Hepatitis C for Primary Care:
From Diagnosis to Cure and Beyond

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She has been highly involved in various research and quality improvement projects using Lean Six-Sigma methodology.

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Disclosures

- Dr. Kelsey Rife and Dr. Kristina Pascuzzi Frangella have no relevant financial or non-financial relationships to disclose relating to the content of this activity.
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Learning Objectives

At the conclusion of this activity, participants will be able to:

1. Assess patients at risk of Hepatitis C virus (HCV) and suggest appropriate testing for diagnosis.
2. Distinguish appropriate counseling and management options for patients with HCV.
3. Demonstrate the impact successful HCV treatment may have on patients' diabetes.

Polling Questions

1. Who feels comfortable diagnosing hepatitis C?
2. Who feels comfortable treating hepatitis C?

Outline

Hepatitis C (HCV) epidemiology

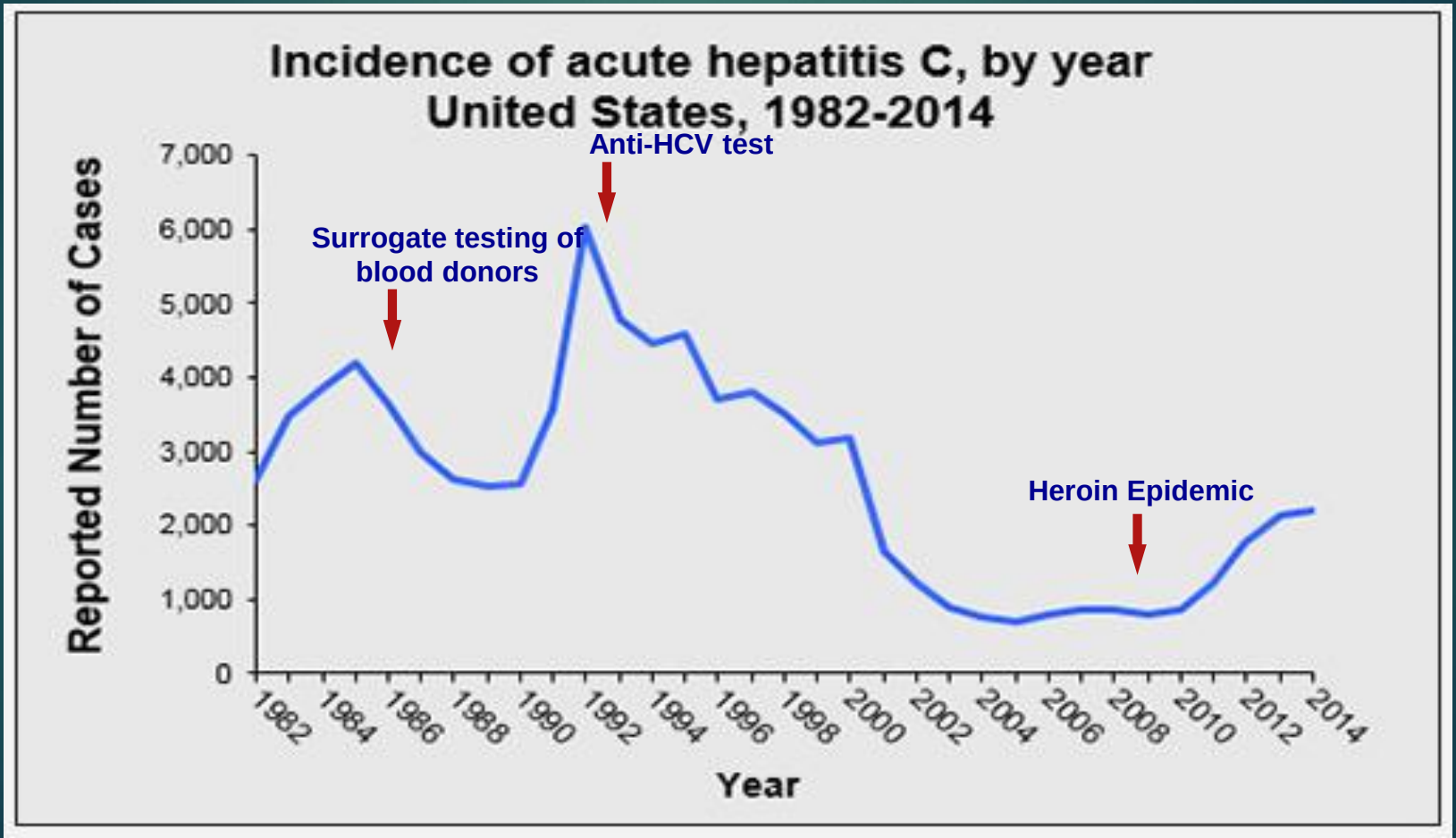
Addressing the needs of your HCV patients

HCV treatment and drug interactions

Benefits beyond the Liver

Epidemiology – United States (US)

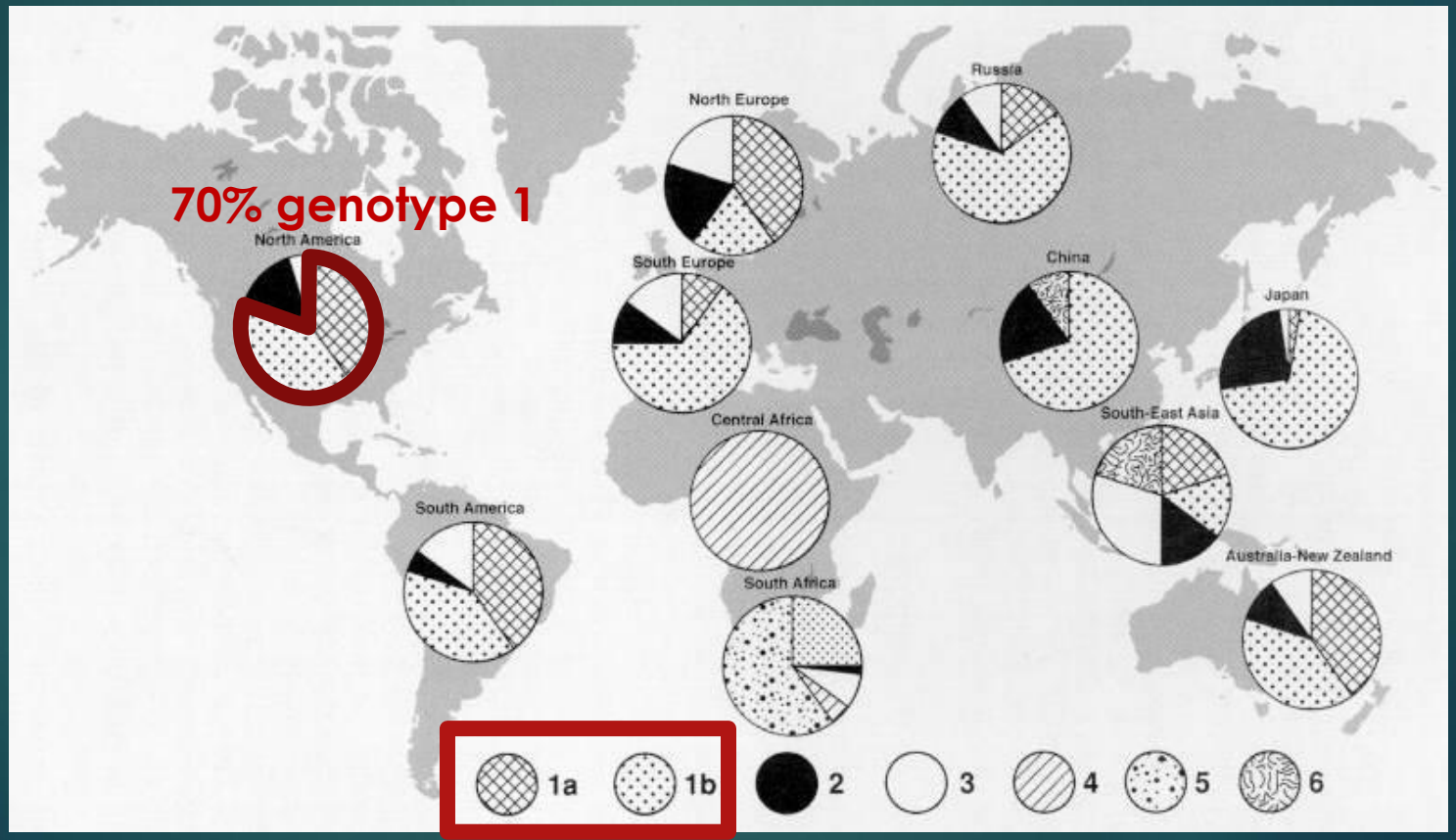
- Most common blood-borne infection
  - Leading cause for end stage liver disease, hepatocellular carcinoma, and liver transplantation in US



http://www.cdc.gov/hepatitis

HCV Etiology

- Single-stranded RNA virus of Flavivirdae family
  - Lacks proofreading polymerase > frequent viral mutations



(Forns, X. et al, 1999)

HCV Screening

- All adults aged 18-70 years: one-time screening
  - Updated in 2020 from previous 1945-1965 "birth cohort" screening recommendation
- Additional risk factors

Blood transfusion before 1992	IV drug use	Blood exposure in job or military
Body piercing/ tattoos in informal setting	High risk sexual behavior	History of hemodialysis

Prevent Spread of Virus

Safe

- Not transmitted through casual contact
  - Hugging
  - Kissing
  - Sharing a glass
  - Eating off the same plate

Avoid

- Do not share personal items
  - Razor
  - Toothbrush
  - Cuticle scissors

Natural History of HCV

Clinical Presentation: often asymptomatic prior to development of cirrhosis

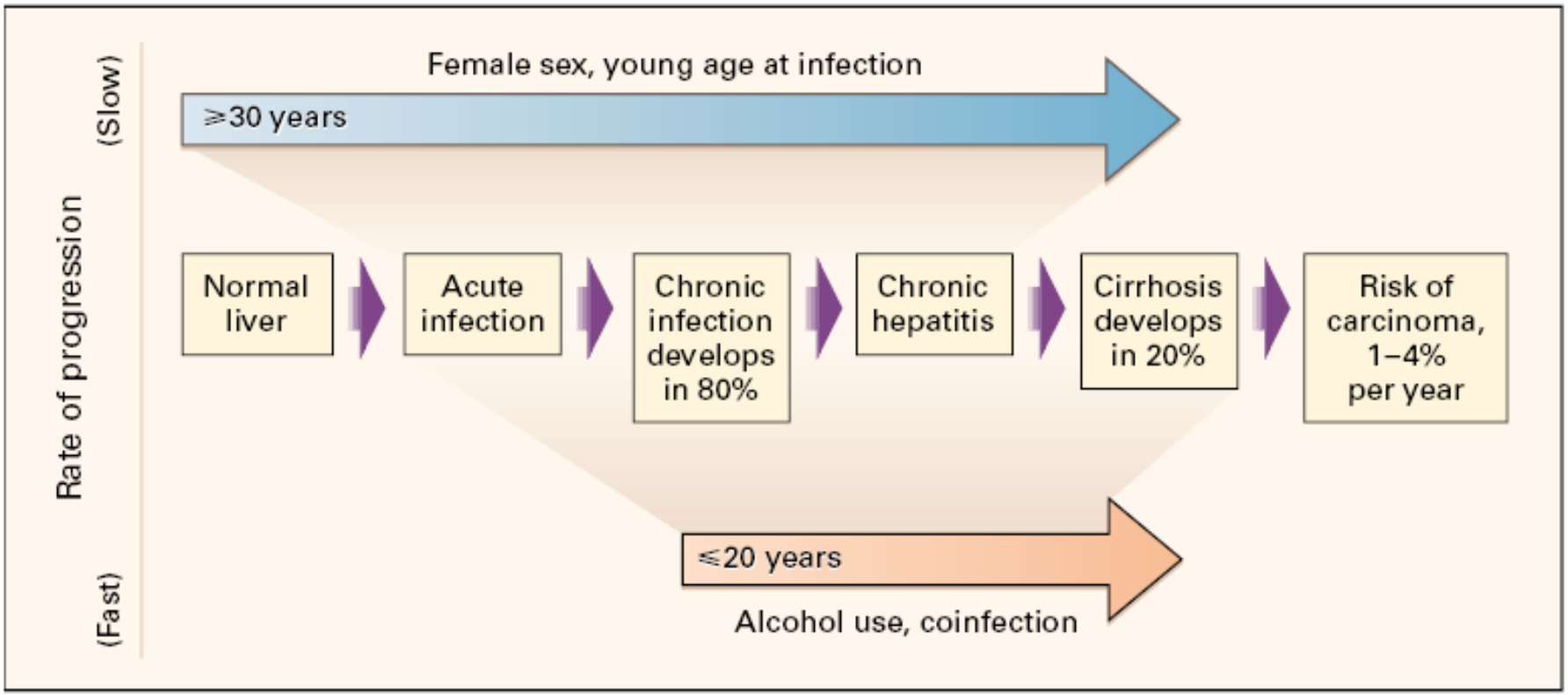


Figure 2. The Natural History of HCV Infection and Its Variability from Person to Person.

(Lauer, G. et al, 2001)

Complications from HCV

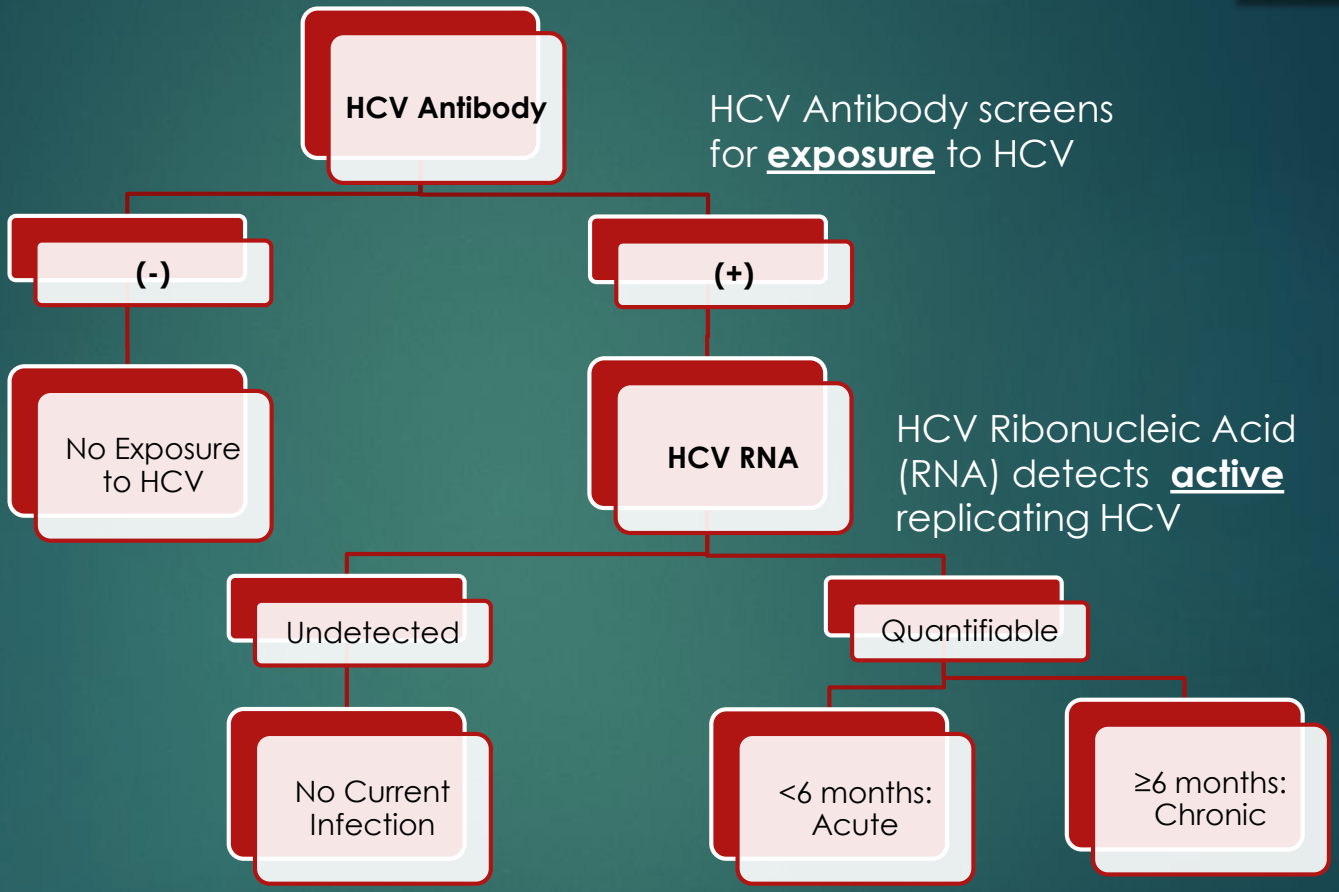
**Hepatic

- Cirrhosis
- End-stage liver disease
- Hepatocellular carcinoma
- #1 indication for liver transplantation in U.S.

Extrahepatic

- Cryoglobulins: immune complexes
  - Vasculitis
  - Glomerulonephritis
  - Dermatologic disorders- Sjögren's syndrome
  - Arthritis
- Impaired glucose tolerance
- Fatigue
- Pain

Diagnosis



Additional Diagnostic Tests to guide regimen selection:

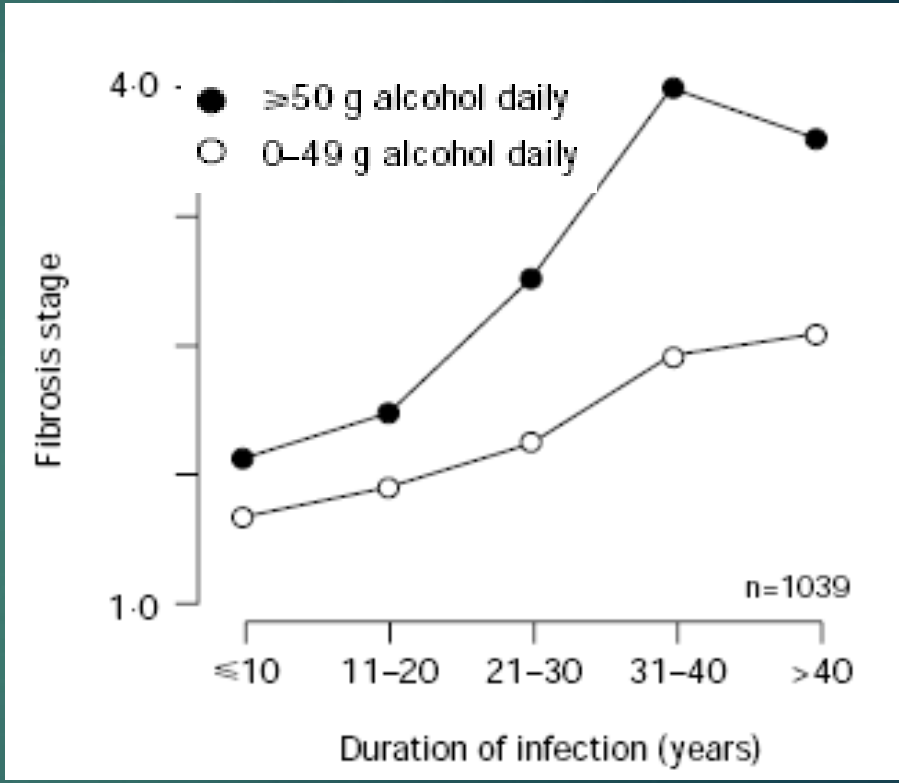
- Genotype (blood test)
- Cirrhosis status (variety of tests may determine degree of fibrosis)

Patient Counseling

- Avoid Alcohol
- Avoid sharing personal items
- Demonstrate good medication adherence
  - Goal 100% adherence to HCV regimen
  - Avoid break in therapy
- Maintain healthy diet and regular exercise routine

Alcohol= "*Gasoline on a Fire*"

- Clinical consequences
  - Increased rate of fibrosis and cirrhosis
  - Increased severity of HCV infection
  - Increased rates of Hepatocellular Carcinoma (HCC)



(Peters, M. G. et al, 2002)
(Poynard T. et al, 1997)

Harm Reduction Strategies

- Assessing for amounts/types of alcohol
- Not sharing needles
- Needle exchange programs
- Treatment groups
- Safe sex practices
- Removing patients from high risk settings
- Stable housing

HAV & HBV Immunizations

- Hepatitis A (HAV)
- Hepatitis B (HBV)
  - Combination Hepatitis A/Hepatitis B vaccine
    - Standard
      - Day 0, month 1, and month 6
    - Accelerated
      - Day 0, 7, 21-30, booster at month 12

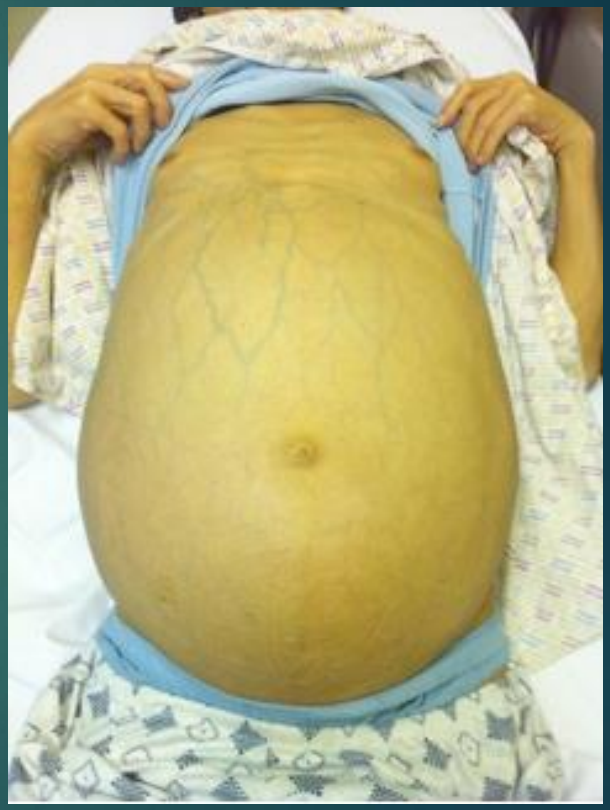
Twinrix Dose	% Seroconversion for HAV	% Seroconversion for HBV
1	93.8	30.8
2	98.8	78.2
3	99.9	98.5

Other Immunizations

- Influenza Vaccine
  - Indicated in chronic liver disease patients
- Pneumococcal Vaccine
  - Pneumococcus implicated in severe sepsis and SBP episodes
  - PneumoRecs Vax Advisor:
    - https://www2a.cdc.gov/vaccines/m/pneumo/pneumo.html
      - Liver disease: Pneumovax 23 indicated < 65 years and 1 dose > 65 years
        - > 65 years old Prevnar 13 (PCV13) falls under shared decision making

Cirrhosis Identification

- Transient elastography
  - ≤ 9.5 kPa: rule out cirrhosis
  - ≥ 12.5 kPa: follow cirrhosis HCV treatment guidance
  - ≥ 19.5 kPa: screen for varices
- Radiographic
  - Surface nodularity
  - Hepatomegaly, splenomegaly
  - Ascites
- Biochemical
  - Platelet count < 150
  - ↑ bilirubin, ↓ albumin, ↑ Internal Normalized Ratio (INR)
- Clinical



(Lim J. K. et al., 2017)

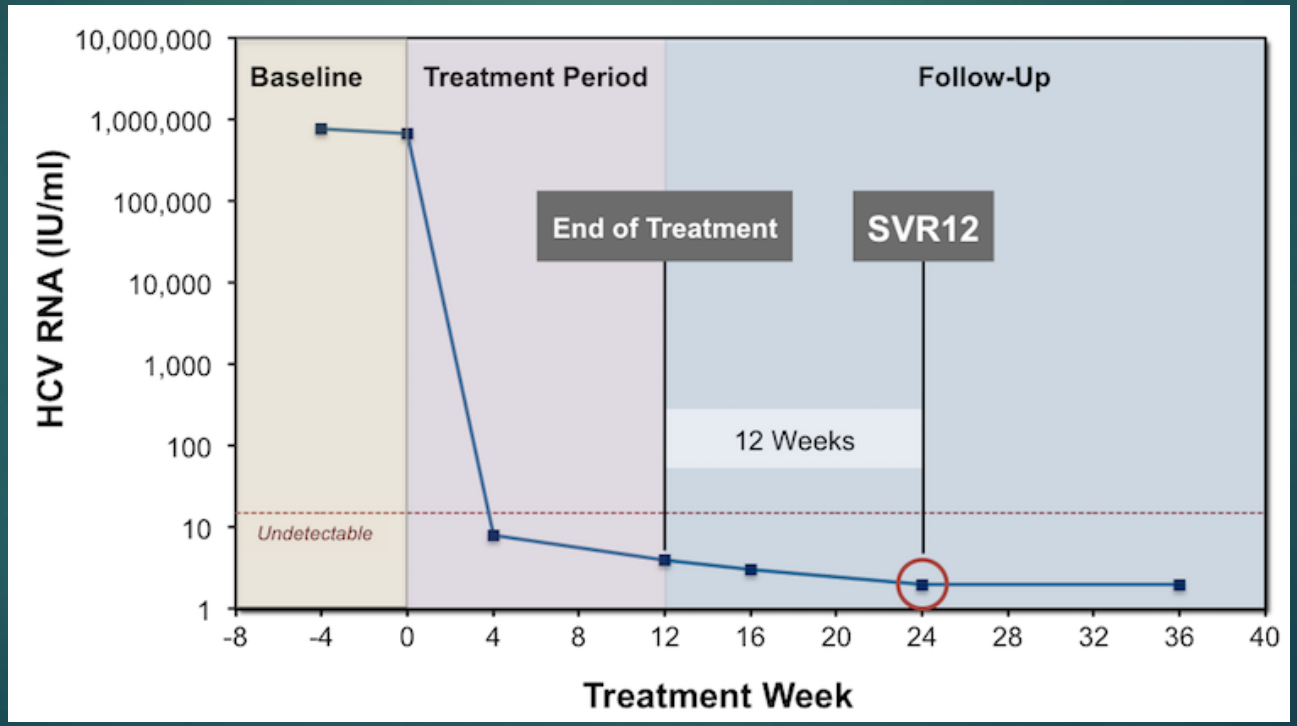
Hepatocellular Carcinoma

- Epidemiology
  - 5th most common type of cancer in men, 9th in women
  - Annual US incidence: 6 per 100,000 in 2010 (rates increasing)
    - Death rate is similar to incidence rate
- HCC in chronic HCV
  - Occurs in advanced liver disease
  - HCV treatment decreases but does not eliminate risk
- Current recommendations
  - Screen at 6-month intervals using ultrasound ± alpha-fetoprotein (AFP)
    - AFP: low sensitivity
    - Ultrasound: sensitivity low in lesions < 1 cm
    - Triple phase CT scan: improved sensitivity when lesions unable to be characterized on ultrasound

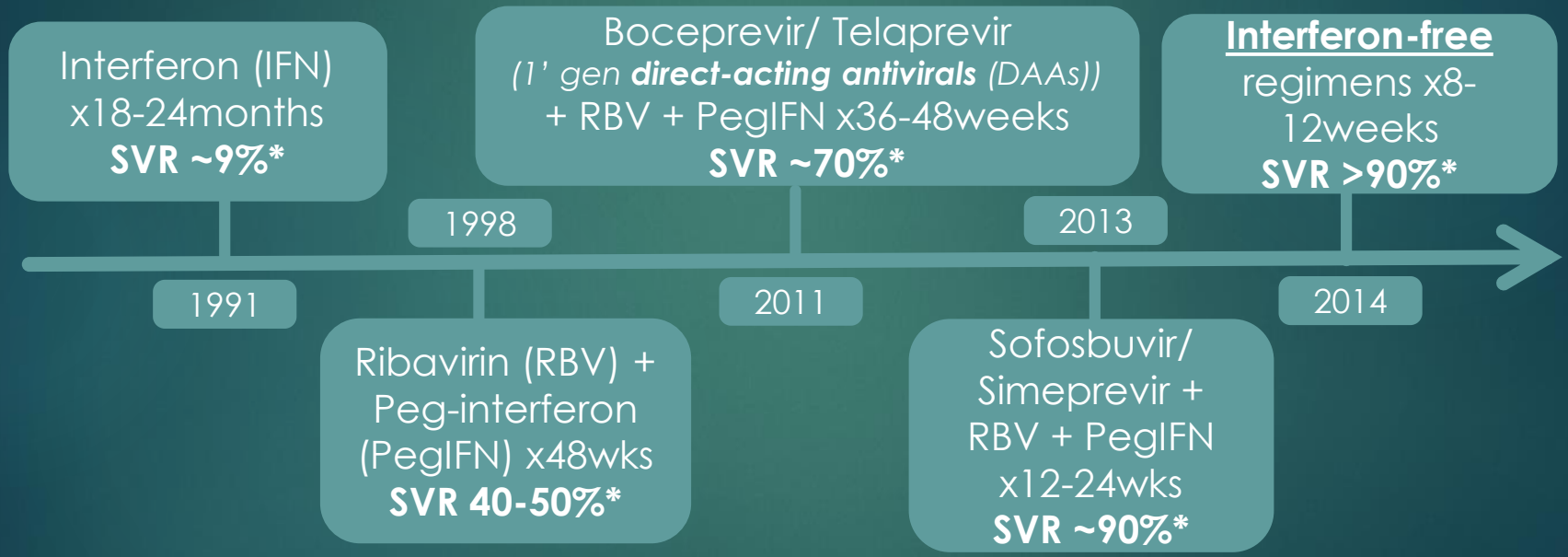
(Bruix J. et al, 2011).
(Marrero J. A. et al, 2018)

Goal of Treatment for HCV

- Sustained virologic response (SVR):
  - Undetectable HCV RNA in serum ≥12 weeks post treatment using polymerase chain reaction (PCR) assay



Evolution of Hepatitis C Treatment

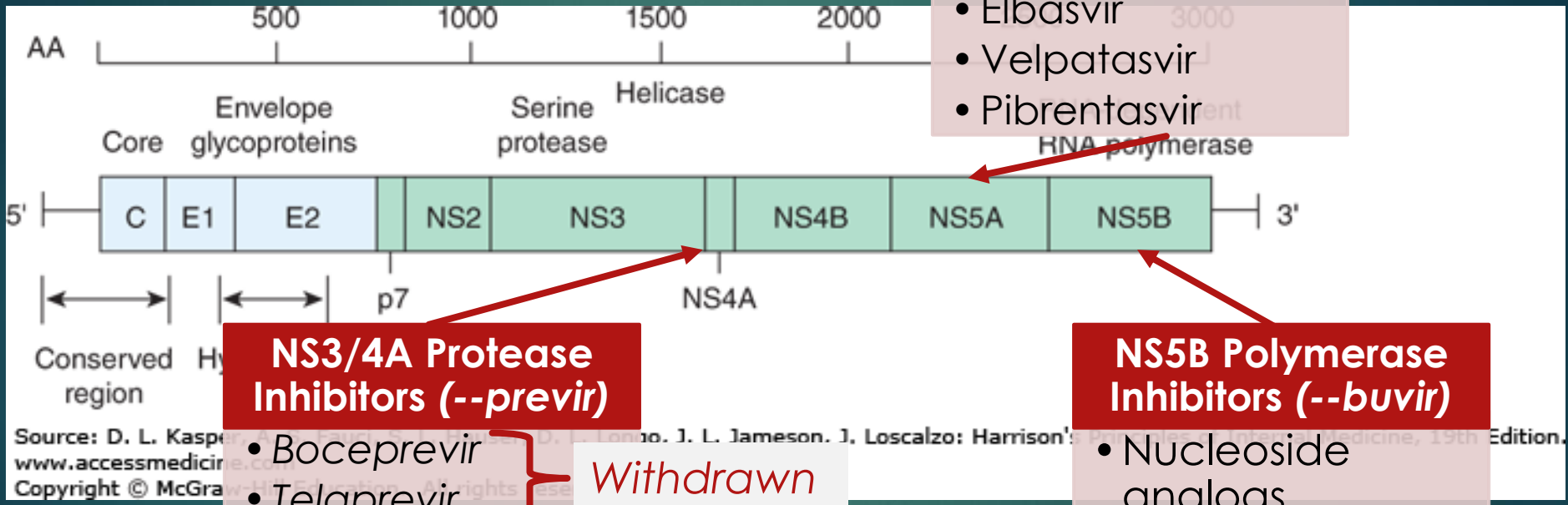


**SVR rates reported for genotype (GT) 1*

HCV DAA Targets

NS5A Inhibitors *(--asvir)*

- Ledipasvir
- Ombitasvir
- Daclatasvir
- Elbasvir
- Velpatasvir
- Pibrentasvir



NS3/4A Protease Inhibitors *(--previr)*

- *Boceprevir*
- *Telaprevir*

Withdrawn

- Simeprevir
- Paritaprevir
- Grazoprevir
- Voxilaprevir
- Glecaprevir

NS5B Polymerase Inhibitors *(--buvir)*

- Nucleoside analogs
  - Sofosbuvir
- Non-nucleoside analogs
  - Dasabuvir

(Jameson, J. L. et al, 2017)

DAA Products

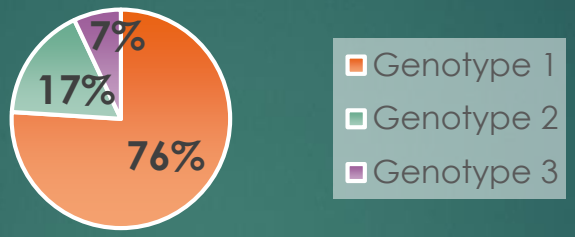
Generic	Brand Name	Genotype
Ledipasvir/sofosbuvir	Harvoni®	1, 4, 5, 6
Elbasvir/grazoprevir	Zepatier™	1, 4
Sofosbuvir/velpatasvir	Epclusa®	1-6
Sofosbuvir/velpatasvir/voxilaprevir	Vosevi®	*DAA Retreatment:*1-6
Glecaprevir/pibrentasvir	Mavyret™	*Naïve & IFN-exp.:* 1-6 *DAA Retreatment:* 1

- Well-tolerated, all-oral medications
- Typical treatment durations 8-12 weeks
- SVR rates ~95%+
- Ribavirin still used as "booster" for patients with poor outcome predictors such as decompensated cirrhosis

Treatment Decisions

- Genotype (GT)
  - GT 1-6

HCV Genotypes in US



- Treatment history
  - Naïve or interferon experienced?
  - History of direct-acting antivirals?
    - Protease inhibitors v. NS5A inhibitors?

- Cirrhosis determination
  - Biopsy
  - Transient elastography >12.5 kPa
  - Aspartate Aminotransferase -to-platelet ratio index (APRI) and fibrosis-4 index (FIB-4) score

Additional Considerations in Regimen Selection

- Renal function
- Severity of cirrhosis
  - Compensated (Child-Pugh A) versus decompensated (Child-Pugh B or C)
- Cost-effectiveness
- Length of therapy
- Pill burden
- Drug interactions
- Comorbidities

Common Drug Interactions- PPIs and H2RAs

- Acid-reducing agents
  - Interacting regimens:
    - Ledipasvir/sofosbuvir
    - Sofosbuvir/velpatasvir (or sofosbuvir/velpatasvir/voxilaprevir)
    - Glecaprevir/pibrentasvir
  - Concern:
    - HCV antivirals require an acidic environment for absorption; acid-reducing agents may reduce absorption > levels > efficacy of HCV antivirals
  - Recommendations:
    - Proton Pump Inhibitors (PPIs): depending on regimen, may need avoided or limit to max equivalent dose of omeprazole 20mg
    - H2 antagonists (H2RA): max equivalent dose of famotidine 40mg q12h dosed at same time and/or 12 hours after HCV antiviral
    - Antacids: space four hours before or after HCV antiviral

Common Drug Interactions- Statins and P-gp Inducers

- Statins
  - Interacting regimens: ALL
  - Concern:
    - HCV antivirals increase levels/ risk of adverse effects of statins
  - Recommendations:
    - Indication for statin 1' prevention: HOLD statin until end of treatment
    - Indication for statin 2' prevention: SWITCH to pravastatin (max dose varies by HCV DAA) until end of HCV treatment
- Potent P-glycoprotein (P-gp) inducers:
  - Interacting regimens: ALL
  - Concern:
    - Increase metabolism and decrease efficacy of HCV antivirals
  - Recommendations:
    - Phenytoin, carbamazepine, oxcarbazepine, etc.: consult to prescribing clinician if patient may be changed to alternative therapy to proceed with HCV treatment

Benefits of HCV Treatment Beyond the Liver

- May improve extrahepatic manifestations:
  - Cryoglobulins: may be severe, but uncommon (2-6%)
    - Vasculitis
    - Glomerulonephritis
    - Dermatologic disorders- Sjögren's syndrome
    - Arthritis
  - Fatigue (50%+)
  - Depression (up to 28%)
  - Type 2 diabetes (~30%)

HCV and Diabetes

- Multifactorial:
  - Comorbid fatty liver disease
  - Fibrosis/cirrhosis
  - HCV core protein ↑phosphorylation of insulin receptor substrate-1
  - ↑Tumor necrosis factor alpha (TNF-α)
    - Effects on insulin receptor substrate-1
    - Mediate hepatic insulin resistance
    - Stimulate lipolysis
    - Down-regulate peroxisome proliferator-activated receptor-γ
    - Interfere with β-cell function

Significant HbA_{1c} Lowering in Patients Achieving a Hepatitis C Virus Cure

Kelsey Rife, PharmD; Alessandra Lyman, PharmD; Sheena LeClerc-Kamieniecki, PharmD; Corinna Falck-Ytter, MD; Kristina Pascuzzi, PharmD; Christopher J. Burant, PhD; and Yngve Falck-Ytter, MD

- **Objective:** assess impact of HCV DAA treatment on glucose control in Veteran patients with Type 2 Diabetes Mellitus (T2DM) at a single center
- **Primary Endpoint:** change in hemoglobin A1c (HbA_{1c})up to 4-months post-treatment in patients achieving sustained virologic response after 12 weeks (SVR12) from HCV treatment
- **Secondary Endpoints:**
  - Change in HbA_{1c} up to 12- & 18-months post-treatment in patients achieving SVR12
  - Change in antihyperglycemic regimen
  - Change in HbA_{1c} and antihyperglycemics in HCV treatment relapses vs. those who achieved SVR12

(Rife K. et al, 2019)

Baseline Characteristics	Patients N = 157 (%)
Age	Mean=62, SD=5.1, Range [45-86]
Male	151 (96%)
Race	
African American	88 (56%)
Caucasian non-Hispanic	55 (35%)
Other/Unknown	12 (8%)
Advanced Fibrotic Liver Disease	66 (42%)
SVR12 Achieved	147 (94%)
Genotype 1	134 (85%)
Regimens	
Ledipasvir/sofosbuvir +/- ribavirin	122 (78%)
Sofosbuvir + ribavirin +/- peginterferon	13 (8%)
Ombitasvir/paritaprevir/ritonavir +/- dasabuvir +/- ribavirin	9 (6%)
Elbasvir/grazoprevir	6 (4%)
Sofosbuvir + simeprevir	5 (3%)
Velpatasvir/sofosbuvir + ribavirin	2 (1%)
No. of Antihyperglycemic Medications	
1	64 (41%)
2	62 (39%)
3	27 (17%)
4	4 (3%)

(Rife K. et al, 2019)

HCV and DM: Outcomes

- Decreased HbA_{1c} 0.67% at 4-months post-treatment in patients who achieved SVR12
  - 7.67% → 7.00% ($p < 0.001$)
- Larger decline in HbA_{1c} for patients with higher HbA_{1c} at baseline
  - Up to ~3% in patients with baseline HbA_{1c} ≥10%
  - Sustained changes at 12- and 18-months post-treatment
- Antihyperglycemics decreased in 30% of patients achieving SVR12
- Comparison of relapsers limited by small numbers (n=8)

(Rife K. et al, 2019)

HCV and DM: Summary

- 80% patients on antihyperglycemics had either a decrease in their HbA_{1C} or a de-escalation of their regimen after successful HCV treatment
- Larger, sustained decline in HbA_{1C} for patients with worse control at baseline
- Warrants close follow-up for T2DM undergoing/ recently completed HCV treatment
- Potential significant benefits of HCV treatment for health outcomes, quality of life, and long-term cost avoidance beyond liver-related morbidity & mortality

(Rife K. et al, 2019)

Key Takeaways

- Significant advancements in HCV treatment have led to well-tolerated, highly curative regimens.
- Identification and referral/management of cirrhosis remains an important role for primary care providers.
- HCV treatment may improve diabetes control in addition to its well-known ability to decrease liver-related morbidity & mortality.

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Resources

www.cdc.gov/hepatitis/hcv/index.htm

www.hcvguidelines.org

www.hep-druginteractions.org

www.hepatitis.va.gov

Questions?

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