication Dosing (cont.)

► Ribavirin :

- Supplied as 200, 400, and 600 mg tabs/capsules
- Genotypes 2 and 3: 400 mg bid
- Other genotypes:

| Weight (in lbs) | Daily dose |
|-----------------|---------------------------|
| < 165# | 400 mg qAM and 600 mg qPM |
| ≥165-231# | 600 mg bid |
| >231# | 600 mg qAM and 800 mg qPM |

► Boceprevir (Victrelis®)

- Genotype 1 only
- Taken in combo with interferon and ribavirin
- 800 mg (4 x 200 mg capsules) 3x daily (every 7-9 hours) with a meal or light snack
- Missed dose:
 - If < 2 hr before next dose, skip missed dose
 - If > 2 hr before next dose, take missed dose

► Telaprevir (Incivek®)

- Genotype 1 only
- Taken in combination with interferon and ribavirin
- 750 mg (2 x 375 mg tablets) 3x daily (every 7-9 hours) with ~20 grams of fat
- Missed dose:
 - If < 4 hr before next dose, skip missed dose
 - If > 4 hr before next dose, take missed dose

SAMPLE HCV BLOOD TESTING SCHEDULE

(Additional testing may be required based on treatment response)

| | CMP | CBC | TSH | HCV PCR* |
|--------------------|-----|-----|-----|----------|
| Baseline | x | x | x | x |
| Week 2 | x | x | | |
| Week 4 | x | x | | x |
| Week 8 | x | x | | x # |
| Week 12 | x | x | x | x |
| Week 18 | x | x | | |
| Week 24 | x | x | x | x |
| Week 30 | x | x | | |
| Week 36 | x | x | x | |
| Week 42 | x | x | | |
| Week 48 | x | x | x | x |
| Week 12 post-Tx | x | x | x | x |
| Week 12 post-Tx | x | x | x | x |

Abbreviations: CMP, Comprehensive Metabolic Panel; CBC, Complete Blood Count; TSH, Thyroid Stimulating Hormone

* Viral loads should be tested with a sensitive assay such as TaqMan® with a lower limit of detection of ~10 IU/ml

Boceprevir-based treatment only

TREATMENT ALGORITHM: BOCEPREVIR

Treatment Duration:

- Cirrhosis and prior null responders: 48 weeks (4 wk P/R + 44 wk P/R/B)
- All others: Response-guided therapy based on HCV PCR (IU/ml) results:

| Wk 4 | Wk 8 | Wk 12 | Wk 24 | Treatment Algorithm |
|-------------|-------|-------|-------|--|
| < 0.5 log ↓ | | | | 4 wk P/R + 44 wk P/R/B |
| | < 9.3 | <100 | <9.3 | Naïve: 4 wk P/R + 24 wk P/R/B Experienced: 4 wk P/R + 32 wk P/R/B |
| | >9.3 | <100 | <9.3 | 4 wk P/R + 36 wk P/R/B + 12 wk P/R |
| | | >100 | | STOP |
| | | | >9.3 | STOP |

(P=pegylated interferon; R=ribavirin; B=boceprevir)

TREATMENT ALGORITHM: TELAPREVIR

Treatment Duration:

- Prior null responders and partial responders:
48 weeks (12 wk P/R/T + 36 wk P/R)
- All others: Response-guided therapy based on HCV PCR (IU/ml) results:

| Wk 4 | Wk 12 | Wk 24 | Treatment Algorithm |
|--------------|--------------|-------|-------------------------|
| <10 | <10 | | 12 wk P/R/T + 12 wk P/R |
| >10 ≤1000 | | | 12 wk P/R/T + 36 wk P/R |
| >1000 | | | STOP |
| | >10 ≤1000 | | 12 wk P/R/T + 36 wk P/R |
| | >1000 | | >1000 |
| | | >10 | STOP |

(P=pegylated interferon; R=ribavirin; T=telaprevir)

SIDE EFFECTS: GENERAL CONSIDERATIONS

- ▶ Every patient will have side effects! Management will improve adherence and outcomes.
- ▶ **Injection timing**: Side effects are often worse the day or two after IFN injection.
 - Take IFN before bedtime and before a day off.
 - PegIntron: take antipyretic 1 hr before injection.
 - Pegasys: take antipyretic 2 hr after injection.
- ▶ **Flu-like symptoms**: Increasing water intake to 3-4 liters daily (15-20 glasses) usually helps.
 - Sip from water bottle throughout the day.
 - Reduce intake in the evening to help with sleep.
 - Flavored waters are ok but sugared caffeinated beverages don't substitute.
- ▶ **Mood Changes**: Almost universal. Try to differentiate insomnia/exhaustion from incipient psychiatric disorders and intervene quickly – sedating antidepressants can be helpful.
- ▶ **Weight Loss**: Reduces treatment outcomes if severe. Encourage small, regular meals and eating favorite, high calorie foods.
- ▶ **Support network**: Supportive family and friends can make or break the treatment. Encourage family members to attend office visits.
- ▶ **Employment vs. Disability**: Focus, endurance, and mood will be impaired, but some find work distractions helpful. Make decisions based on type of work and medication tolerability.

SIDE EFFECTS: COMMON ISSUES

► **Hematologic:**

▪ **Hemolytic anemia:**

- Test Hb bi-weekly or weekly if dropping rapidly.
- If Hb <10, reduce ribavirin dose.
 - With Pegasys, reduce dose to 600 mg/d.
 - With PegIntron, reduce dose to 12 mg/kg/d, or 8 mg/kg/d if still low when rechecked.
- If Hb < 8.5, discontinue ribavirin.
 - Restart riba at 600 mg/d; raising dose above 800 mg not recommended.
- EPO unnecessary once virus is undetectable
 - If used, erythropoietin is dosed at 40K IU/wk and darbepoietin is dosed at 100 mcg/wk.
- PI dose reduction NOT recommended.

▪ **Neutropenia:**

- Opinions on actionable threshold vary widely.
- G-CSF used rarely except in cirrhotics.
- African-Americans tend to have lower baseline ANC and may reach action thresholds earlier.
- General recommendations: ANC <750, ↓ IFN by 25-50%; ANC <500, d/c IFN until ANC >1000.

▪ **Thrombocytopenia:**

- General recommendations: if platelets are <50K, reduce IFN by 50%, if platelets are <25K, d/c IFN.
- Management strategies vary widely.

SIDE EFFECTS: COMMON ISSUES

► **Systemic:**

- **Nausea/vomiting/weight loss:** Try split-dosing ribavirin to tid or qid. Antiemetics such as prochlorperazine or promethazine, hydroxyzine, H2 blockers, or PPIs can help.
- **Diarrhea:** Clear liquids, avoid milk products; Imodium or loperamide may help.
- **Dysgeusia:** May benefit from foods that are cold, aromatic, or acidic; ginger; dark chocolate. Possible benefit from zinc sulfate, 220 mg bid.
- **Anorectal pain:** Can be severe with telaprevir. Assess fat intake: ensure high fat meal and no medication interactions. Try local agents like Prep-H or Anusol ± hydrocortisone.

► **Dermatologic**

- **Rash/Itch:** Lightly coat skin with sealing emollients like Vaseline after bathing. Steroid ointments and oral antihistamines like Benadryl or hydroxyzine may be useful. Telaprevir can cause a severe rash requiring treatment discontinuation.
- **Injection site reactions:** Change injection site weekly to minimize risk for local inflammation.
- **Alopecia:** Will not be complete and hair will regrow. Reassurance is mostly needed; gentle treatment of hair and scalp will minimize impact.

SIDE EFFECTS: COMMON ISSUES

► Neuropsychiatric

- Insomnia:
 - Assess sleep hygiene, caffeine, nicotine.
 - Don't take ribavirin at bedtime.
 - Start with sedating antihistamines or low dose sedating antidepressants like amitriptyline 25-50 mg qhs, trazodone 50-100 mg qhs, mirtazapine 15 mg qhs.
 - Use sedatives like zolpidem or short-acting benzos with care.
 - If on PI, check for drug-drug interactions.
- Depression:
 - Consider pre-treating persons with psych history.
 - Assess for and treat insomnia.
 - SSRI's considered first line agents, individualize treatment based on side effect profile (e.g., activating antidepressant if fatigue is problematic).
 - If on PI, check for drug-drug interactions.
- **Mood instability:** May be severe.
 - Assess for insomnia and depression/mania.
 - Mood stabilizing antipsychotics such as quetiapine or aripiprazole can help.
 - If on PI, check for drug-drug interactions.

HELPFUL REFERENCES

AASLD Practice Guidelines: Free availability online.

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- Zeuzem S, et al. Telaprevir for retreatment of HCV infection. *N Engl J Med* 2011;364(25):2417-2428.

Websites:

- **CDC Viral Hepatitis Section:**
www.cdc.gov/ncidod/diseases/hepatitis
- **Veterans Affairs:** www.hepatitis.va.gov
- **HCV Advocate:** www.hcvadvocate.org.
Packed with information about viral hepatitis.
- **Hepatitis Central:**
www.hepatitis-central.com. Research & treatment news.

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