Hepatitis C Treatment for Primary Care Providers

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UNM HCV Elimination Project
Project ECHO

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Objectives:

Review risks for Hepatitis C transmission and identify appropriate populations for screening and treatment.

Describe risks of untreated Hepatitis C and benefits of treatment.

Empower audience participants to identify their role in HCV elimination strategies.

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No financial disclosures

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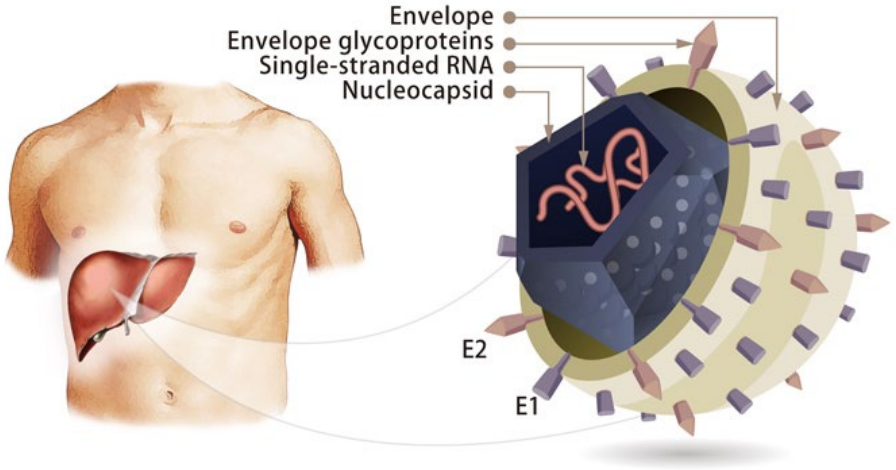
Hepatitis C

- Liver infection caused by the Hepatitis C Virus (HCV)
- Blood borne
- Acute vs. Chronic infection
- Initially, chronic infection is usually asymptomatic.
- No vaccine
- No pre-exposure or post exposure prophylaxis



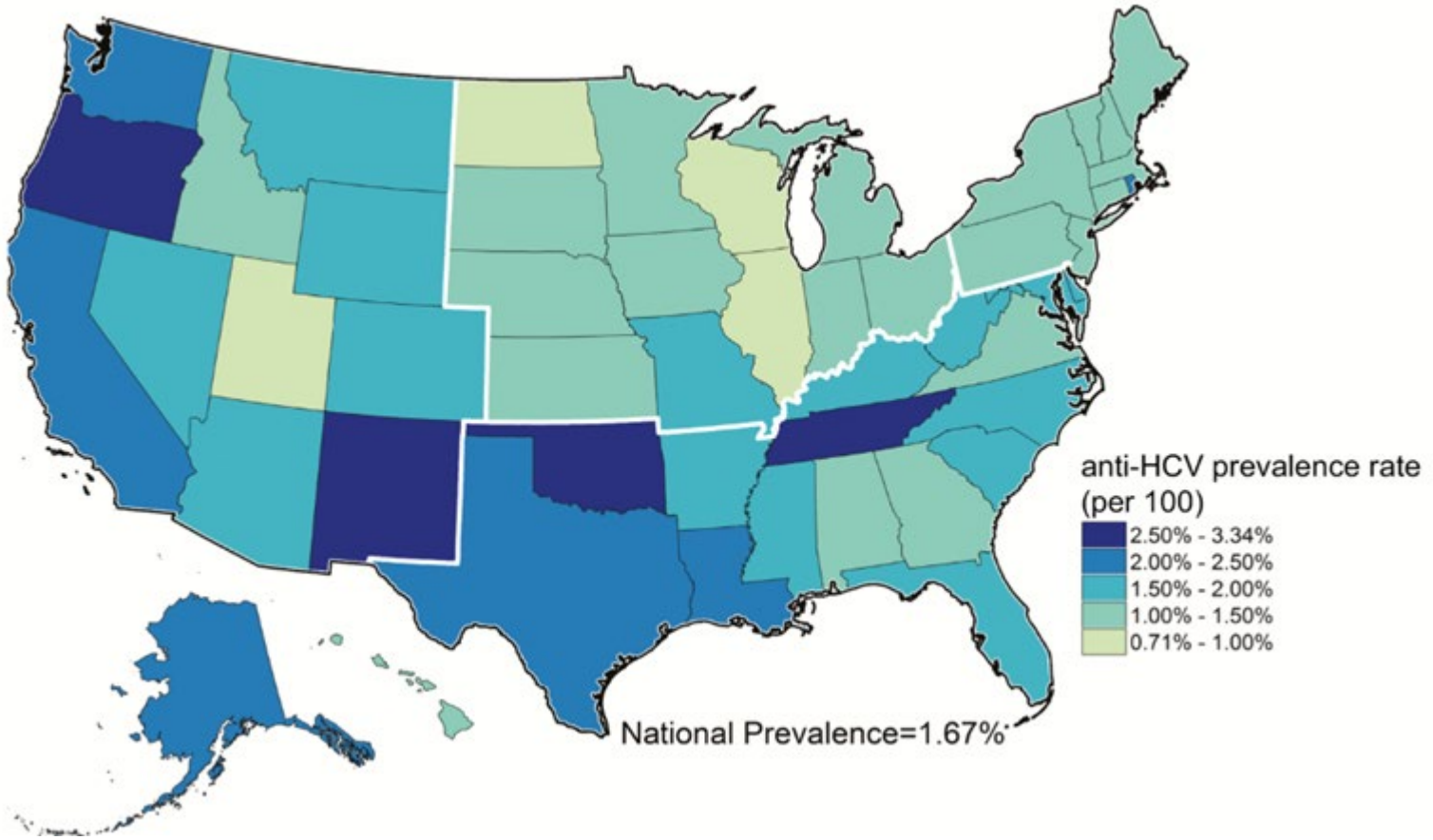
Hepatitis C (HCV) Pandemic

- 1% of world population chronically infected (NM & UNM populations higher)
- 71 Million people
- Leading cause of liver-related deaths worldwide
  - Approx. 670,000 annually
- 20% aware of their infection [2]

1. (Krekulova et al., 2021)

2. (Applegate et al., 2018)

U.S. HCV Antibody Prevalence



(Rosenberg et al., 2017)

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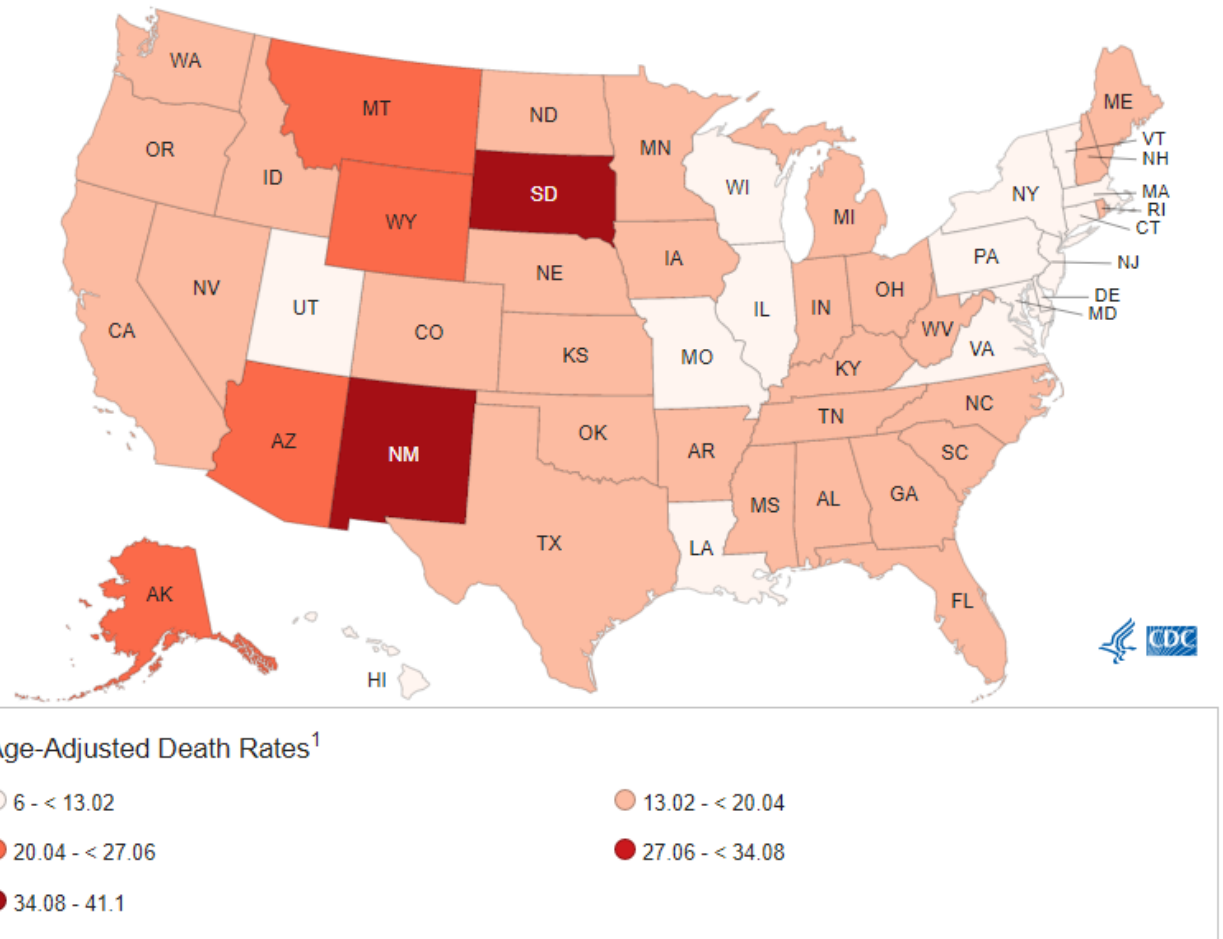
Chronic Liver Disease/Cirrhosis Mortality by State

Print

Make a selection from the filters to change the visualization information.

Year

2021



Leading Causes of Death

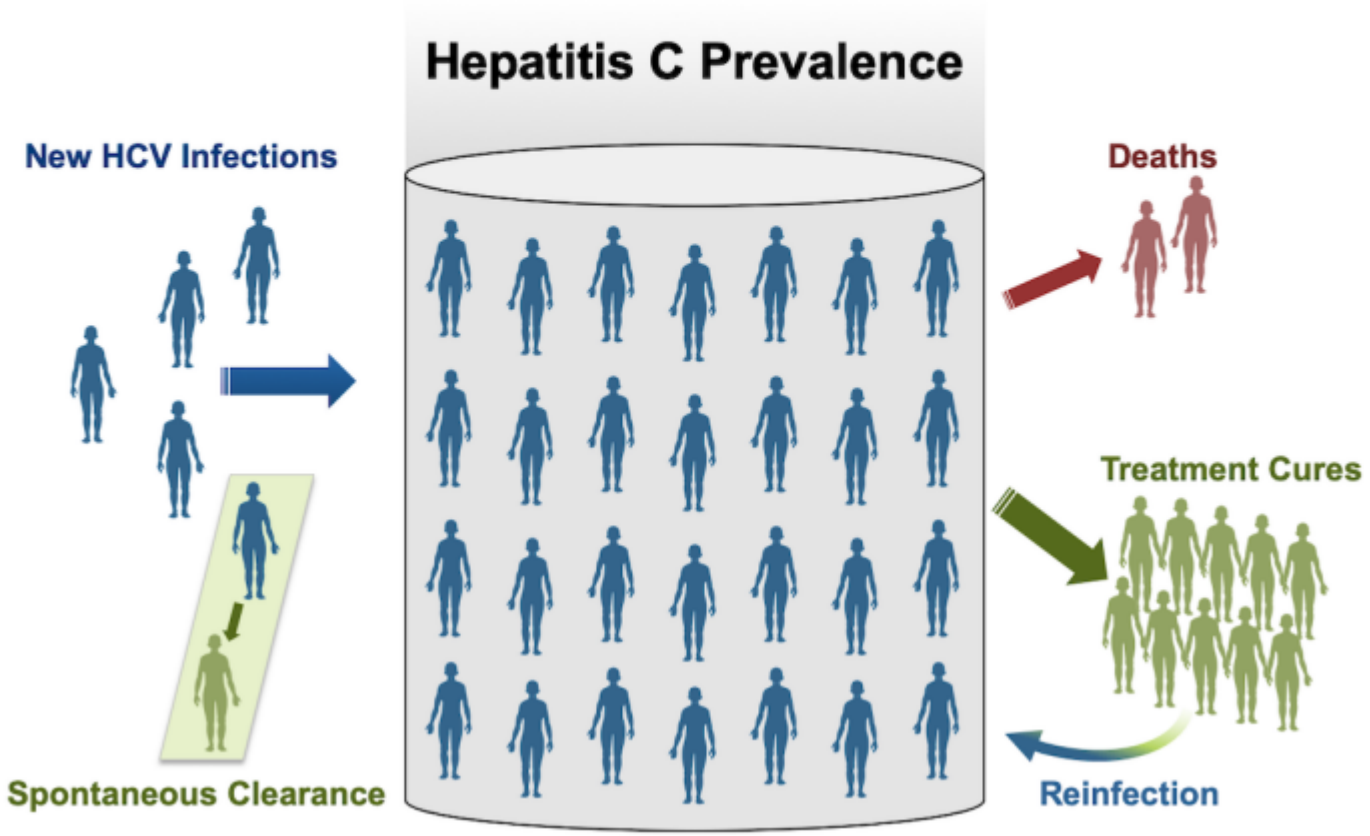
1. Heart Disease
2. Cancer
3. COVID-19
4. Accidents
5. Chronic Lower Respiratory Diseases
6. Stroke
7. Chronic Liver Disease/Cirrhosis
8. Diabetes
9. Alzheimer's Disease
10. Suicide

CDC. (2022)

Figure 11 Dynamics of HCV Prevalence in the United States

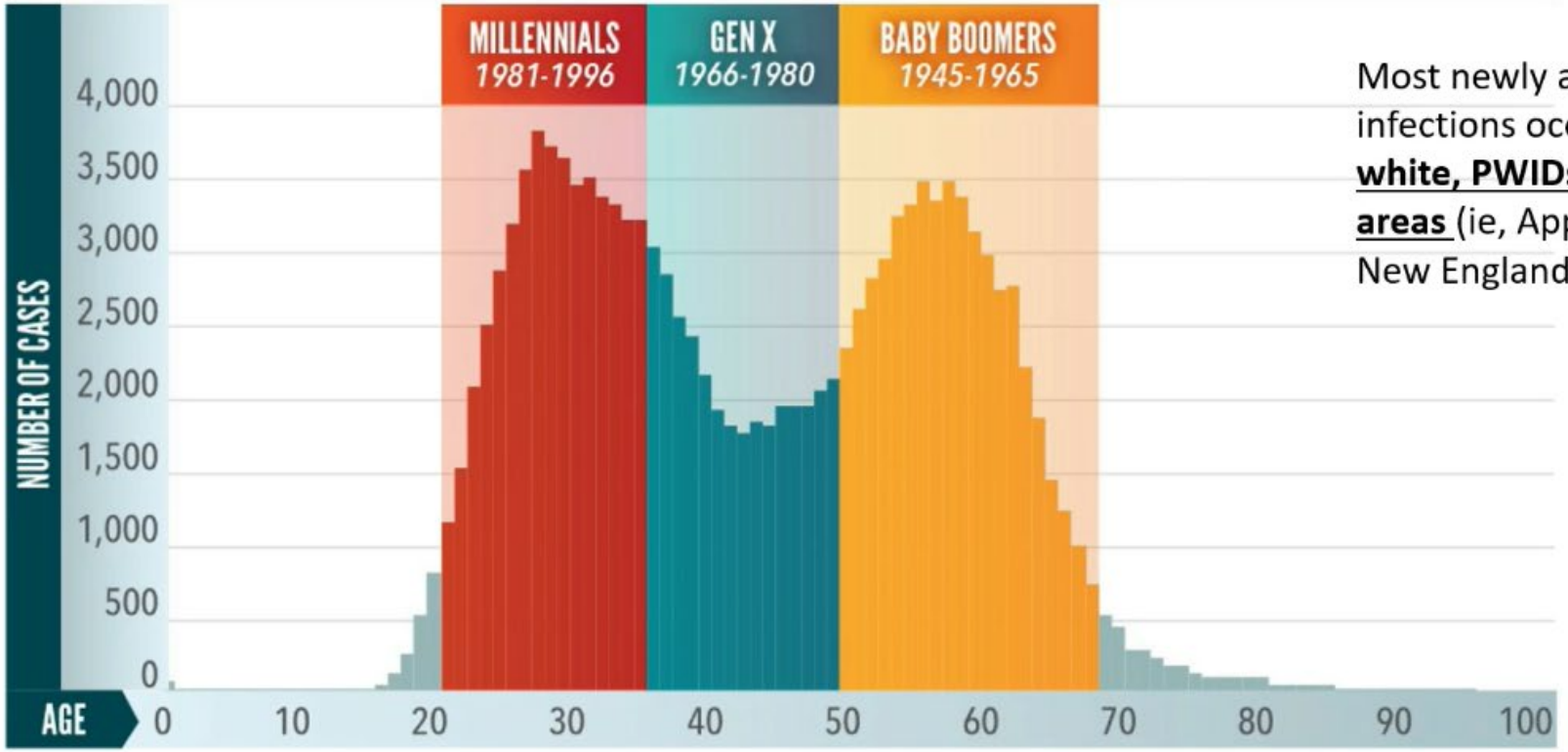
This illustration shows the dynamics of HCV prevalence in the United States (persons living with chronic HCV infection) are impacted by multiple factors, including number of new infections, spontaneous resolution of new infections, deaths, treatment-related cure, and reinfection.

Source: Illustration by David H. Spach, MD



Patients have also changed:

HCV is now bimodal and strategies to achieve cure must be tailored to the audience



Most newly acquired acute HCV infections occurred among **young, white, PWIDs, who live in non-urban areas** (ie, Appalachian, Midwestern, and New England states)

Centers for Disease Control and Prevention. NCHHSTP Newsroom. https://www.cdc.gov/nchhstp/newsroom/2020/hepatitis-c-impacting-multiple-generations.html#Graphics. Accessed October 12, 2020.

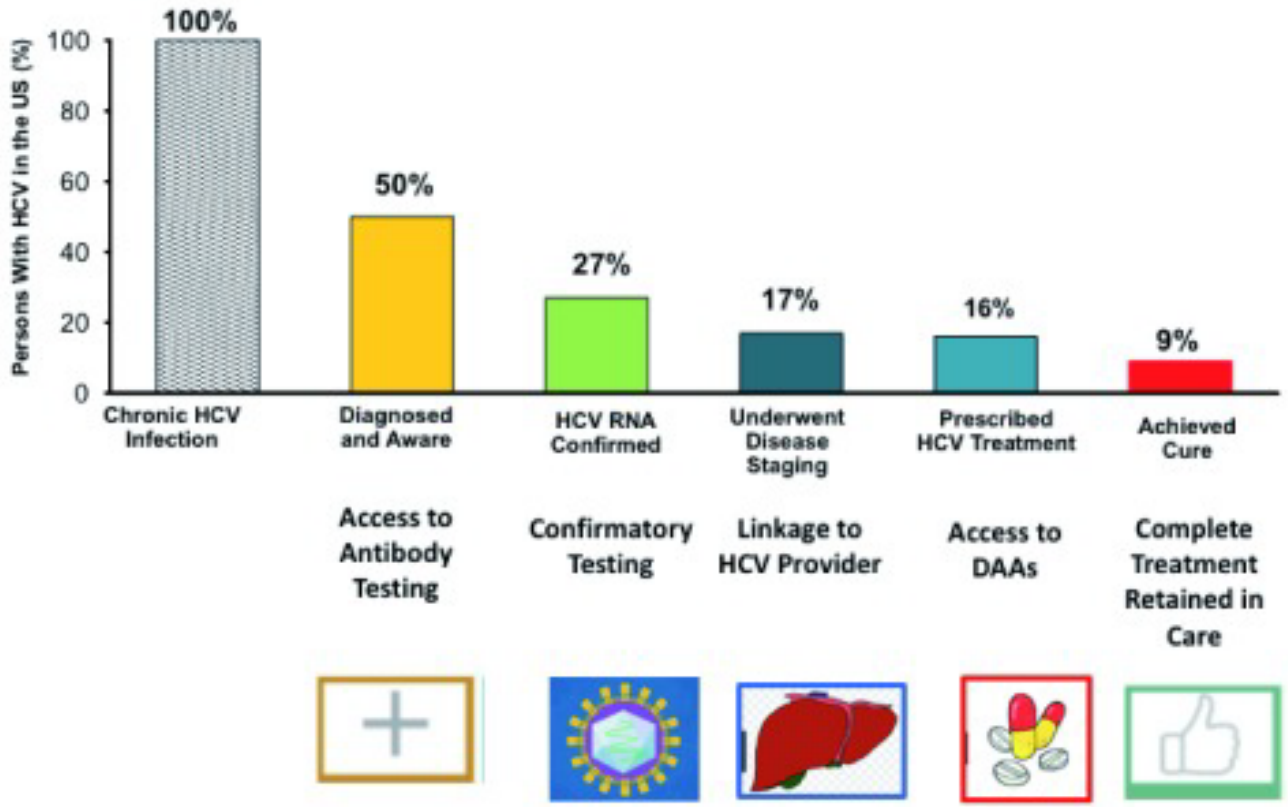
Ryerson AB, et al. *MMWR Morb Mortal Wkly Rep*. 2020;69:399-404.

World Health Organization Elimination Goals

- Reduction in new infections by 90% by 2030, compared with the 2015 baseline
- 65% reduction in mortality
- Increase in the proportion of diagnosed people with HCV infection up to 90%

(Krekulova et al., 2021)

HCV Care Cascade



(Terrault N. A., 2019)

Universal Screening

Final Recommendation Statement

Hepatitis C Virus Infection in Adolescents and Adults: Screening

Recommendations made by the USPSTF are independent of the U.S. government. They should not be construed as an official position of the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services.

Recommendation Summary

Population	Recommendation	Grade (What's This?)
Adults aged 18 to 79 years	The USPSTF recommends screening for hepatitis C virus (HCV) infection in adults aged 18 to 79 years.	B

To read the recommendation statement in *JAMA*, select here.

To read the evidence summary in JAMA, select here.

See the Clinician Summary for a more detailed summary of the recommendation for clinicians.

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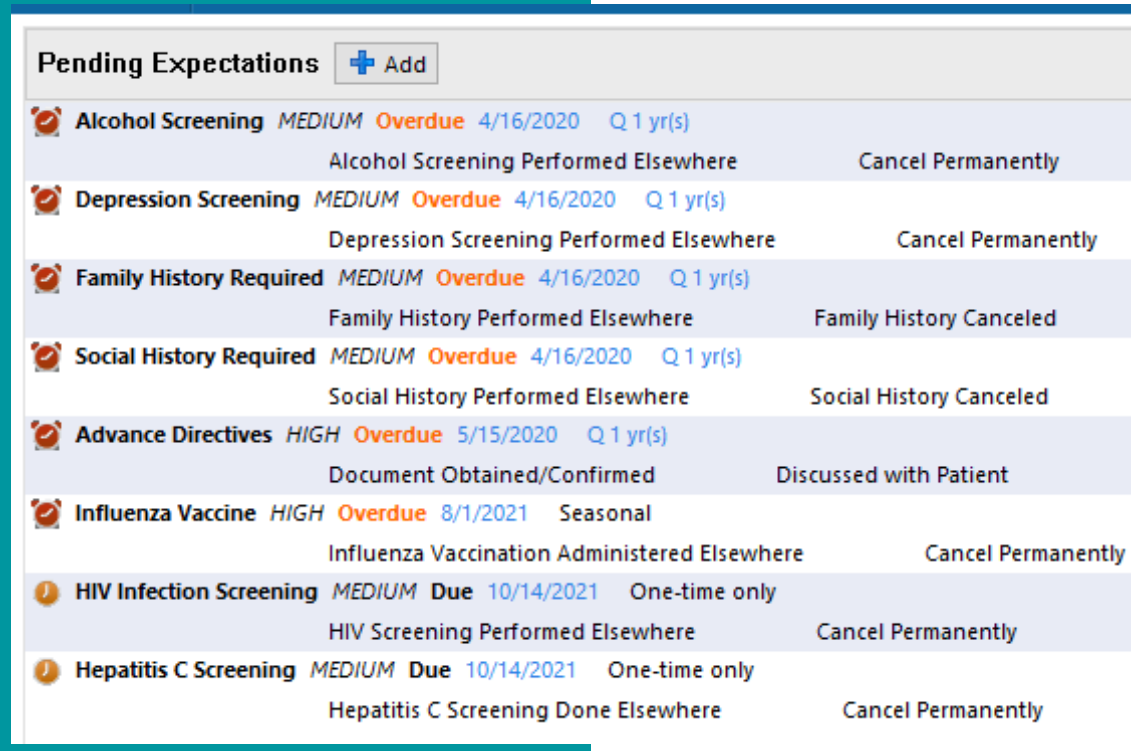
(U.S. Preventative Services Task Force. (2021)

Routine Screening



Decreases stigma
Integrates into routine care
Insurance coverage

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Risk-based screening

- History of injection drug use
- People living with HIV
- Maintenance hemodialysis
- Persistently abnormal ALT levels
- Any person who requests HCV testing
- HIV Pre-exposure prophylaxis (PrEP) therapy monitoring
- Exposure—such as needlestick injury

(Centers for Disease Control and Prevention, 2021).

What is Reflex Testing for Hep C?

"When antibody testing is reactive or equivocal, a reflex HCV quantitative RNA viral load test is performed."

- Confirming HCV is 2-step process
- Spontaneous clearance and/or prior treatment

Tricore, 2021

HCV DX Examples

Hepatitis Virus	
Hepatitis C Antibody	Nonreactive: (N
Hepatitis C Signal/Cutoff Ratio	* 0.04
Hepatitis C Realtime PCR	Not Indicated
Hepatitis C PCR Log	Not Indicated
HCV Interpretation	No HCV antibod

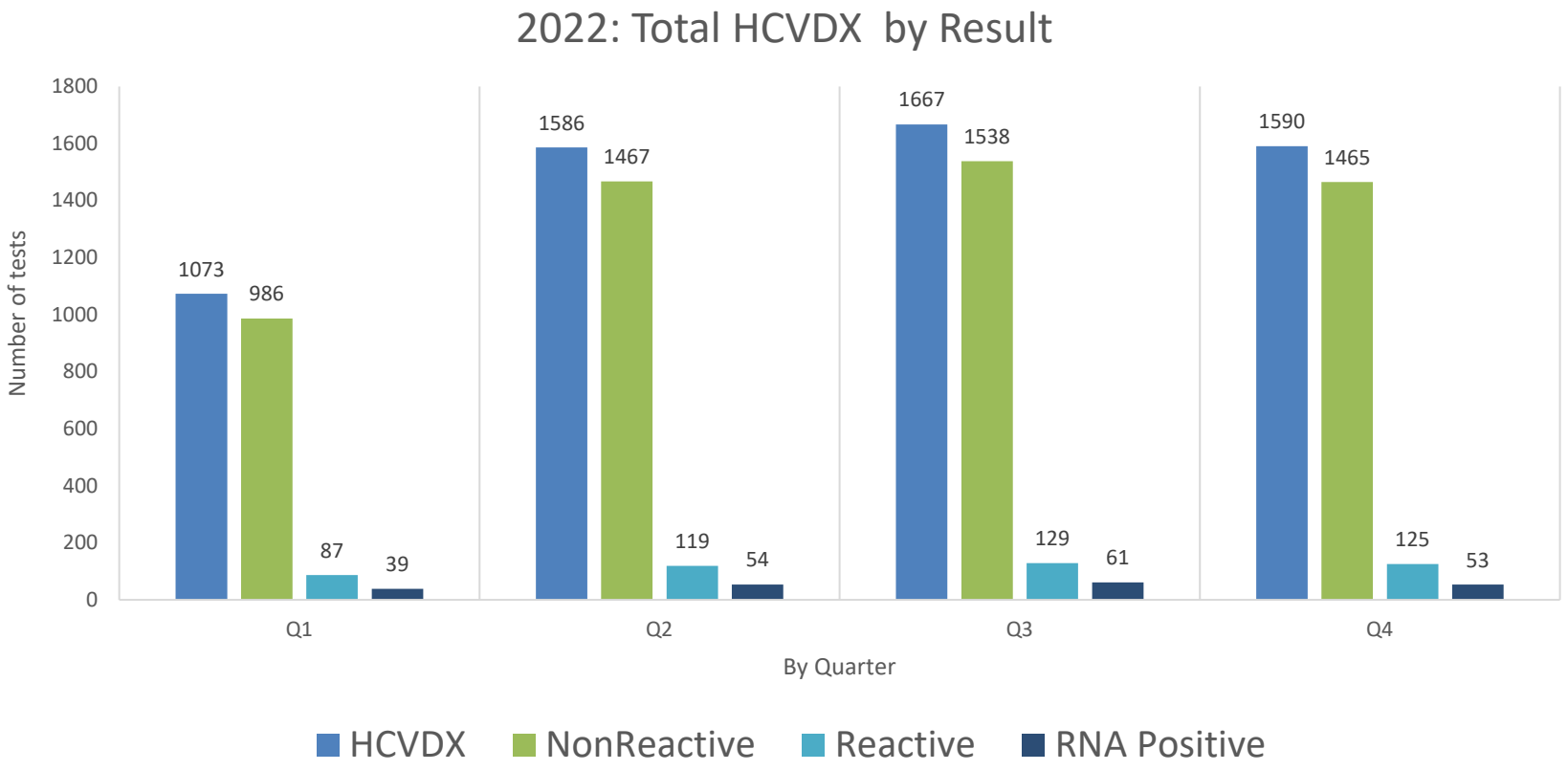
Hepatitis Virus	
Hepatitis C Antibody	(A) Reactive: (HCV antibodies detected. R
Hepatitis C Signal/Cutoff Ratio	* (H) 2.67
Hepatitis C Realtime PCR	Hepatitis C Virus RNA not detected.
Hepatitis C PCR Log	Not Required
HCV Interpretation	(A) No laboratory evidence of current HCV

No infection.
No treatment/referral indicated.

Hepatitis Virus	
Hepatitis A IGM Antibody	Nonreactive
Hepatitis A total Antibody (IGG/IGM)	(A) Reactive
Hepatitis B Surface Antigen	Nonreactive [2]
Hepatitis B Surface Antibody Titer	* (H) 13
Hepatitis B Core IGG Antibody	Nonreactive
Hepatitis B Core IGM Antibody	Nonreactive
Hepatitis C Antibody	(A) Reactive [2]
Hepatitis C Signal/Cutoff Ratio	* (H) >11.00; * (H) >11.00
Hepatitis C Realtime PCR	2,270,000
Hepatitis C PCR Log	6.4
HCV Interpretation	(A) HCV RNA detected. Laboratory ev

Active viremia,
Treatment/referral indicated.

HCVDX Usage @ UNMHS



- 7070 Total HCVDX Tests
  - 6431 Nonreactive
  - 629 Reactive
  - 8.9% Ab Reactivity
- 3.86% rate of confirmed viremia in all patients screened
- 43.4% rate of confirmed viremia from AB reactive

Data from UNM Clinical Practice Excellence, Analysis by Hep C Project team

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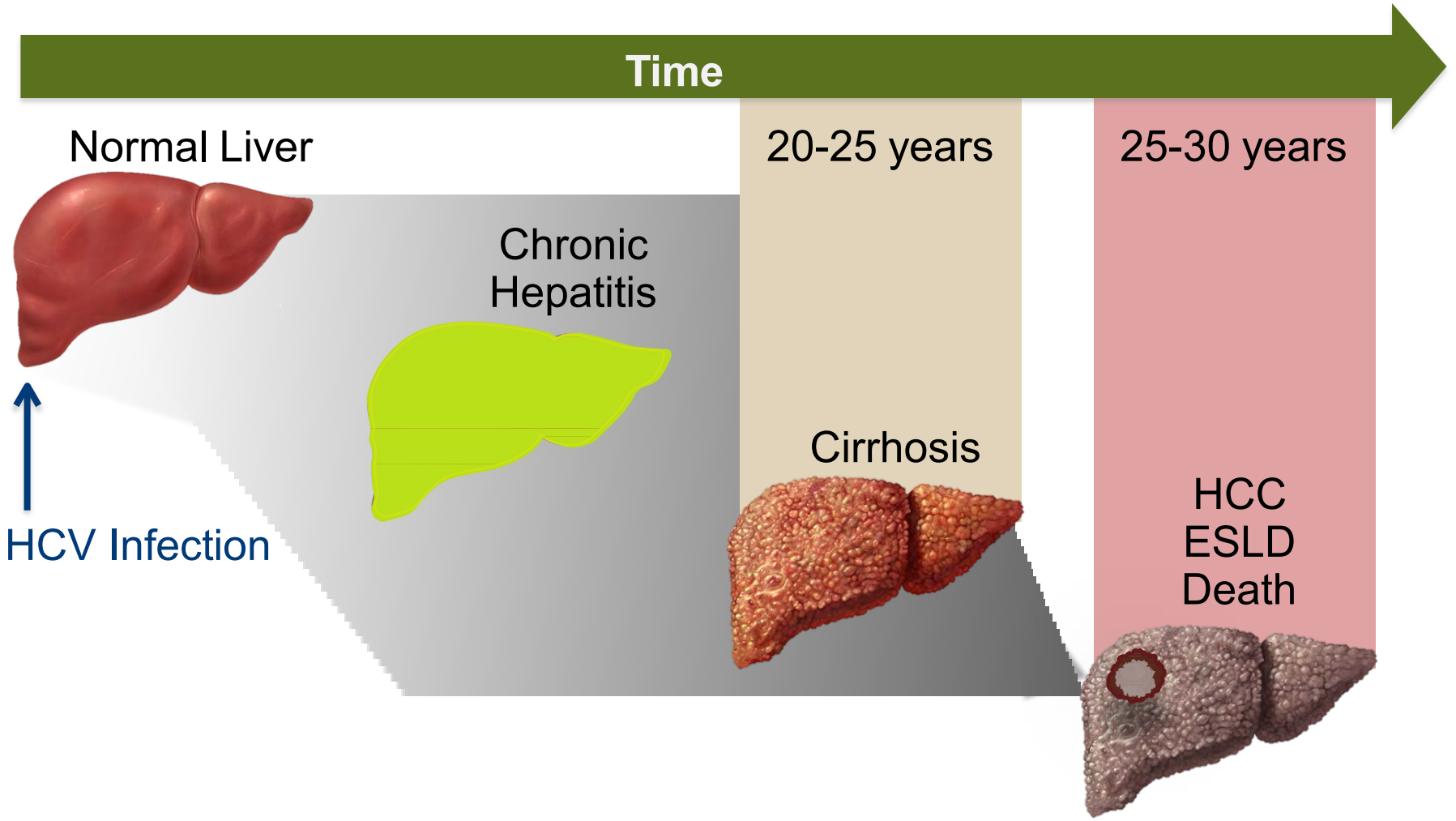
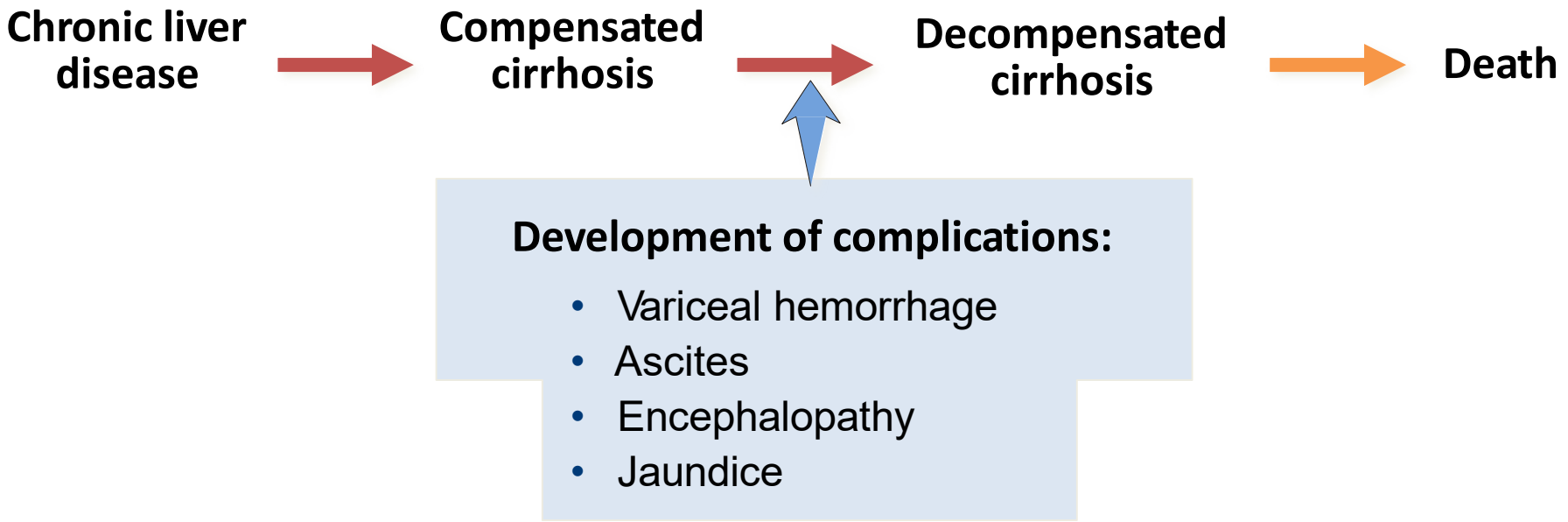
Hepatitis C: Progression of Disease



Hepatitis web study

Natural History of Chronic Liver Disease



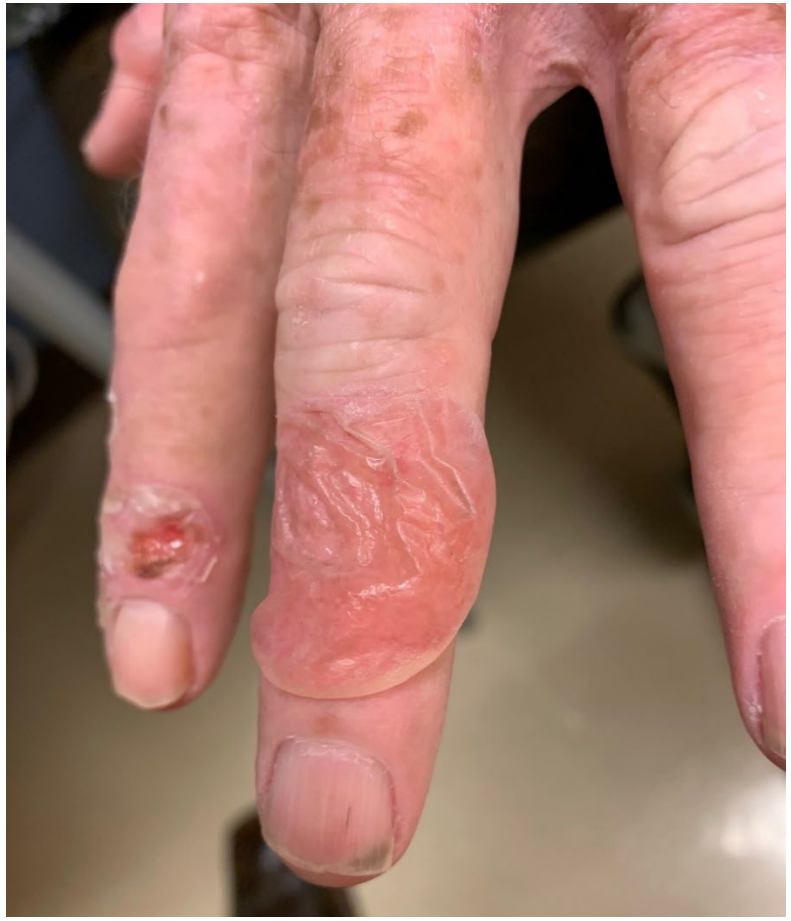
Extrahepatic Manifestations

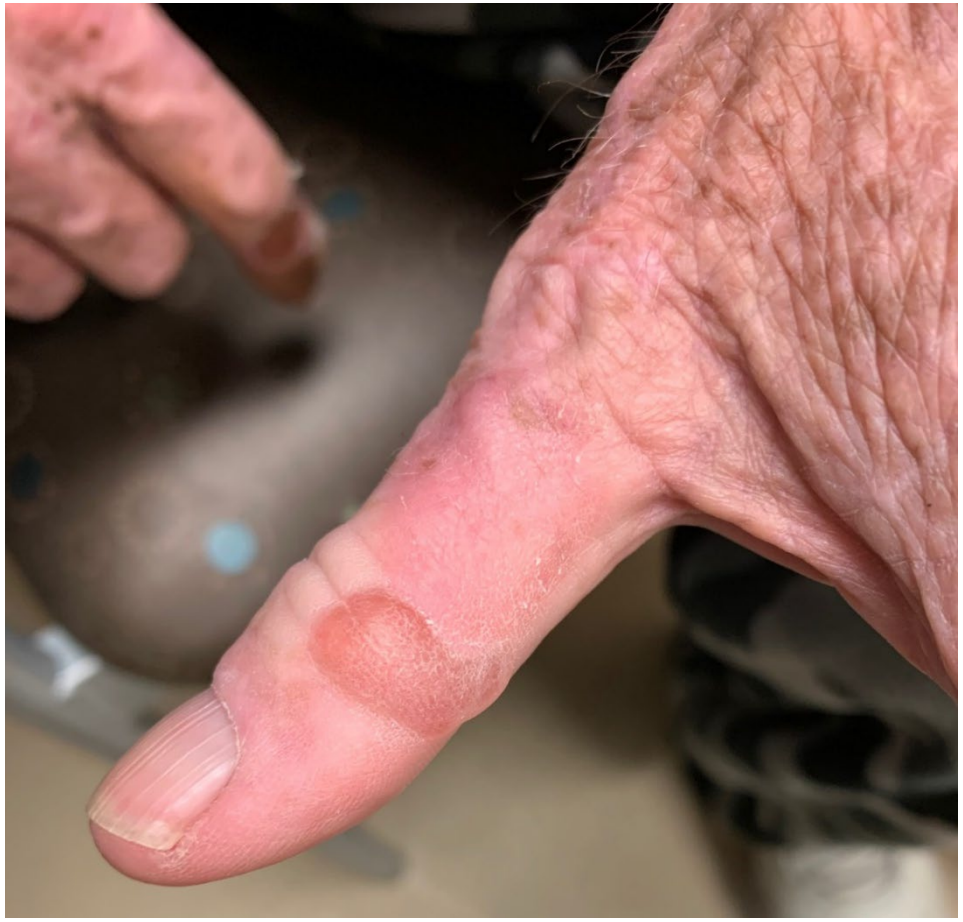
- Glomerulonephritis
- Essential mixed cryoglobulinemia
- Porphyria cutanea tarda
- Non-Hodgkin's lymphoma
- Diabetes Mellitus [2]
  - meta-analysis of 34 studies estimated that the risk was increased by almost 70 percent in HCV-infected patients compared with non-infected controls (OR 1.7)

1. (CDC, 2021)

2. (White et al., 2008)

Porphyria cutanea tarda





Photos (A. Skiles)

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Perinatal Transmission

- Systematic Review of 109 studies estimated Maternal to Child Transmission Rate:
  - Mono-infected – 5.6% (95% confidence interval [CI], 4.2%-7.8%)
  - Co-infected with HIV – 10.8% (95% CI, 7.6%-15.2%)

(Benova et al., 2014)

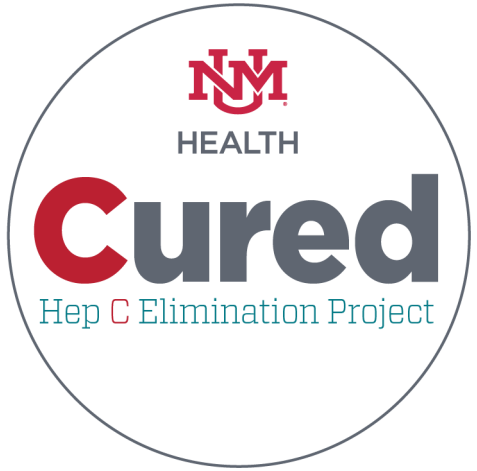
“Labour Pains”

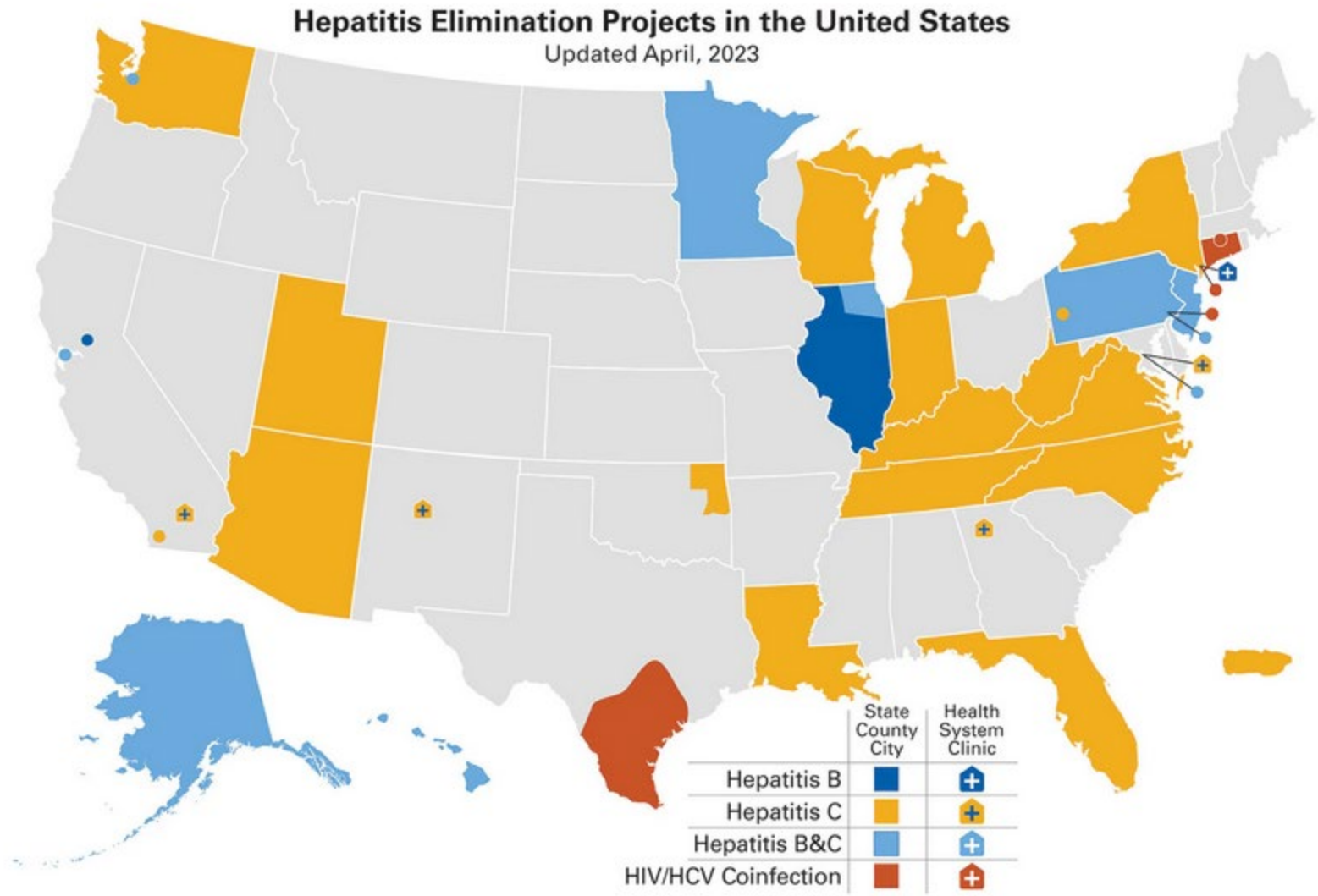
- DAA therapy not approved in pregnant or lactating patients
- Left out of the treatment cascade, creating a gap in treatment access
- Strategies needed to keep women linked into care post-partum and treat when they stop breastfeeding
- Evidence indicates poor follow up after post-partum care
- Treatment gap serves as a gender imbalance and obstructs women from the benefit of cure

(Judd et al., 2021)

Challenges with Linkage to Care

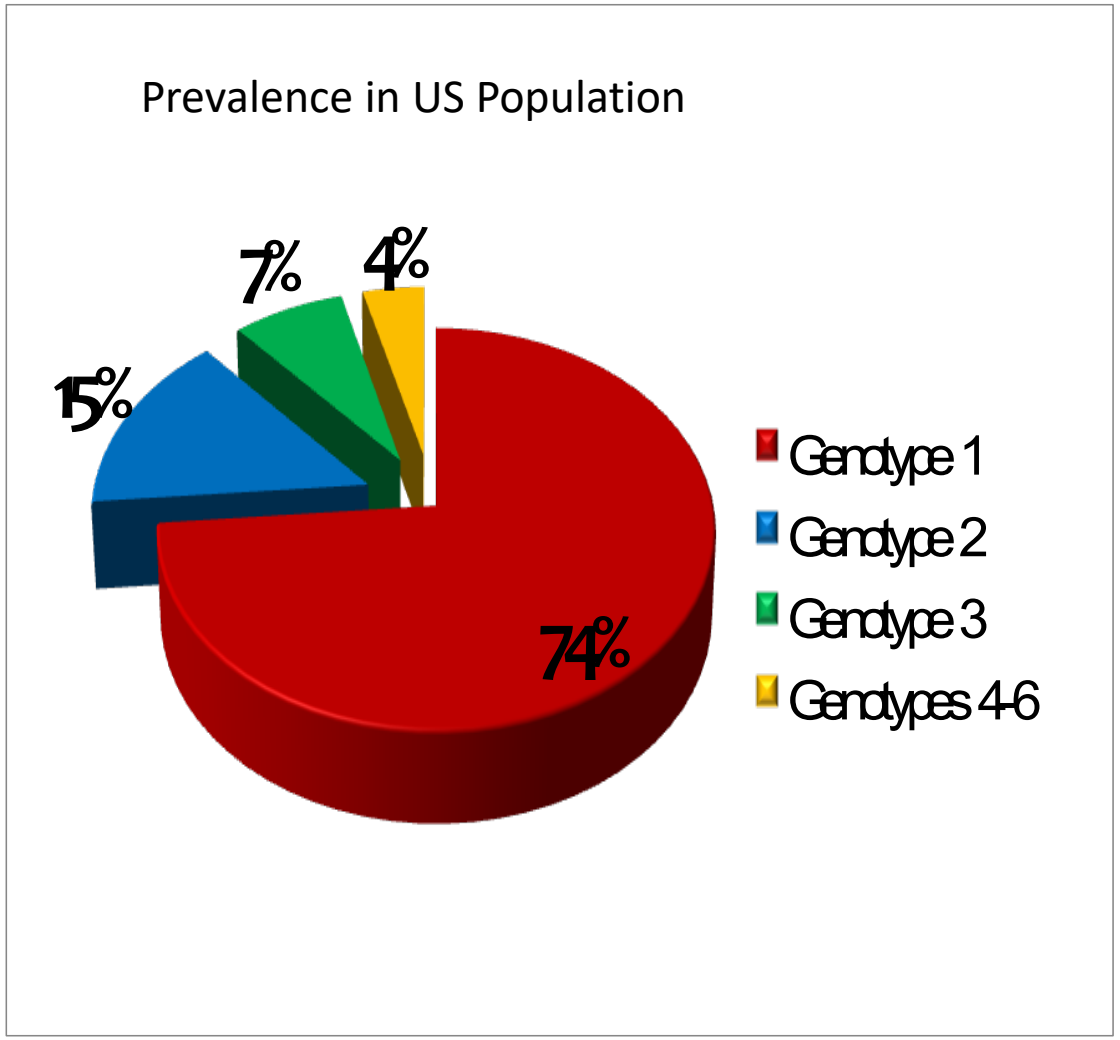
- Missing or incorrect contact info
- Pt not aware of diagnosis or referral
- Lack of transportation
- Housing insecurity/instability





https://www.hhs.gov/hepatitis/mapping-hepatitis-elimination-in-action/index.html

Hepatitis C Genotypes

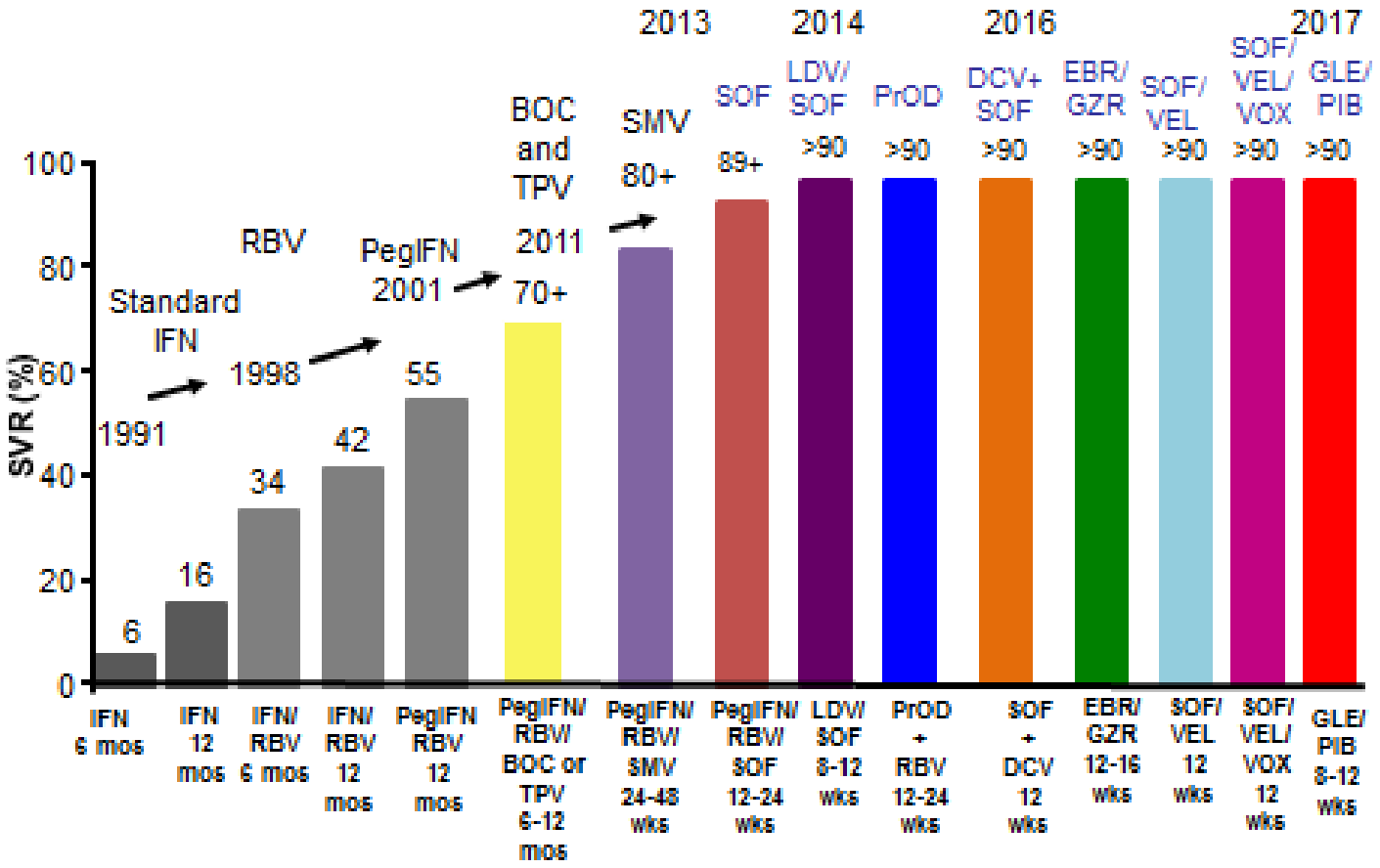


- 6 major genotypes (1-6), most with subtypes
- GT 3 associated with higher mortality, steatohepatitis

HCV Very Curable
(95%+ cure rate)

Costs decreasing

The Evolution of Highly Effective Treatment



Graphic courtesy of Paulina Deming, PharmD., Project ECHO

Goals of HCV Therapy

- Cure
  - Defined as sustained virologic response (SVR)
  - HCV RNA not detectable at least 12 weeks after completing HCV therapy
- Improvements in liver function
  - Improvements in fibrosis
  - Prevent decompensation
- Improvements in extrahepatic manifestations of HCV
- Prevent deaths due to liver disease complications
- Prevent liver cancer
- Reduce rates of liver cancer recurrence

Differences in Therapy

- Interferon Based
  - Injectable
  - Long duration of treatment
  - High side effect profile
  - Multiple laboratory abnormalities
  - Low cure rates
- Direct Acting Antivirals
  - Oral
  - Short durations
  - Minimal side effects
  - Minimal laboratory abnormalities
  - High cure rates

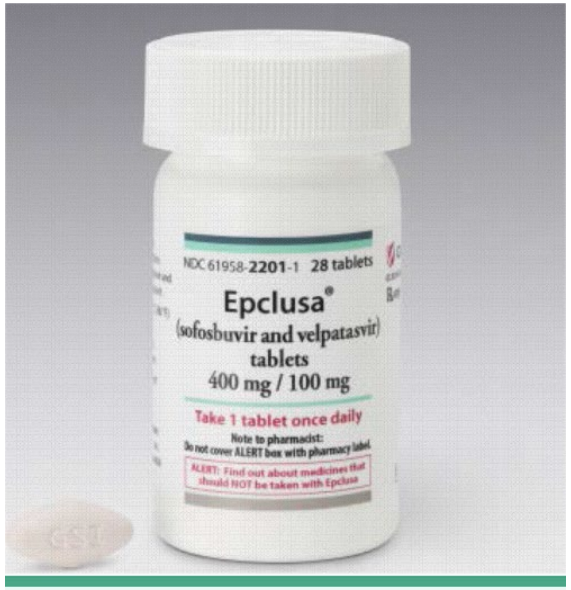
HCV Direct Acting Antivirals (DAAs) Generic Name	Brand Name	Comments
Glecaprevir/Pibrentasvir	Mavyret®	Pan-genotypic
Sofosbuvir/ Velpatasvir	Epclusa® agEpclusa®	Pan-genotypic
Ledipasvir/Sofosbuvir	Harvoni® agHarvoni®	Limited use, for genotype 1 and 4 only
Elbasvir/ Grazoprevir	Zepatier®	Limited use, for genotype 1 and 4 only
Sofosbuvir/ Velpatasvir/ Voxilaprevir	Vosevi®	Pan-genotypic
Other Therapies		
Ribavirin	Ribasphere®, RibaPak®, Copegus®, Rebetol®	

DAAs which work on all the genotypes are considered "pan-genotypic"

HBV Reactivation Risk in HCV

- FDA warning issued 2016 following 24 reported cases of HBV reactivation in patients treated with HCV DAAs
  - 2 deaths
  - 1 liver transplant
- Mechanism of reactivation unclear
  - HCV DAAs do not have immunosuppressive effects
- Current recommendations are to “evaluate patients for potential coinfection of HCV and HBV”
  - ***All patients should be tested for anti-HBc, HBsAg, anti-HBs***

Sofosbuvir/ Velpatasvir (SOF/VEL)



- Fixed-dose combination of sofosbuvir (NS5B inhibitor) and velpatasvir (NS5A inhibitor)
- Approved for chronic HCV genotypes 1, 2, 3, 4, 5, or 6 for 12 weeks
- Administration
  - 1 tablet once daily with or without food
  - Requires acidic environment for absorption

Who Can Be Treated with Sofosbuvir/ Velpatasvir?

- Patients without cirrhosis
- Patients with cirrhosis, including Child's class A, B or C cirrhosis
- Patients with renal insufficiency including patients on dialysis
- Approved for use in pediatric patients 3 years old and older

Glecaprevir/ Pibrentasvir (G/P)

- Combination of
  - Glecaprevir an NS3/4A protease inhibitor
  - Pibrentasvir an NS5A inhibitor
- Dosage and administration: 3 tablets once daily with food
- Indicated for 8-12 weeks

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Who Can Be Treated with Glecaprevir/ Pibrentasvir?

- Patients without cirrhosis
- Patients with Child's class A cirrhosis (compensated cirrhosis)
- Do not use in patients with Child's Class B or Child's Class C cirrhosis (decompensated cirrhosis)
- Patients with renal insufficiency including patients on dialysis

- Approved for use in children 3 yo and older

Sofosbuvir/ Velpatasvir/ Voxilaprevir

- Combination of
  - NS5B polymerase inhibitor (Sofosbuvir);
  - NS5A inhibitor (Velpatasvir);
  - NS3/4A protease inhibitor (Voxilaprevir)
- Administration
  - One tablet once daily with food
- Indicated for patients who were previously failed by DAA therapy

Who Can Be Treated with SOF/VEL/ VOX?

- Patients without cirrhosis
- Patients with Child's class A cirrhosis (compensated cirrhosis)
- Patients with renal insufficiency including hemodialysis

- Not recommended in patients with Child's Class B or C cirrhosis

Ribavirin

- **Limited use**
  - Added to treatment in specific clinical scenarios
    - Patients with decompensated cirrhosis who can tolerate ribavirin
    - For patients who have specific HCV resistance concerns
- Well-known toxicity profile
  - Hemolytic anemia
  - Teratogenic
    - Pregnancy category X

Child-Pugh Classification of Cirrhosis for Drug Dosing

	1 Point	2 Points	3 Points
Encephalopathy	None	Moderate	Severe
Ascites	Absent	Mild-Moderate	Severe/ Refractory
Bilirubin (mg/dL)	< 2	2 - 3	> 3
Albumin (g/dL)	> 3.5	2.8 - 3.5	< 2.8
INR (PT Prolongation *sec over control)*	<1.7 (0-4)	1.7-2.3 4-6	>2.3 (>6)

Note: ***Child Pugh Score is calculated only for patients with cirrhosis***

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Child-Pugh Interpretation of Hepatic Function in a Patient with Cirrhosis

C-P Score (Class)	***Liver Function***
5-6 (A)	Compensated
7-9 (B)	Decompensated
> 9 (C)	

Serious liver injury was reported in patients taking protease inhibitor therapy- **do not use protease inhibitor based therapies in patients with Childs B or C cirrhosis**

Treatment Options for Patients with Decompensated Cirrhosis

- Sofosbuvir/velpatasvir plus ribavirin x 12 weeks
  - Use of ribavirin requires frequent monitoring for hemolytic anemia
- Sofosbuvir/velpatasvir x 24 weeks
- All protease inhibitor therapy is contraindicated in decompensated cirrhosis due to reports of serious liver injury

What Predicts Treatment Success or Failure?

- Patients who are treatment naïve and non-cirrhotic have very high SVR rates
- Underlying cirrhosis can decrease SVR
- Medication adherence

Side Effect Profile of DAAs

- Prior treatments:
  - Interferon:
    - Flu-like symptoms: fever, headache, myalgia
    - Fatigue
    - Depression
    - Irritability
    - Insomnia
    - Nausea/ vomiting
    - Anorexia
    - Cognitive dysfunction
  - Ribavirin:
    - Rash
    - Nausea/vomiting
    - Headache

- DAAs:
  - Overall very well tolerated
  - Most commonly reported side effects:
    - Headache
    - Fatigue
    - Nausea
    - Diarrhea (reported with voxilaprevir)

Rapid Improvements in Inflammation

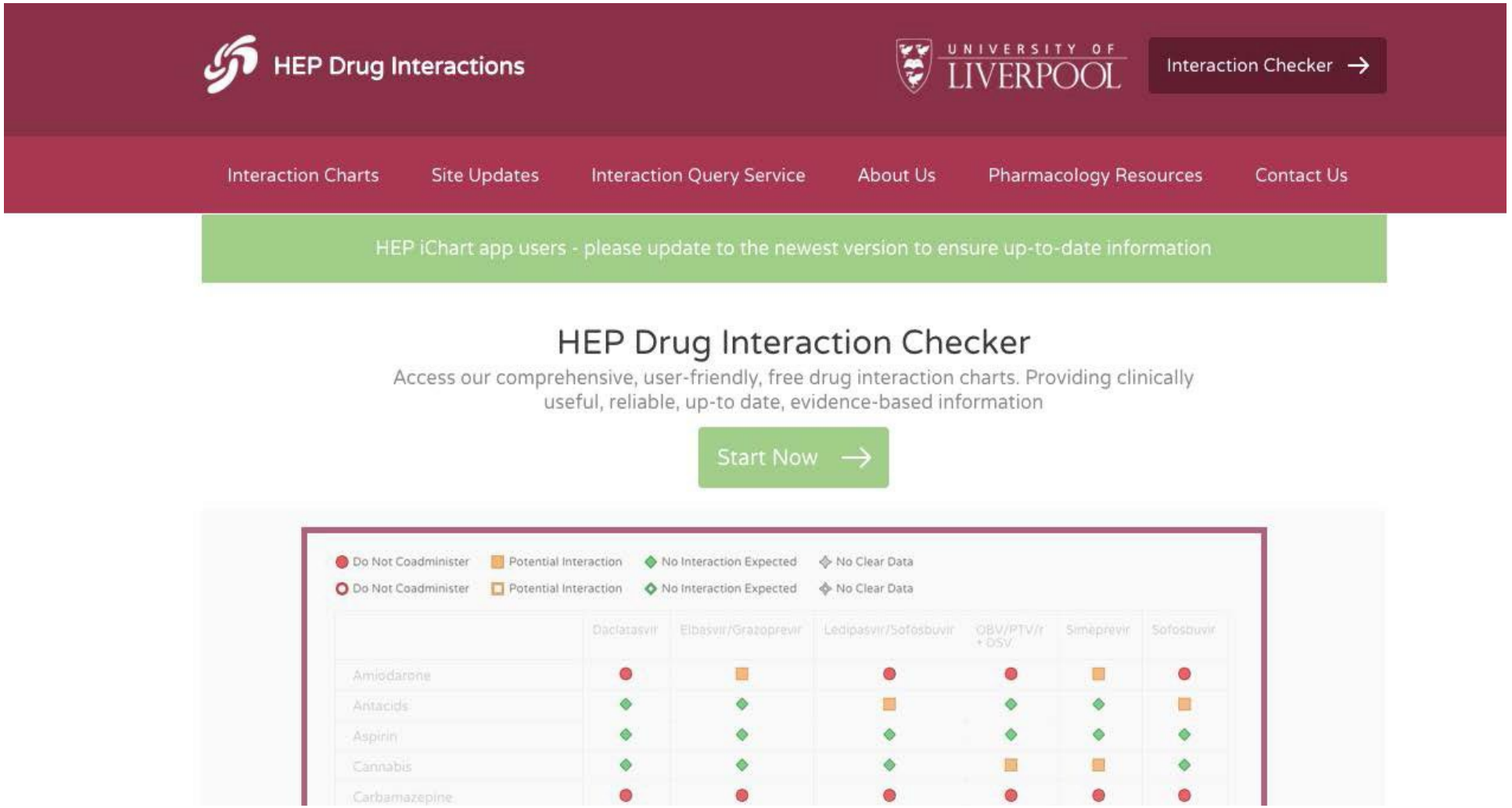
Week	Baseline	Week 1	Week 2	Week 4	Week 8	Week 12	Week 24
Actual Date	06/01/2017	06/08/2017	06/15/2017	06/29/2017	07/27/2017	08/24/2017	11/16/2017
WBC	5.9	6.8	6.1	4.8	5.3	5.6	7.0
ANC	3.5	2.8	3.4	2.2	2.6	3	3.4
HGB	14.1	13.9	13.3	14.2	13.8	14.3	14.2
HCT	43.6	41.0	40.8	42.8	41.3	42.5	43.3
Platelets	322	363	308	253	273	276	315
Creatinine	.088	0.89	0.87	0.82	0.89	0.82	0.78
AST SGOT	74	14	16	13	13	15	18
ALT SGPT	102	42	15	11	13	12	16
Total Prot	6.7	6.6	7.1	6.7	6.4	7.1	7.2
Albumin	3.9	3.8	4.2	4.2	4.0	4.3	4.2
T. Bili	0.3	0.2	0.3	0.4	0.4	0.3	0.5
Dir Bili							
Alk Phos	53	42	43	40	47	44	56
HCV RNA	5910			ND			
HCV Log	3.772						

Other Main Drug Interaction Concerns for DAAs

- Statins:
  - Interactions vary by DAA and statin
  - Safest option may be to hold statin during HCV therapy
- Acid suppressive therapy:
  - **Velpatasvir requires acidity for absorption**
  - Recommend minimizing acid suppressive therapy in all patients undergoing HCV therapy
- Avoid amiodarone
  - Amiodarone with sofosbuvir and other DAA: Serious symptomatic bradycardia

Major Drug-Drug Interactions for all Direct Acting Antivirals

- **Carbamazepine**
- **Oxcarbazepine**
- **Phenytoin**
- **Phenobarbital**
- **Rifampin**
- Expected to ↓ concentrations
- DO NOT USE WITH HCV THERAPY!



www.hep-druginteractions.org
Also available as an app: hepichart

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What About Medications in Patients with HCV?

Current Medications:

Medication name:	Dosage:	Frequency	Medication name:	Dosage:	Frequency

Current Method of Birth Control: _____

If oral contraceptive, does it contain ethinyl estradiol? ☐ Yes ☐ No

→ Avoid ethinyl estradiol with glecaprevir/pibrentasvir

- Studies in pregnancy currently enrolling

"Despite the lack of a recommendation, treatment can be considered during pregnancy on an individual basis after a patient-physician discussion about the potential risks and benefits"

- **Bottom line: Recommend birth control in all female patients of childbearing age/capacity**

- HCVguidelines.org
- Accessed January 25, 2022

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- HCV Community ECHO
  - Wednesday 3PM, case presentations & treatment recommendations
  - Didactic lectures
  - Using technology to amplify scarce resources
- Monthly provider training for HCV treatment

- Email HCVEcho@salud.unm.edu to register

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Resources

- ECHO HCV guidelines- link provided in weekly email
  - Includes links to decision trees, flowsheets, resources, patient education material
- AASLD/IDSA HCV Treatment Guidelines:
  - Available at: http://www.hcvguidelines.org
- HCV Drug Interactions (University of Liverpool):
  - Available at: http://www.hep-druginteractions.org
- Educational material, clinical calculators, HCV therapy summaries (University of Washington)
  - Available at: http://www.hepatitisc.uw.edu

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