Hepatitis B and C in Remote and Indigenous Communities

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Faculty Presenter Disclosure

- I have no relationships with financial sponsors

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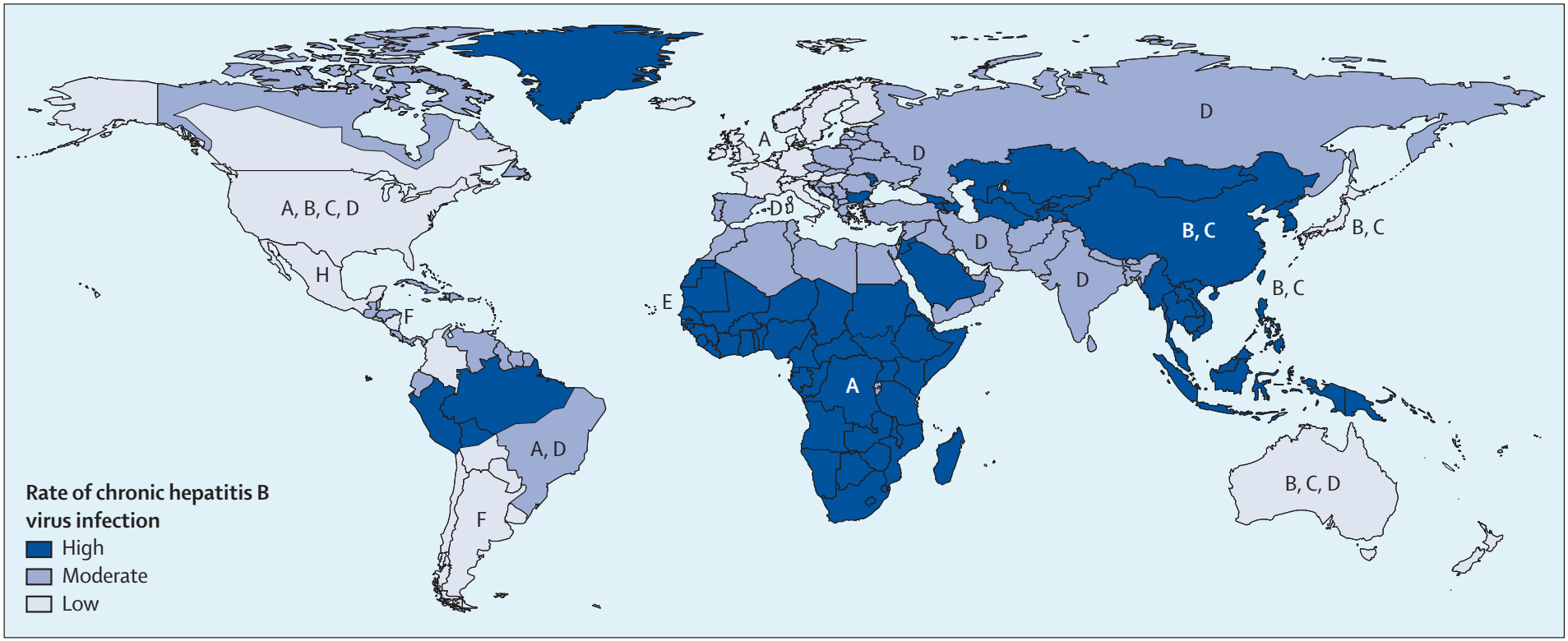
Mitigating Potential Bias

- No mitigation has been required
- Content in this talk does not relate to any of the above disclosures

Objectives

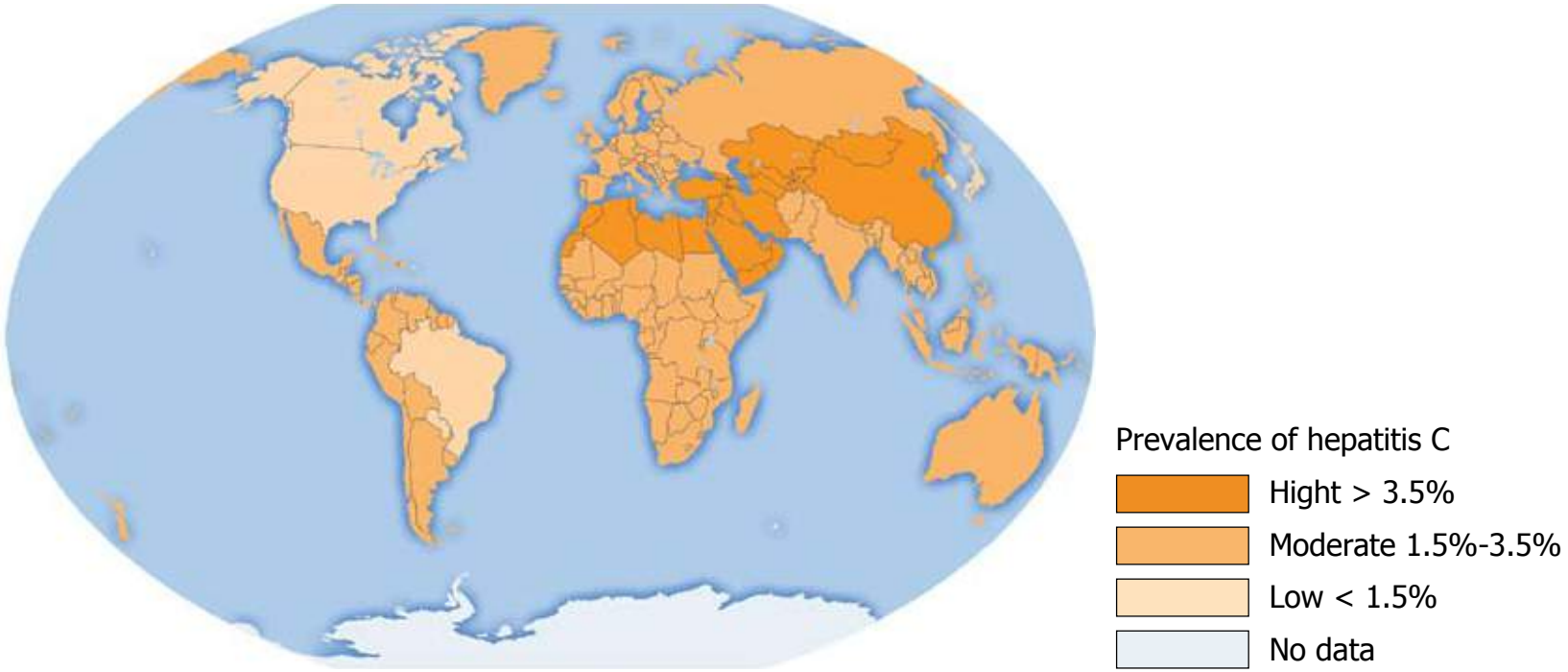
- Describe the prevalence of viral hepatitis in indigenous populations in Canada
- Discuss the natural history of chronic hepatitis B and C
- Interpret appropriate laboratory tests for hepatitis B and C
- Evaluate a patient with hepatitis B and C
- Outline a management plan for a patient with hepatitis B and C

HBV Epidemiology



Trepo et al. Lancet 2014; 384:2053-63.

HCV Epidemiology



Morozov et al. World J Hepatol 2018; 10: 186-212.

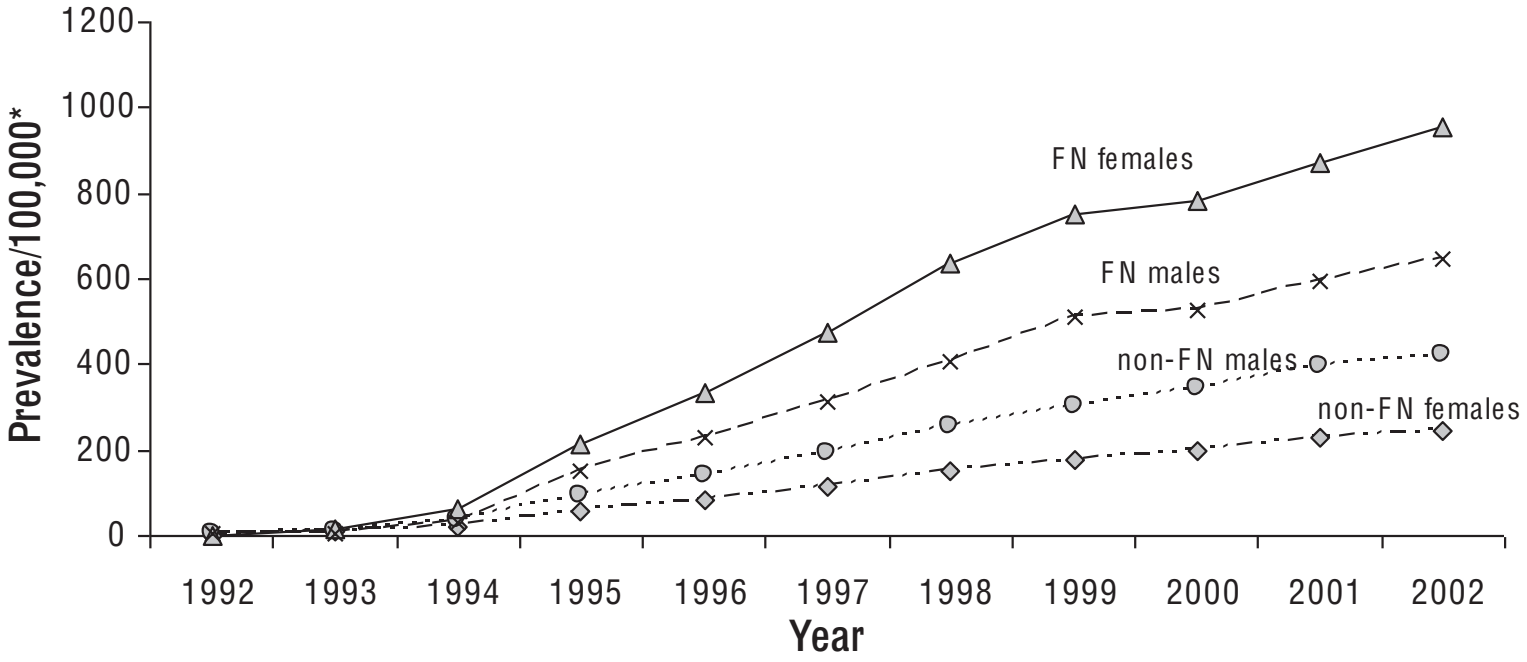
Viral Hepatitis in Canadian Indigenous

Virus	Study year	Subjects (n)	Ethnicity	Prevalence (%)	Investigator
Hepatitis A	1980	494	Inuit	75	Minuk et al 1982 (9)
		48	White	17	
	1983	172	Inuit	76	Minuk et al 1985 (6)
	2000	293	Inuit	82	Minuk et al (unpublished)
	1995–1996	212	First Nations	72	Moses et al 2002 (7)
		53	Metis	42	
		119	Non-Aboriginal	28	
	2000	315	First Nations	95	Minuk et al 2003 (8)
Hepatitis B*	1980	720	Inuit	4/27	Minuk et al 1982 (9)
	1983–1985	8282	Inuit	4/25	Larke et al 1986 (13)
		3140	Dene	3/22	
		2776	Non-Aboriginal	0.3/9	
		2156	Inuit	7/26	Baikie et al (14)
			White	0/3	
	2000	190	Inuit	2/11	Minuk et al (unpublished)
	1995–1996	217	First Nations	2/10	Moses et al 2002 (7)
		53	Metis	2/12	
		134	Non-Aboriginal	5/9	
	1992	2166	First Nations	0.3/10	Martin et al 2002 (15)
Hepatitis C	1980	720	Inuit	0.3/1.0†	Minuk et al 1991 (16)
	2000	190	Inuit	18	Minuk et al (unpublished)
	Unknown	Unknown	92% First Nations	41	Prince Albert Seroprevalence Study (17)
	1995–1996	217	First Nations	19	Moses et al 2002 (7)
		53	Metis	22	
		134	Non-Aboriginal	14	
	2000	315	First Nations	2	Minuk et al 2003 (8)

**Indicates infected/exposed; †Indicates initial/retested result*

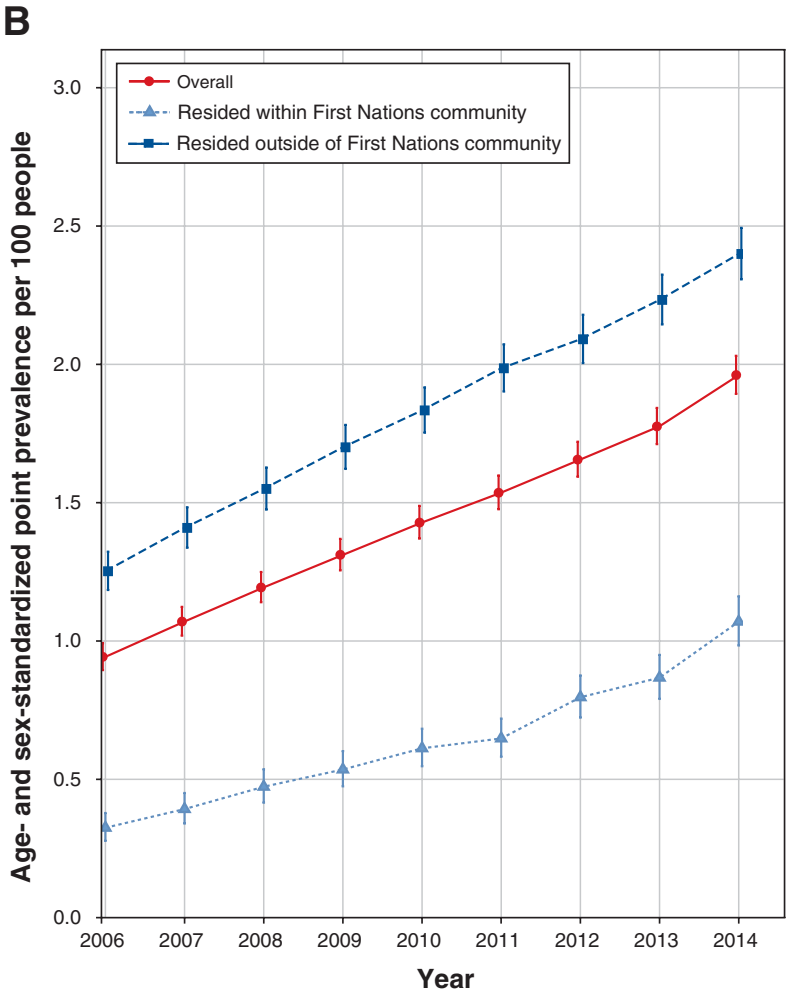
Minuk et al. Can J Gastroenterol 2003; 17: 707-12.

Hepatitis C in Canadian Indigenous



Uhanova et al. Can J Gastroenterol 2013; 27: 336-40.

Hepatitis C in Canadian Indigenous



Mendlowitz et al. CMAJ Open 2021; E886-95.

HBV Screening Recommendations

The U.S. Preventive Services Task Force and CDC recommend screening in:

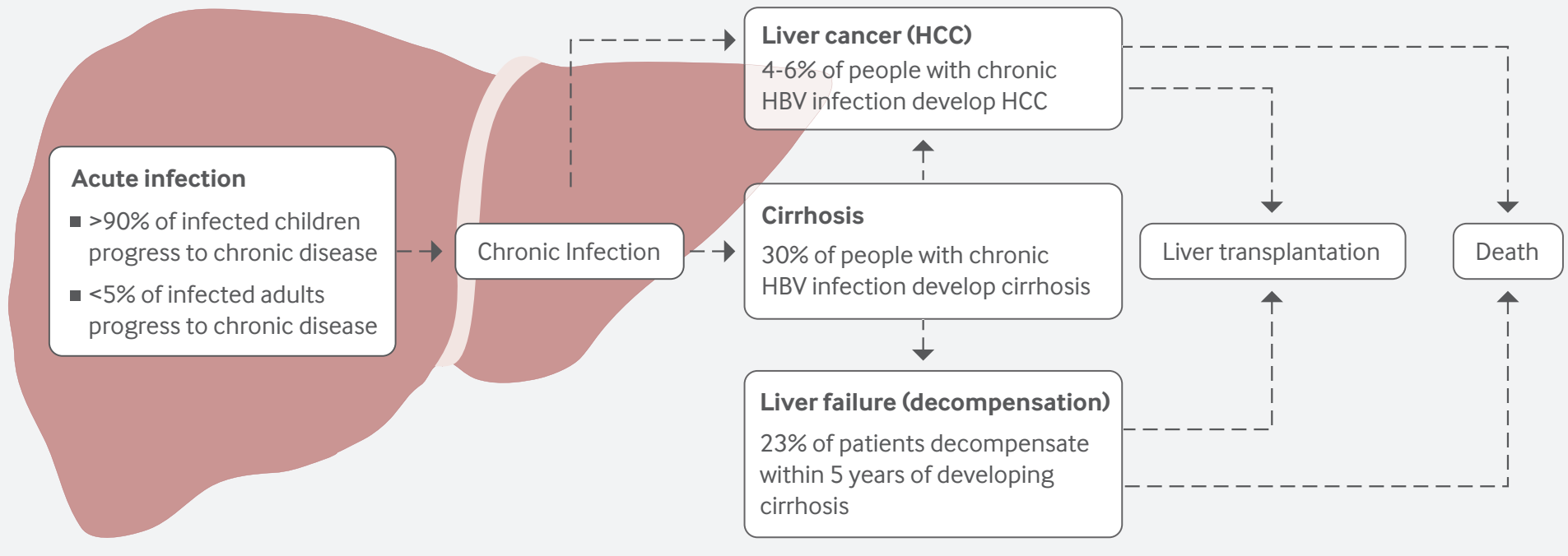
- Household contacts or sex partners of persons with hepatitis B
- Injection drug users
- Men who have sex with men
- Persons born in regions with ≥ 2% prevalence of chronic hepatitis B (e.g., Africa, Asia, Eastern Europe)
- Persons born in the United States who were not vaccinated as infants and whose parents are from regions with ≥ 8% prevalence of chronic hepatitis B
- Persons who are positive for HIV
- Pregnant women

The CDC additionally recommends screening in:

- Donors of blood, plasma, organs, tissue, or semen
- Infants born to mothers positive for hepatitis B surface antigen
- Persons on hemodialysis, cytotoxic therapy, or immunosuppressive therapy
- Persons who are sources of blood or bodily fluids that may expose others, requiring postexposure prophylaxis
- Persons with elevated alanine or aspartate transaminase levels of unknown etiology

Wilkins et al. AAFP 2019; 99:315-323.

HBV Natural History



Sundaram et al. BMJ 2015; 351: h4263.

HBV Evaluation

Hepatitis B surface antigen (HBsAg)

Hepatitis B e antigen (HBeAg) and antibody (anti-HBe)

Hepatitis B virus DNA

IgM antibody to hepatitis B core antigen (anti-HBc IgM) (if acute hepatitis B is suspected)

Routine chemistry panel (including alanine and aspartate aminotransferase, alkaline phosphatase, creatine phosphokinase, lactate dehydrogenase, total and direct bilirubin, albumin, total protein, blood urea nitrogen and creatinine)

Complete blood count

Prothrombin time

Quantitative immunoglobulin levels

Alpha-fetoprotein

Antibody to hepatitis C virus (anti-HCV)

Antibody to hepatitis A virus (anti-HAV)

Antibody to hepatitis D virus (anti-HDV)

Antibody to human immunodeficiency virus (anti-HIV)

Abdominal ultrasound

Liver fibrosis assessment
-Serum markers
-Fibroscan
-MR elastography
-Liver biopsy

Rotman et al. Hepatology 2009; 49: s22-27.

HBV Serology

Variable	Description
HBsAg	Acute or chronic HBV infection
HBeAg	High level HBV replication and infectivity
Anti-HBc (IgM)	Acute HBV infection
Anti-HBc (IgG)	Recovered or chronic HBV infection
Anti-HBs	Recovered HBV infection or vaccination
Anti-HBe	Low level HBV replication and infectivity
HBV DNA	Level of HBV replication

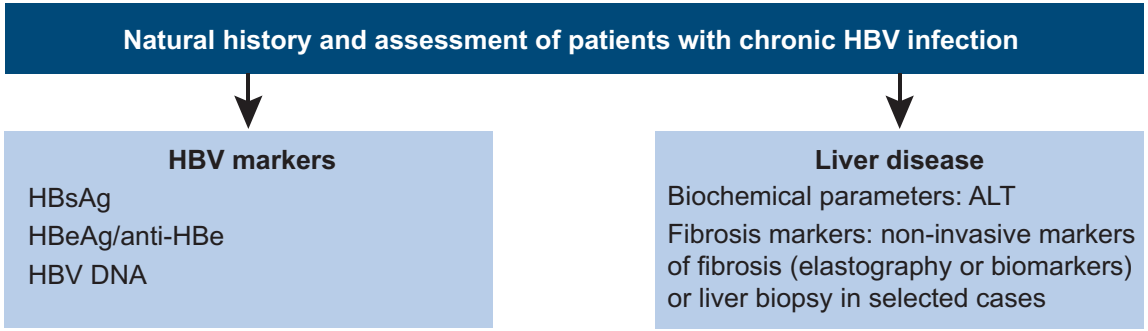
Liang. Hepatology 2009; 49 (5 Suppl): S13-21.

Serology Interpretation

HBsAg	Anti-HBc	Anti-HBs	IgM anti-HBc	Interpretation
Negative	Negative	Negative		Susceptible
Negative	Negative	Positive, >10 mIU/mL		Immune due to vaccination
Negative	Positive	Positive		Immune due to natural infection
Positive	Negative	Negative	Negative	Early acute infection
Positive	Positive	Negative	Positive	Acutely infection
Positive	Positive	Negative	Negative	Chronic infection
Negative	Positive	Negative		Either: 1. Recovering from acute HBV infection 2. Distantly immune: test not sensitive enough to detect a very low level of anti-HBs in serum 3. Susceptible with a false positive anti-HBc 4. Chronically infected with undetectable level of HBsAg present in serum

Malakouti et al. J Clin Transl Hepatol 2017; 5: 394-403.

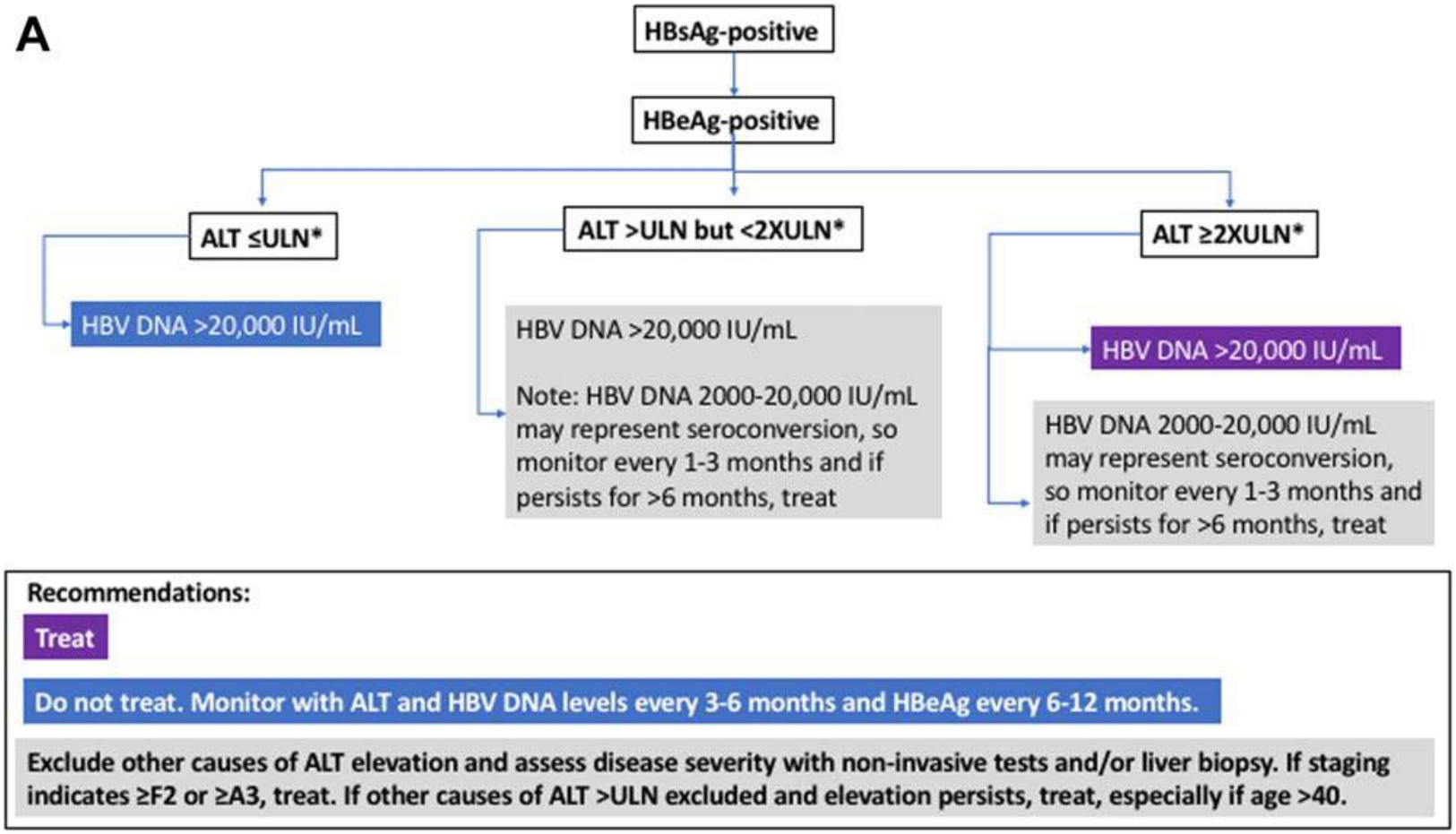
Phases of Chronic HBV



	HBeAg positive		HBeAg negative	
	Chronic infection	Chronic hepatitis	Chronic infection	Chronic hepatitis
HBsAg	High	High/intermediate	Low	Intermediate
HBeAg	Positive	Positive	Negative	Negative
HBV DNA	>10^7 IU/ml	10^4-10^7 IU/ml	<2,000 IU/ml°°	>2,000 IU/ml
ALT	Normal	Elevated	Normal	Elevated*
Liver disease	None/minimal	Moderate/severe	None	Moderate/severe
Old terminology	Immune tolerant	Immune reactive HBeAg positive	Inactive carrier	HBeAg negative chronic hepatitis

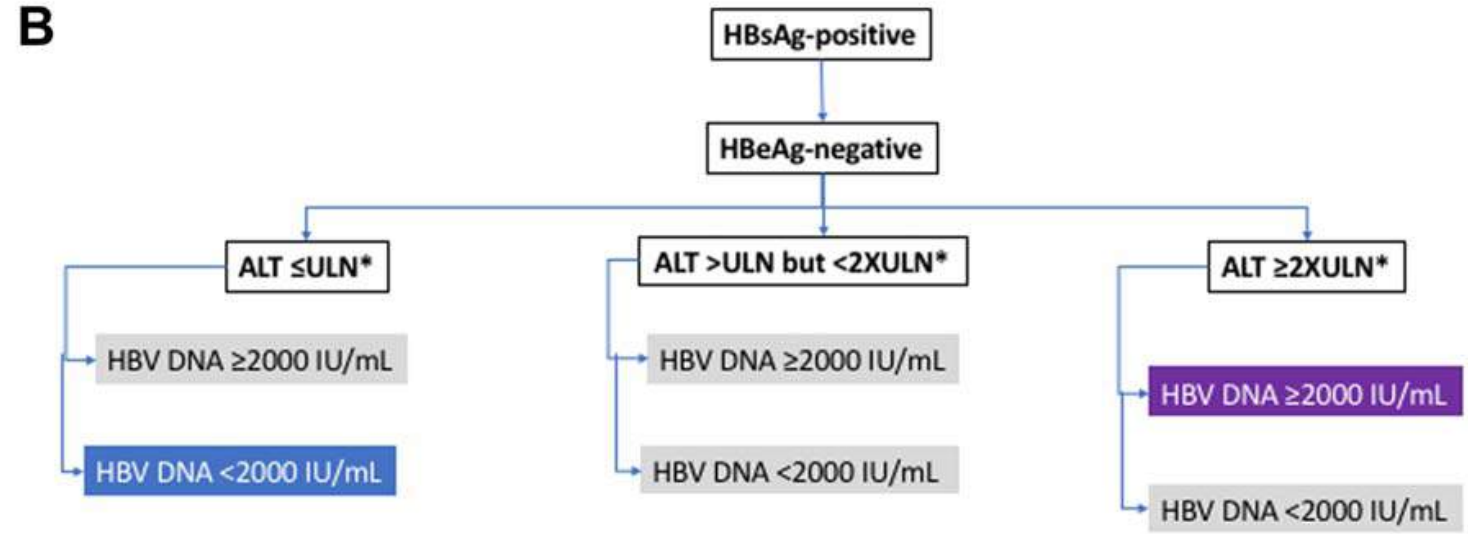
EASL. J Hepatol 2017; 67: 370-98.

HBV Treatment Algorithm



Terrault et al. Hepatology 2018; 67: 1560-99.

HBV Treatment Algorithm



Recommendations:

Treat

Do not treat. Monitor with ALT and HBV DNA levels every 3-6 months and HBsAg annually.

If ALT ≤ULN, monitor ALT and HBV DNA every 3 months for 1 year, then every 6 months.
If ALT elevated, exclude other causes of ALT elevation and assess disease severity with non-invasive tests and/or liver biopsy. If staging indicates ≥F2 or ≥A3, treat. If persistent ALT >ULN with HBV DNA ≥2000 IU/mL, treat, especially if age >40.

**The upper limits of normal for ALT in healthy adults is reported to be 29 to 33 U/L for males and 19 to 25 U/L for females. An upper limit of normal for ALT of 35 U/L for males and 25 U/L for females is recommended to guide management decisions.*

Terrault et al. Hepatology 2018; 67: 1560-99.

HBV Treatment

Drug	Dosage in Adults	Dosage in Children	Pregnancy Category	Potential Side Effects	Monitoring on Treatment
Preferred Agents					
TAF	25 mg daily	N/A	B Insufficient human data on use during pregnancy	Lactic acidosis, nephrotoxicity, hepatotoxicity, pancreatitis	Creatinine, phosphate, urinalysis at baseline, then as clinically indicated; Liver function tests at baseline and for several months Lactic acid if clinical concern Test for HIV before treatment initiation
Entecavir (ETV)	0.5 or 1.0 mg daily	≥2 years: weight based to 10-30 kg; >30 kg: 0.5 mg daily	C	Lactic acidosis	Lactic acid if clinical concern
TDF	300 mg daily	≥12 years: 300 mg daily	B	Nephropathy, Fanconi syndrome, osteomalacia, lactic acidosis	Creatinine clearance at baseline/annually If at risk for renal impairment, serum phosphate, urine glucose, protein at least annually Consider bone density study at baseline/during treatment Lactic acid if clinical concern Test for HIV before treatment initiation
PEG-IFN-2a	180 µg weekly	N/A	C	Adults: flu-like symptoms, fatigue, mood disturbances, cytopenias, autoimmune disorders Children: anorexia and weight loss	CBC (every 1-3 months) TSH (every 3 months) Clinical monitoring for autoimmune, ischemic, neuropsychiatric, and infectious complications
Not Recommended					
LAM	100 mg daily	≥2 years: 3 mg/kg daily to maximum 100 mg	C	Pancreatitis Lactic acidosis	Amylase/lipase, lactic acid if clinical concern
Telbivudine	600 mg daily	N/A	B	Creatine kinase elevations and myopathy Peripheral neuropathy Lactic acidosis	Creatine kinase, lactic acid, nerve conduction study if clinical concern
ADV	10 mg daily	≥12 years: 10 mg daily	C	Acute renal failure Fanconi syndrome Nephrogenic diabetes insipidus Lactic acidosis	Creatinine clearance at baseline/annually If at risk for renal impairment, serum phosphate, urine glucose, protein at least annually Consider bone density study at baseline/during treatment Lactic acid if clinical concern
IFN-α-2b	N/A	≥1 year: 6 million IU/m^2 three times per week	C	Adults: flu-like symptoms, fatigue, mood disturbances, cytopenias, autoimmune disorders Children: anorexia and weight loss	CBC (every 1-3 months) TSH (every 3 months) Clinical monitoring for autoimmune, ischemic, neuropsychiatric, and infectious complications

Ahn et al. Clin Liver Dis 2018; 12: 19-23.

HBV Recommendation

Persons Who Are HBsAg Positive Should:

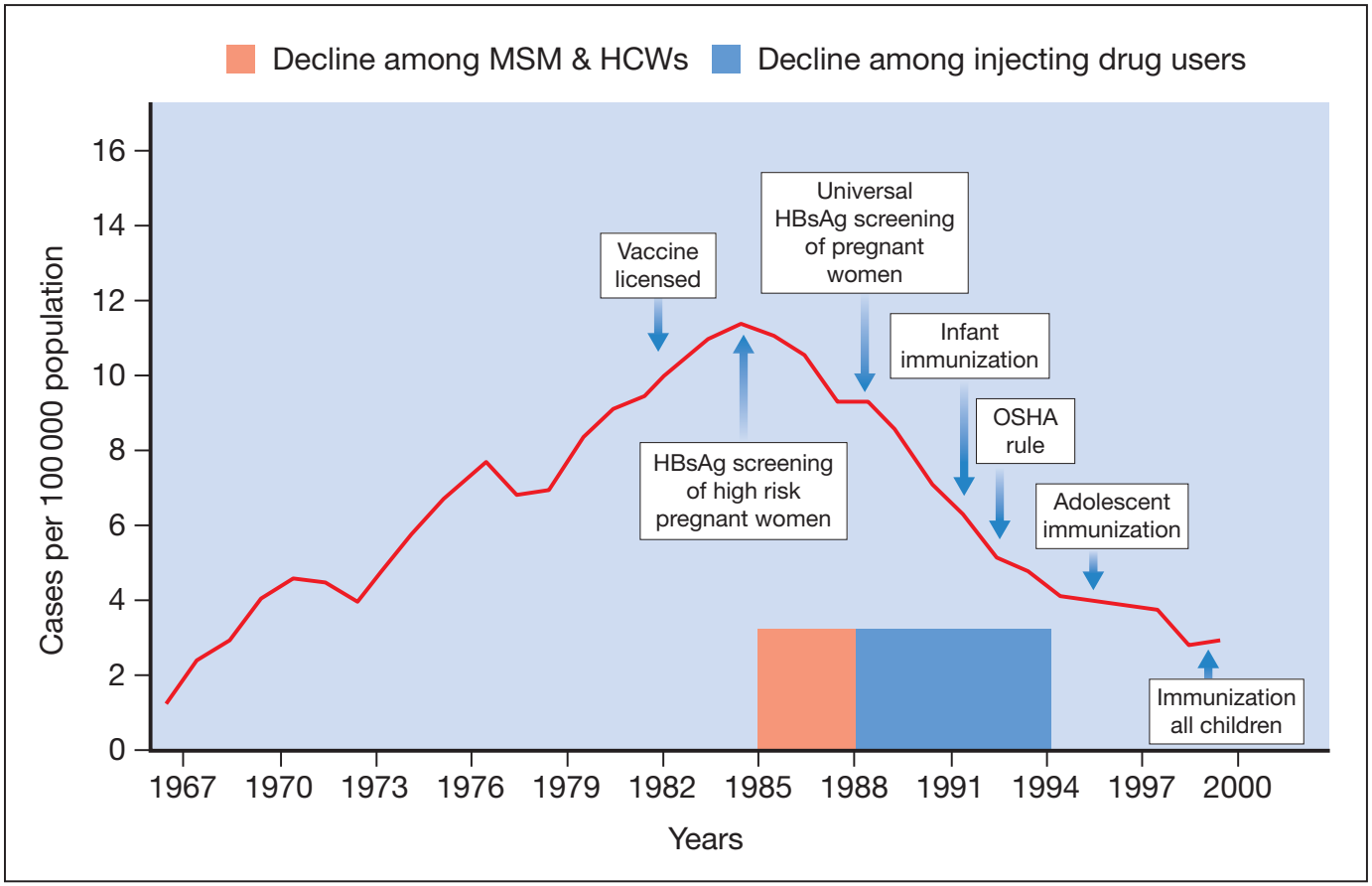
- Have household and sexual contacts vaccinated
- Use barrier protection during sexual intercourse if partner is not vaccinated or is not naturally immune
- Not share toothbrushes or razors
- Not share injection equipment
- Not share glucose testing equipment
- Cover open cuts and scratches
- Clean blood spills with bleach solution
- Not donate blood, organs, or sperm

Children and Adults Who Are HBsAg Positive:

- Can participate in all activities, including contact sports
- Should not be excluded from daycare or school participation and should not be isolated from other children
- Can share food and utensils and kiss others

Terrault et al. Hepatology 2018; 67: 1560-99.

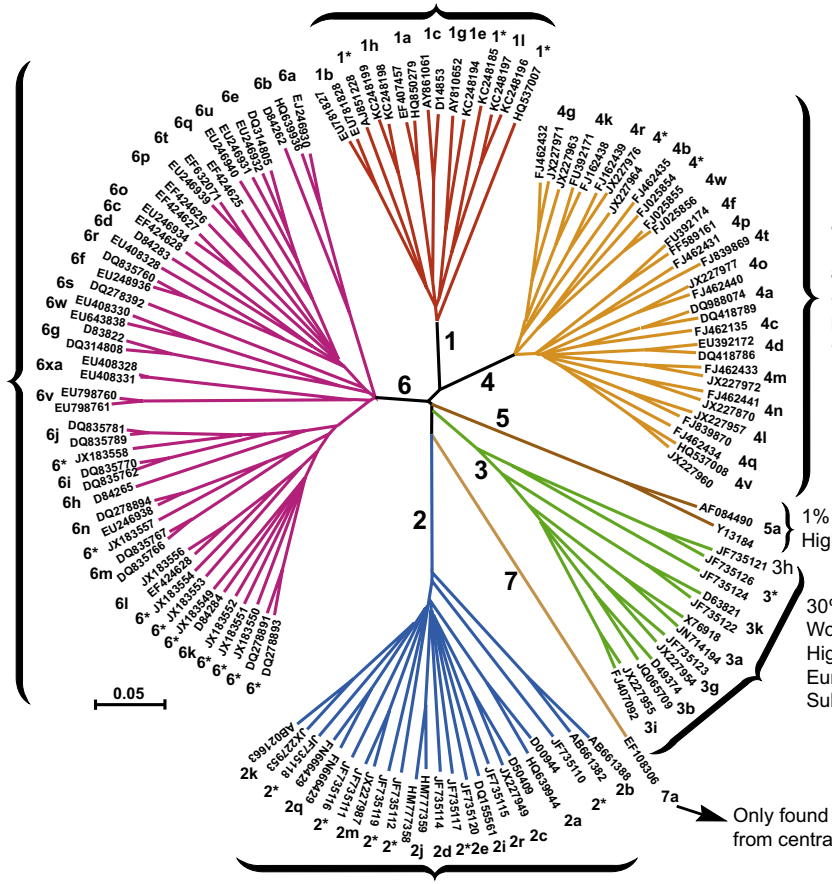
HBV Prevention



Zakim and Boyer's Hepatology. 5th edition. Chapter 31: Hepatitis B.

HCV Genotypes

46% of all HCV infections. Worldwide distribution.
Subtypes 1a and 1b most prevalent. Subtype 1a widespread IDU.
Subtype 1b – iatrogenic spread.



6% of all HCV infections.
Prevalent in southeast Asia. Subtype 6a – IDU spread in Hong Kong and Vietnam.

8% of all HCV infections.
Highly prevalent in middle East and north and central Africa.
Subtype 4a – iatrogenic spread, primarily in Egypt.
Subtype 4d – IDU spread in European cities.

1% of all HCV infections.
Highly prevalent in South Africa.

30% of all HCV infections.
Worldwide distribution
Highly prevalent in northern Europe and south Asia.
Subtype 3a – widespread IDU.

7a → Only found in a few individuals from central Africa.

9% of all HCV infections. Worldwide distribution.
Highly prevalent in western Africa. Subtype 2a and 2b most prevalent.
Subtypes 2a and 2b – iatrogenic spread.

Bukh. J Hepatol 2016; 65: S2-21.

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HCV Risk Factors

Risk factor–based screening[24]

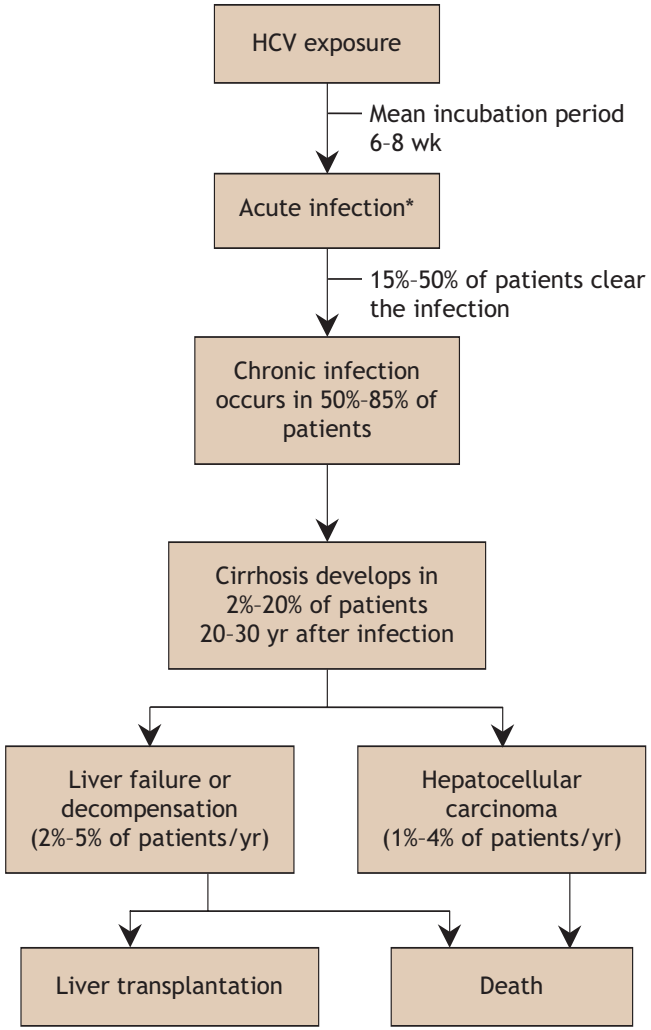
- History of current or past (even once) injection drug use*
- Received health care or personal services where there is a lack of infection prevention and control practices
- Received a blood transfusion, blood products or organ transplant before 1992 in Canada
- History of or current incarceration
- Born or resided in a region where hepatitis C prevalence is > 3%, such as:
  - Central, East and South Asia;
  - Australasia and Oceania;
  - Eastern Europe;
  - Subsaharan Africa;
  - North Africa or Middle East
- Born to a mother who is HCV-infected
- History of sexual contact or sharing of personal care items with someone who is HCV-infected*
- HIV infection, particularly men who have sex with men*
- Received chronic hemodialysis treatment
- Elevated alanine aminotransferase

Population-based screening[25]

- Born between the years 1945 and 1975

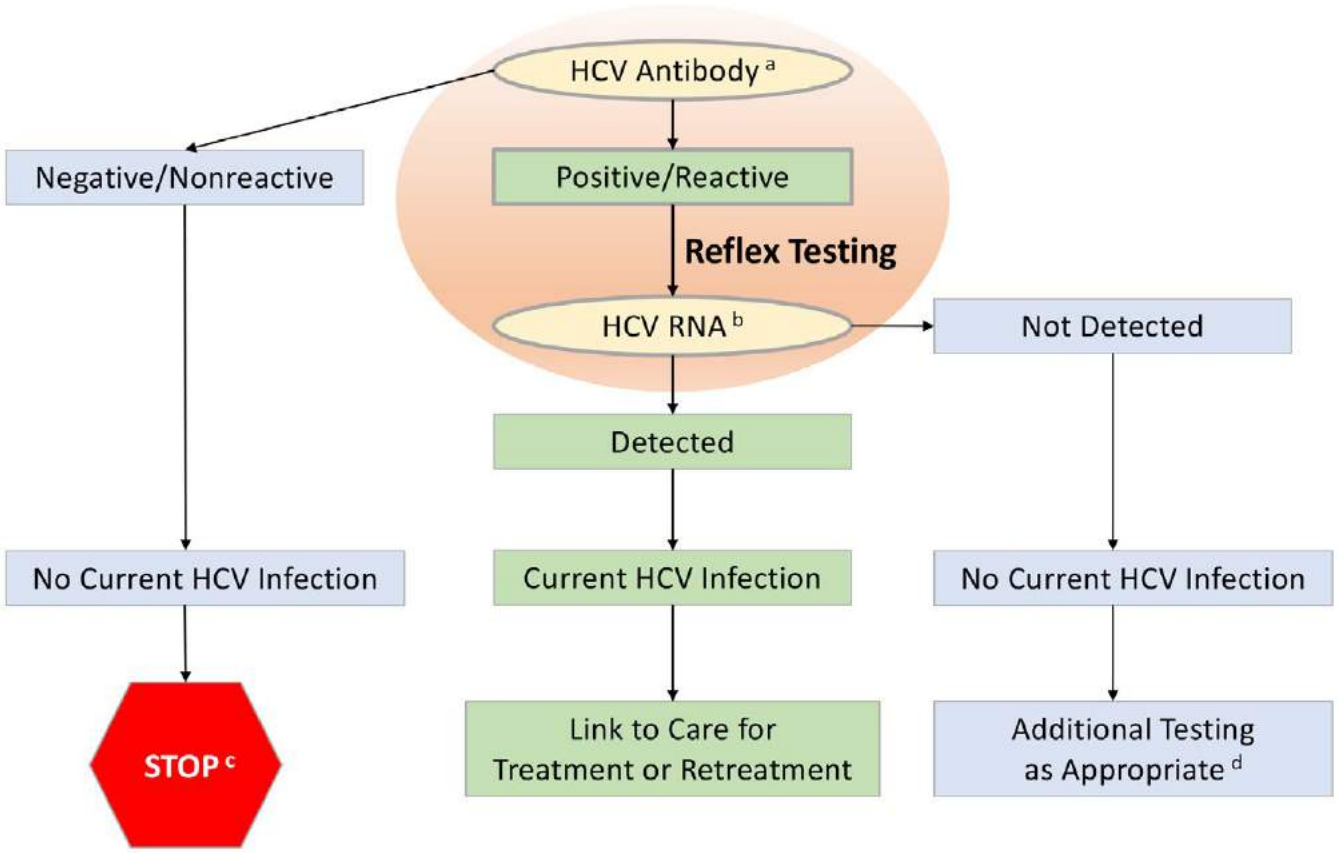
Shah et al. CMAJ 2018; 190: E677-87.

Natural History HCV



Wong et al. CMAJ 2006; 174: 649-59.

HCV Testing



AASLD-IDSA. Hepatology 2020; 71: 686-721.

HCV Pre-treatment

PRETREATMENT ASSESSMENT*

- **Calculate FIB-4 score.**
- **Cirrhosis assessment**: Liver biopsy is not required. For the purpose of this guidance, a patient is presumed to have cirrhosis if they have a FIB-4 score >3.25 **or** any of the following findings from a previously performed test.
  - Transient elastography indicating cirrhosis (eg, FibroScan stiffness >12.5 kPa)
  - Noninvasive serologic tests above proprietary cutoffs indicating cirrhosis (eg, FibroSure, Enhanced Liver Fibrosis Test, etc)
  - Clinical evidence of cirrhosis (eg, liver nodularity and/or splenomegaly on imaging, platelet count <150,000/mm^3, etc)
  - Prior liver biopsy showing cirrhosis
- **Medication reconciliation:** Record current medications, including over-the-counter drugs, and herbal/dietary supplements.
- **Potential drug-drug interaction assessment:** Drug-drug interactions can be assessed using the AASLD/IDSA guidance or the University of Liverpool drug interaction checker.
- **Education:** Educate the patient about proper administration of medications, adherence, and prevention of reinfection.

- **Pretreatment laboratory testing**

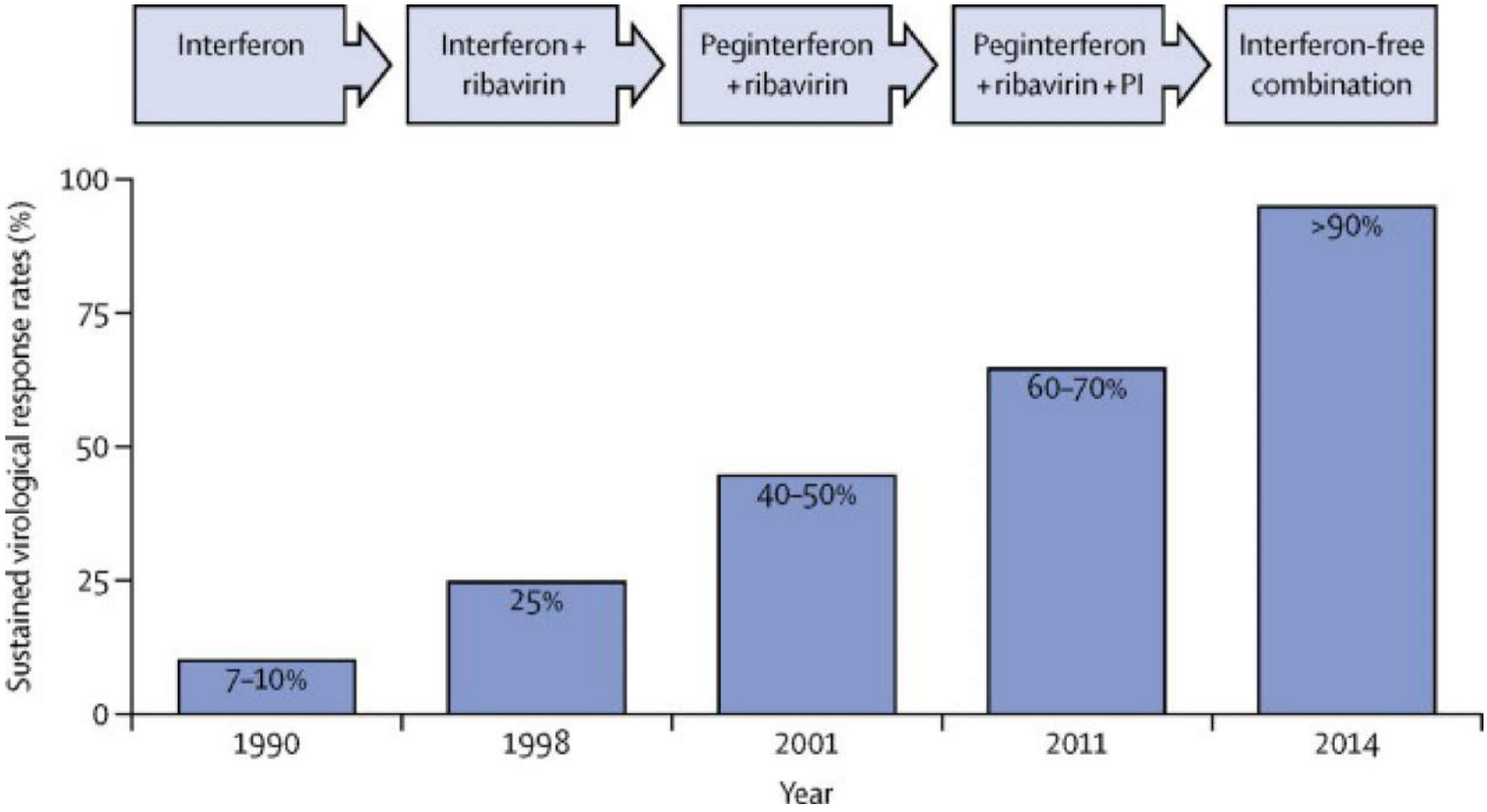
  Within 6 months of initiating treatment:
  - Complete blood count (CBC)
  - Hepatic function panel (ie, albumin, total and direct bilirubin, alanine aminotransferase [ALT], and aspartate aminotransferase [AST])
  - Calculated glomerular filtration rate (eGFR)

  Any time prior to starting antiviral therapy:
  - Quantitative HCV RNA (HCV viral load)
  - HIV antigen/antibody test
  - Hepatitis B surface antigen

  Before initiating antiviral therapy:
  - Serum pregnancy testing and counseling about pregnancy risks of HCV medication should be offered to women of childbearing age.

AASLD-IDSA. Hepatology 2020; 71: 686-721.

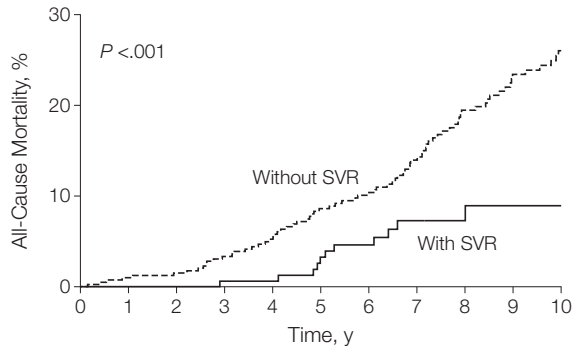
HCV Treatment Evolution



Webster et al. Lancet 2015; 385: 1124-35.

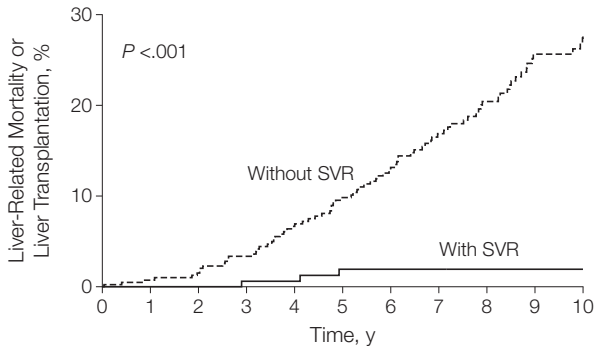
Outcomes After Achieving A Cure

All-cause mortality



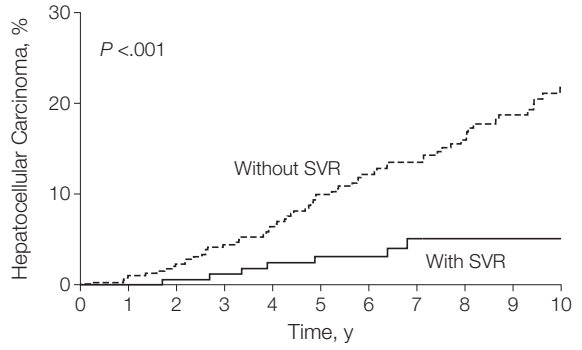
No. at risk											
Without SVR	405	393	382	363	344	317	295	250	207	164	135
With SVR	192	181	168	162	155	144	125	88	56	40	28

Liver-related mortality or liver transplantation



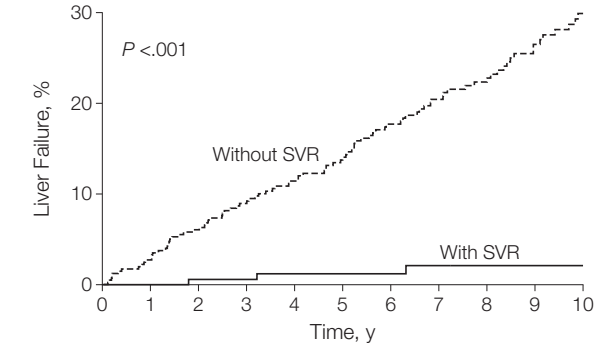
No. at risk											
Without SVR	405	392	380	358	334	305	277	229	187	146	119
With SVR	192	181	168	162	155	144	125	88	56	40	28

Hepatocellular carcinoma



No. at risk											
Without SVR	405	390	375	349	326	294	269	229	191	151	122
With SVR	192	181	167	161	152	142	124	86	54	39	27

Liver failure



No. at risk											
Without SVR	405	384	361	337	314	288	259	216	184	143	113
With SVR	192	180	166	160	152	141	123	88	56	40	28

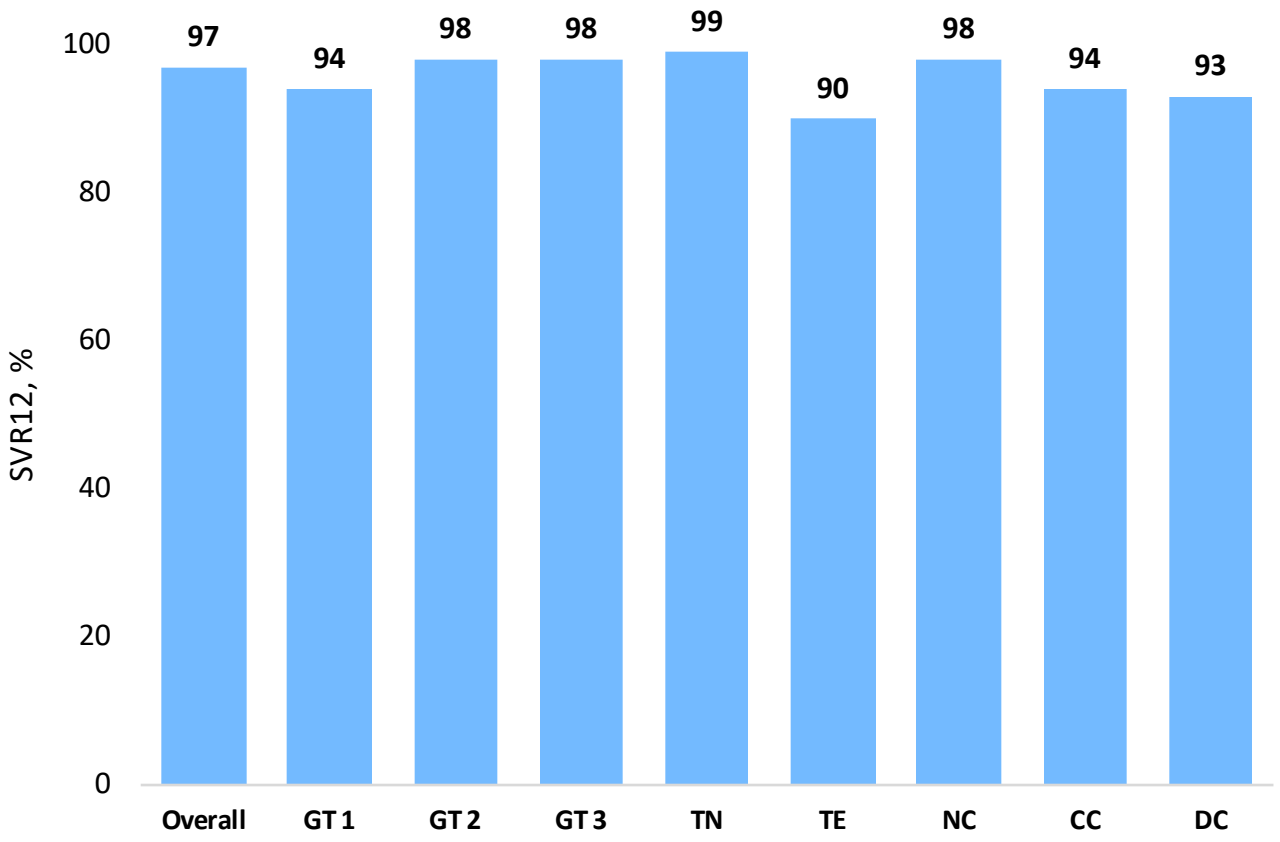
van der Meer et al. JAMA 2012; 308: 2584-93.

HCV Treatment Regimens

Regimen	HCV genotype						
	1a	1b	2	3	4	5	6
Ledipasvir/sofosbuvir (Harvoni)	8–12 wk†	8–12 wk†	NR	+ ribavirin 12 wk	12 wk	12 wk	12 wk
Elbasvir/grazoprevir (Zepatier)	12–16 wk ± ribavirin‡	8–12 wk§	NR	+ sofosbuvir x 12 wk	12 wk	NR	NR
Paritaprevir/ritonavir/ombitasvir + dasabuvir (Holkira Pak)	+ ribavirin 12 wk	12 wk	NR	NR	Paritaprevir/ ritonavir/ ombitasvir + ribavirin 12 wk	NR	NR
Sofosbuvir + daclatasvir (Sovaldi + Daklinza)	12 wk	12 wk	12 wk	12 wk	NR	NR	NR
Sofosbuvir/velpatasvir (Epclusa)	12 wk	12 wk	12 wk	12 wk	12 wk	12 wk	12 wk
Glecaprevir/pibrentasvir (Maviret)	8 wk	8 wk	8 wk	8 wk	8 wk	8 wk	8 wk
Sofosbuvir/velpatasvir/ voxilarevir (Vosevi)¶	NR	NR	NR	NR	NR	NR	NR

Shah et al. CMAJ 2018; 190: E677-87.

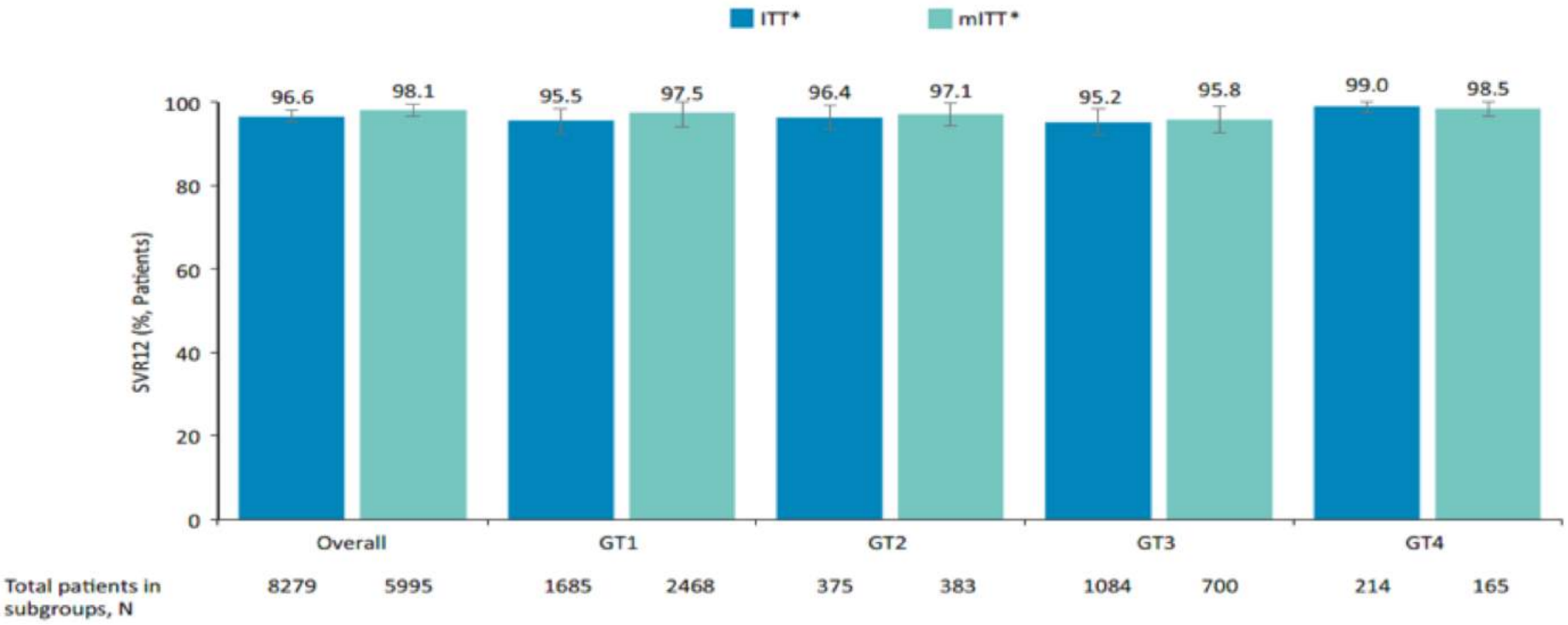
Sofosbuvir/Velpatasvir



TN=treatment-naïve
TE=treatment-experienced
NC=non-cirrhotic
CC=compensated cirrhotic
DC=decompensated cirrhotic

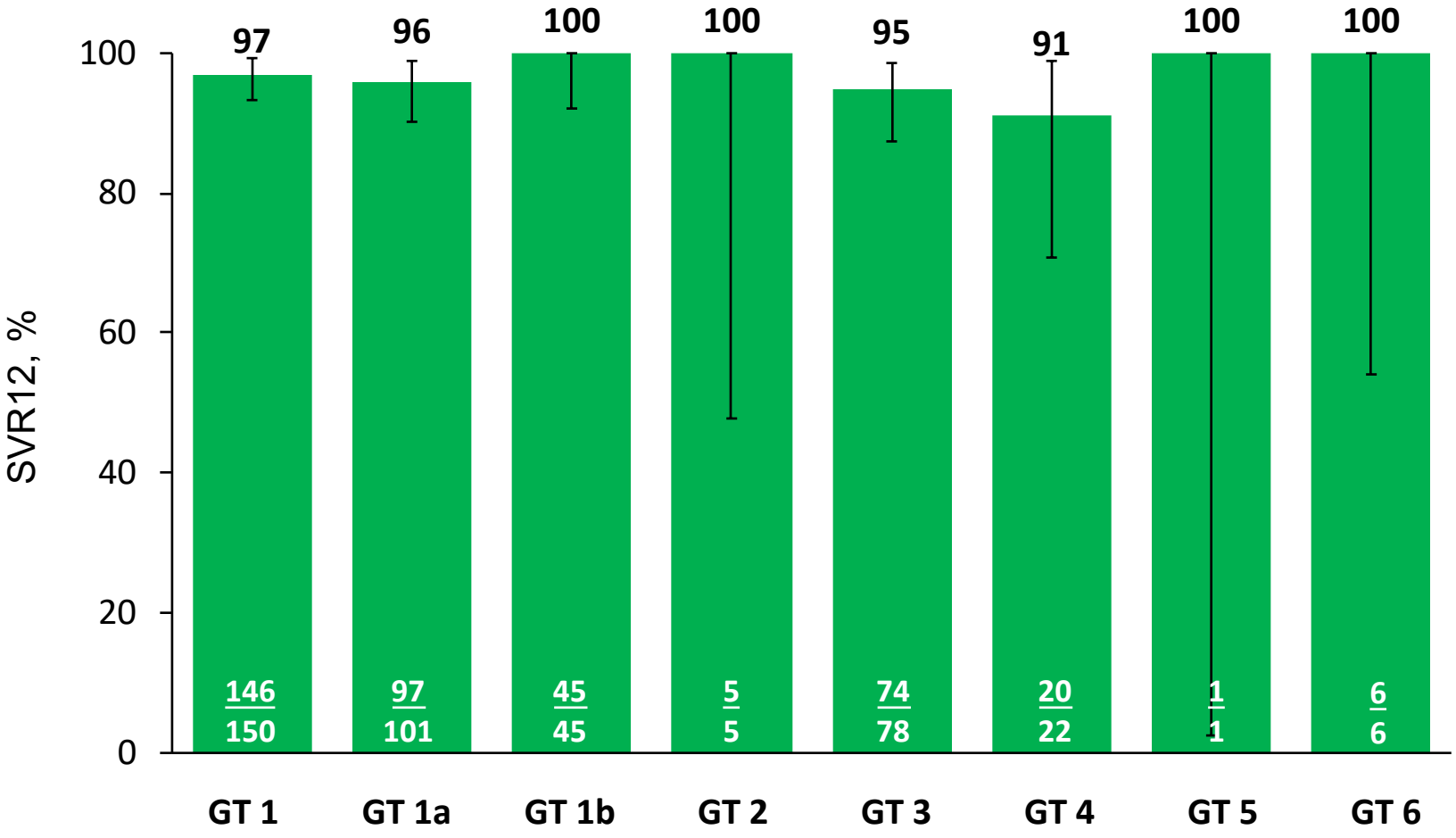
Landis et al. AASLD 2017, Poster 1096

Glecaprevir/Pibrentasvir



Negro et al. AASLD/EASL HCV Special Conference 2019 #31

Sofosbuvir/Velpatasvir/Voxilaprevir



Bourliere et al. AASLD 2016, Oral 194

HCV Post-treatment

POST-TREATMENT ASSESSMENT OF CURE (SVR)	FOLLOW-UP AFTER ACHIEVING VIROLOGIC CURE (SVR)	FOLLOW-UP FOR PATIENTS WHO DO *NOT* ACHIEVE A VIROLOGIC CURE
• Assessment of quantitative HCV RNA and a hepatic function panel are recommended 12 weeks or later following completion of therapy to confirm HCV RNA is undetectable (virologic cure) and transaminase normalization. • Assessment for other causes of liver disease is recommended for patients with elevated transaminase levels after achieving SVR.	• No liver-related follow-up is recommended for noncirrhotic patients who achieve SVR. • Patients with ongoing risk for HCV infection (eg, intravenous drug use or MSM engaging in unprotected sex) should be counseled about risk reduction, and tested for HCV RNA annually and whenever they develop elevated ALT, AST, or bilirubin. • Advise patients to avoid excess alcohol use.	• Patients in whom initial HCV treatment fails to achieve cure (SVR) should be evaluated for retreatment by a specialist, in accordance with AASLD/IDSA guidance. • For patients unable to be retreated, assessment for disease progression every 6 to 12 months with a hepatic function panel, CBC, and INR is recommended. • Advise patients to avoid excess alcohol use.

AASLD-IDSA. Hepatology 2020; 71: 686-721.

Barriers to Treatment

Patient-related barriers

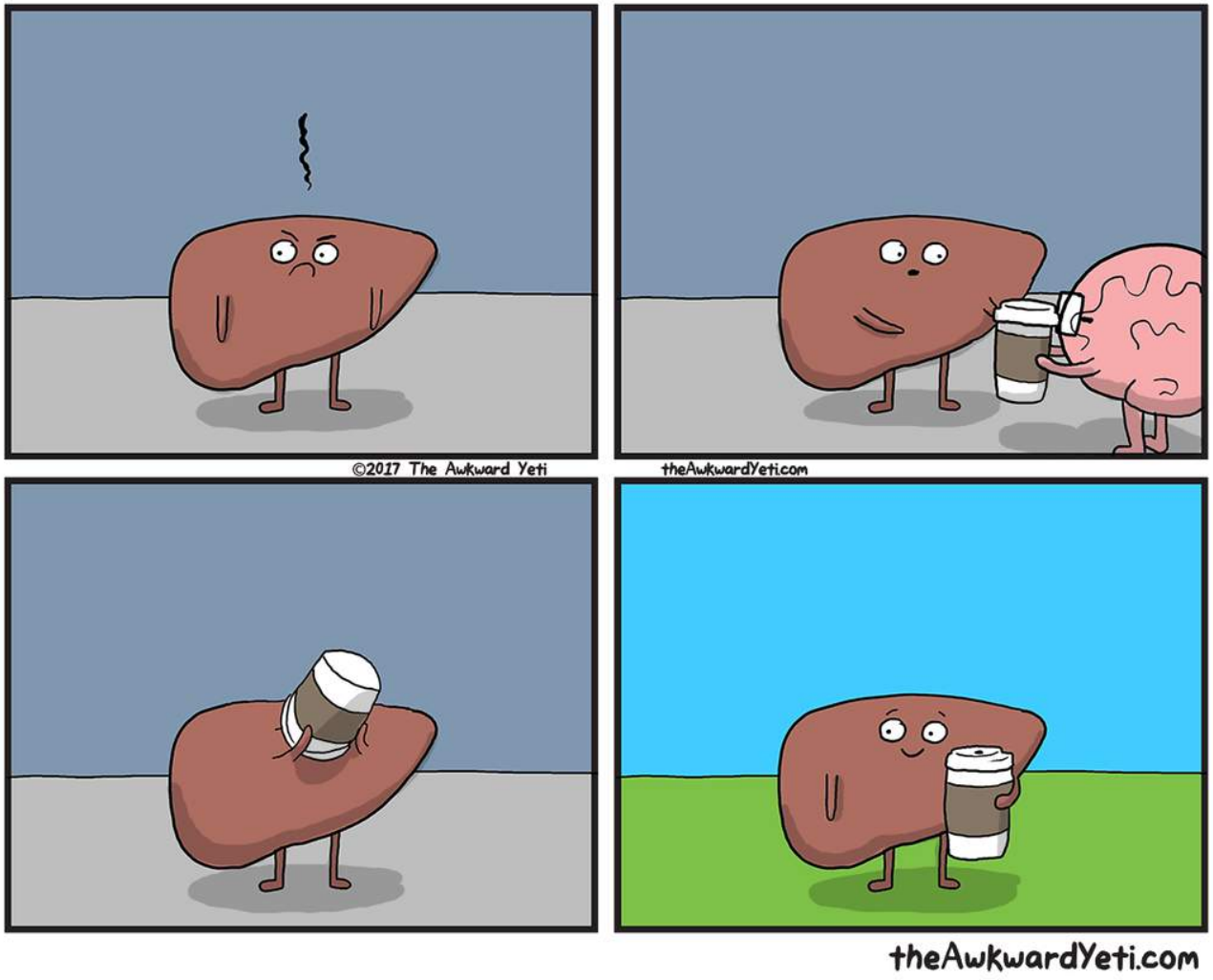
- Patients have other more urgent medical or social priorities.
- Patients have mental health problems that limit their abil ity to engage in HCV care.
- Patients continue to use injection drugs.
- Patients are poorly adherent to lab or clinic appointments.

Health system-related barriers

- I have not had enough training to provide good HCV care.
- I have insufficient or inadequately trained support staff (e.g., nursing and administrative staff).
- Patients have poor access to mental health treatment (e.g., psychiatry, psychology, and social work).
- Provincial restrictions on HCV treatment eligibility make it difficult for me to treat my patients.
- Patients who use injection drugs have poor access to harm reduction services or opioid substitution therapy.

Chan et al. Can Liver J 2018; 1: 231-9.

Thank You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