Hepatitis C

UPDATE 2023 – WHERE ARE WE NOW

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Disclosures

- None

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Hepatitis C 2023

- Background
- Treatment review
- Special cases
- Future considerations

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HCV facts

Goal now is to identify cases and link to care –not "make better drugs"

- 2.4 million people with viremia in the USA
- Risk factors
  - PWID are at greatest risk (intranasal, IV)
  - MSM (8%)
  - Unknown (homelessness)
  - Perinatal transmission (2%-15%)
  - Organ transplant from HCV antibody (+) donor (80-95%)
  - Blood and blood products extremely rare as cause since 1992
- Reinfection is possible and common

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Sequelae of HCV infection prior to DAA era

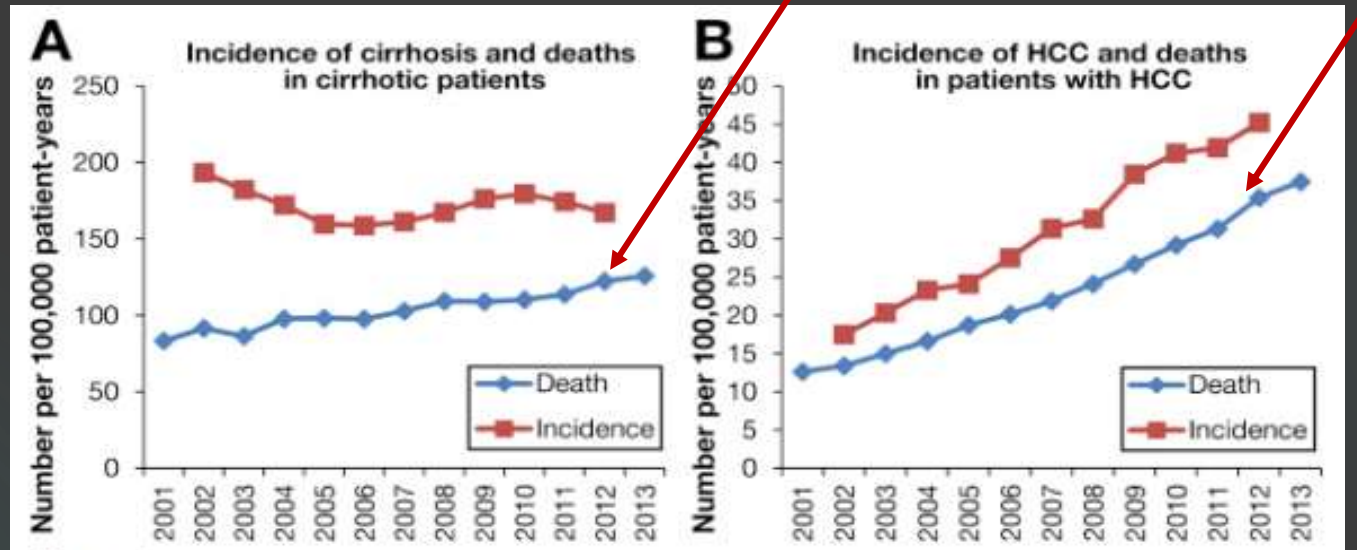

Figure 4

Trends in the incidence and mortality of cirrhosis and HCC between 2001 and 2013 in the VA health care system. HCC, hepatocellular carcinoma.

Beste LA et al. Trends in burden of cirrhosis and hepatocellular carcinoma by underlying liver disease in US veterans, 2001-2013. Gastroenterology. 2015;149(6):1471–82

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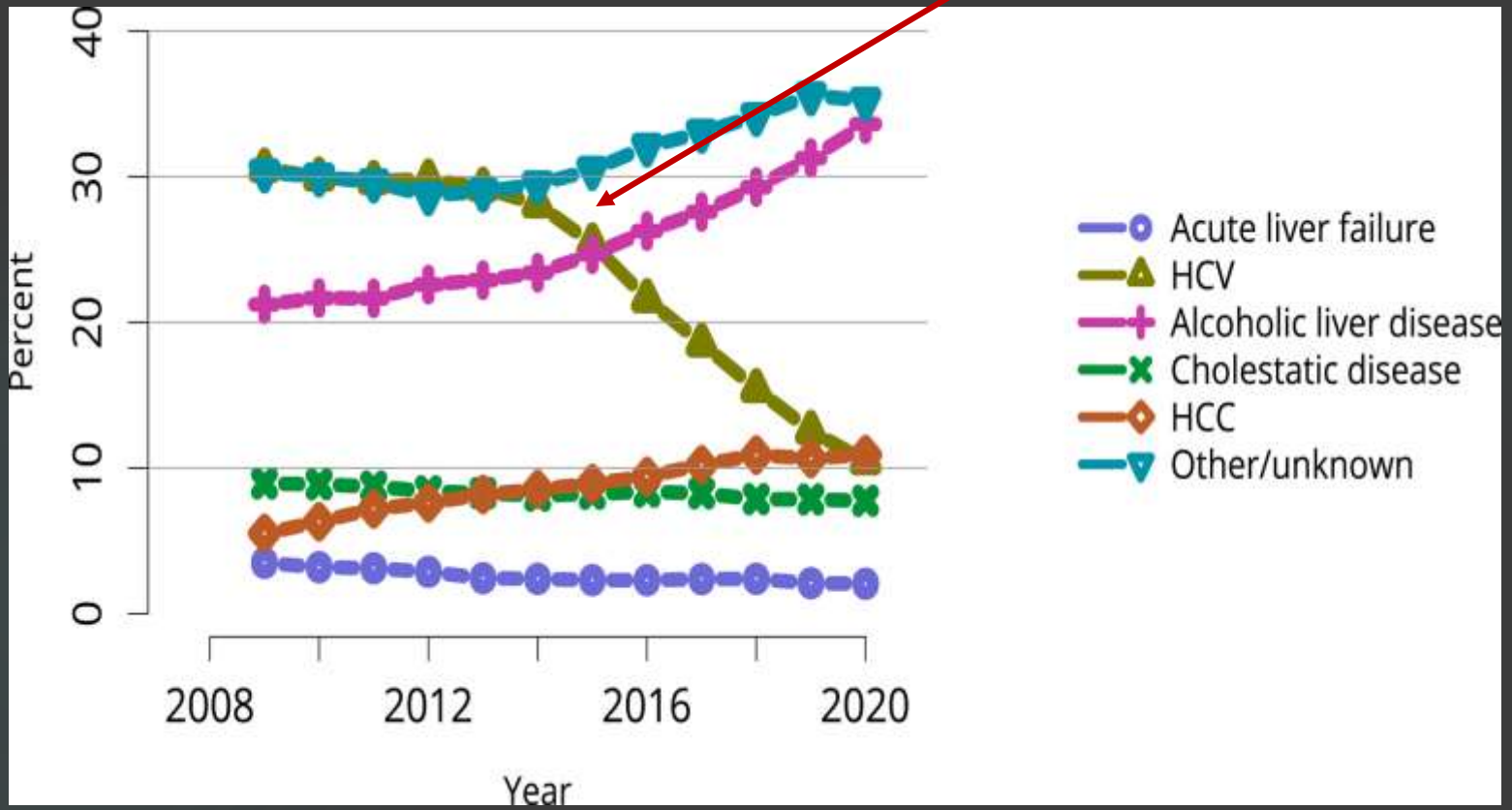
Effect of HCV SVR on liver transplant rates



SRTR, 2020

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Effect of HCV SVR on mortality

Table 2. Clinical Events According to Treatment Response

Outcomes	With SVR			Without SVR			
	Events, No.	Observation Period, Person-Years	Rate per 100 Person-Years (95% CI)	Events, No.	Observation Period, Person-Years	Rate per 100 Person-Years (95% CI)	*P* Value[b]
Any event[a]	18	1260	1.43 (0.77-2.09)	169	2921	5.79 (4.91-6.66)	<.001
All-cause mortality	13	1283	1.01 (0.46-1.56)	100	3410	2.93 (2.36-3.51)	<.001
Liver-related mortality or liver transplantation	3	1283	0.23 (<0.01-0.50)	103	3120	3.20 (2.58-3.82)	<.001
Hepatocellular carcinoma	7	1270	0.55 (0.14-0.96)	76	3222	2.63 (1.83-2.89)	<.001
Liver failure	4	1271	0.31 (<0.01-0.62)	111	3066	3.62 (2.95-4.29)	<.001

Abbreviation: SVR, sustained virological response.
[a] Any event is the composite of all analyzed outcomes, to which only the first event contributed in case of multiple events in an individual patient.
[b] *P* value is based on unadjusted Cox proportional hazards regression analyses, including SVR as a time-dependent covariate.

Van der Meer et al, JAMA, 2012

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Why can't we vanquish Hepatitis C?

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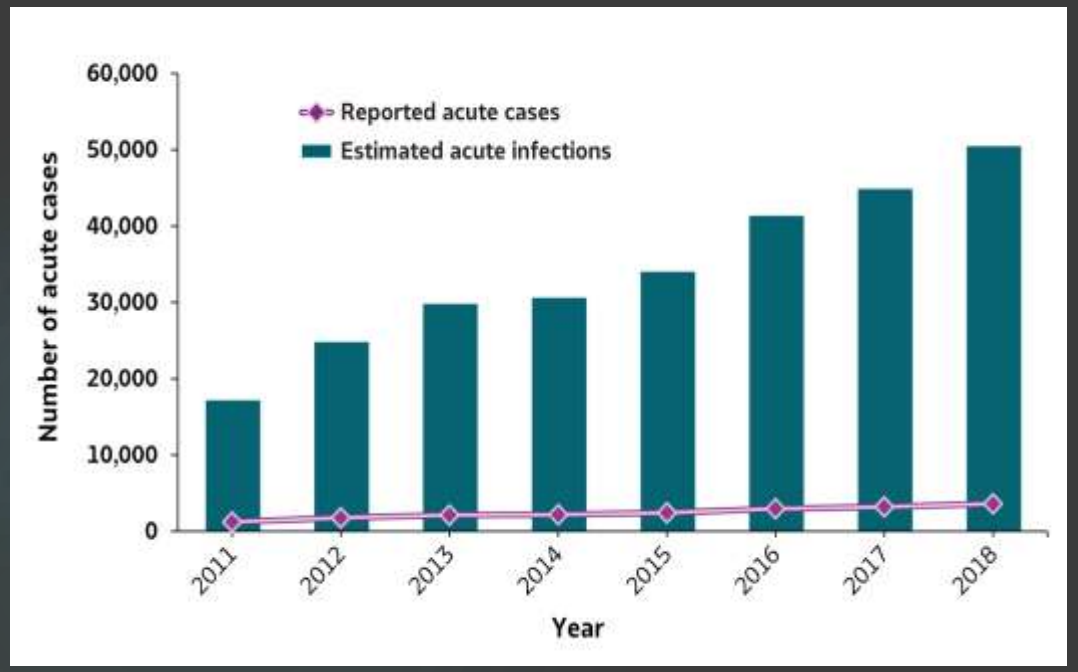
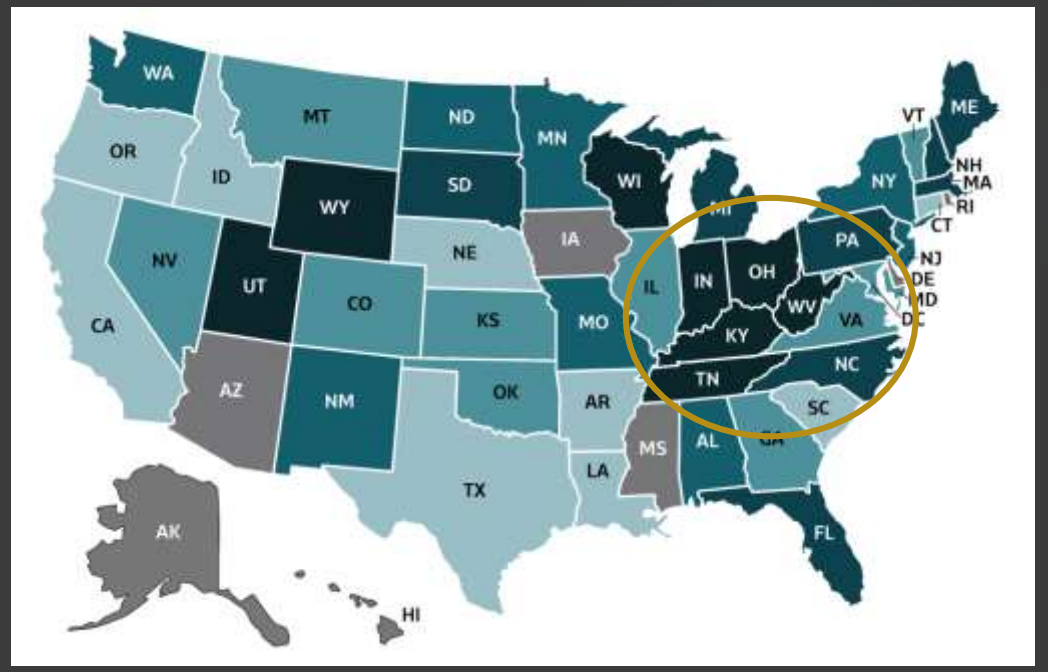
Acute Hepatitis C is increasing in the US





CDC,2019

New infections are the biggest impediment to the WHO goal of HCV eradication by 2030

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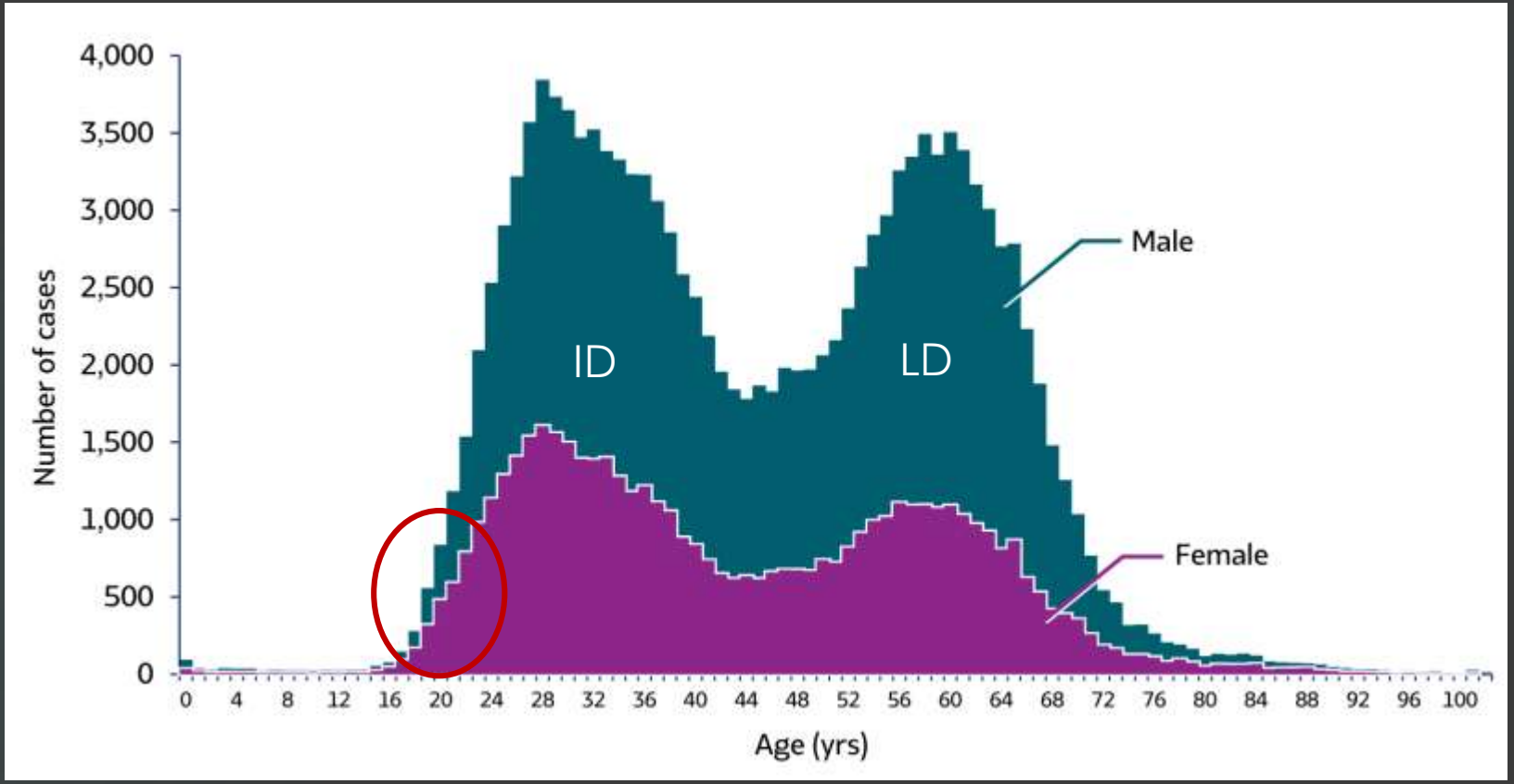
New diagnosis of Hepatitis C in the US



CDC,2019

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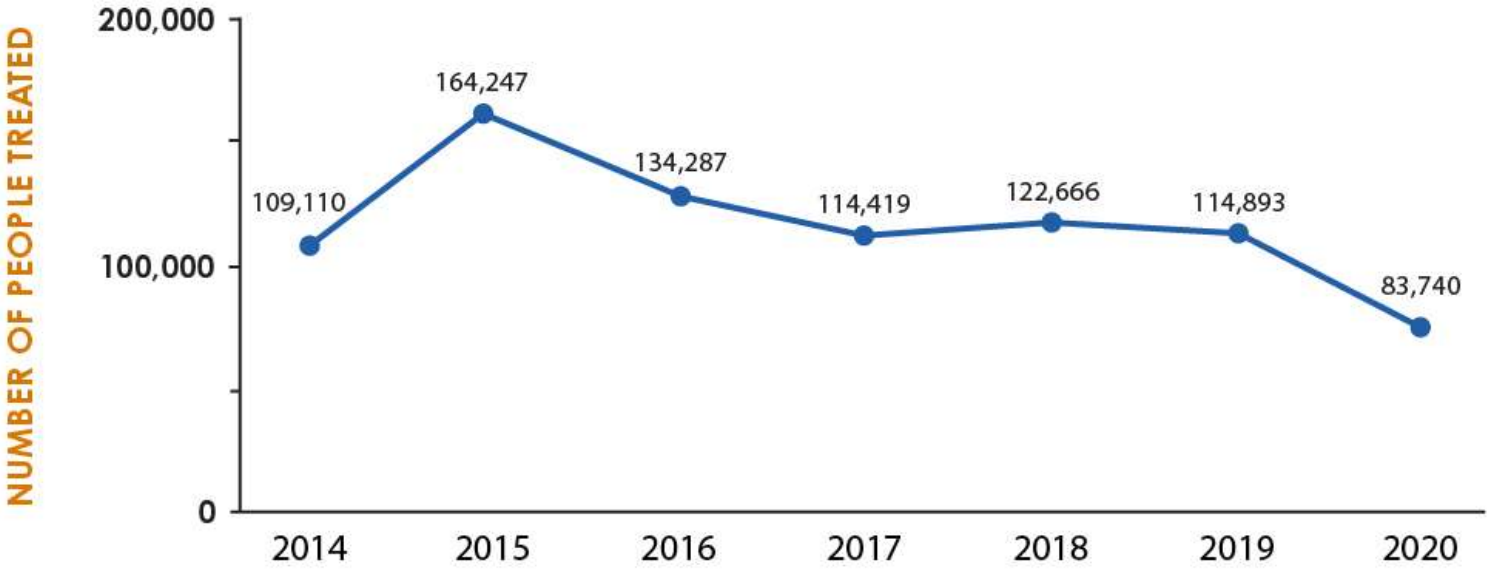
THE NUMBER OF PEOPLE WHO INITIATED* HEPATITIS C TREATMENT IN THE U.S. DECLINED FROM 2015 TO 2020

COVID-19-related disruptions to hepatitis C testing and treatment likely contributed to the decline in 2020



*Based on national prescription claims data

For more information, visit
cdc.gov/nchhstp/newsroom

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

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Identify infected patients:
Screening for HCV infection

Recommendations for One-Time Hepatitis C Testing
RECOMMENDED
One-time, routine, opt out HCV testing is recommended for all individuals aged 18 years or older.
One-time HCV testing should be performed for all persons less than 18 years old with activities, exposures, or conditions or circumstances associated with an increased risk of HCV infection (see below).
Prenatal HCV testing as part of routine prenatal care is recommended with each pregnancy.
Periodic repeat HCV testing should be offered to all persons with activities, exposures, or conditions or circumstances associated with an increased risk of HCV exposure (see below).
Annual HCV testing is recommended for all persons who inject drugs, for HIV-infected men who have unprotected sex with men, and men who have sex with men taking pre-exposure prophylaxis (PrEP).

www.hcvguidelines.org

Facilitate care for HCV

- PCP and public education
- EMR pop up screening
- OB/GYN screening at pregnancy
- Screening at federally qualified health clinics
- ED screening
- "Reflex" lab testing
- Fibrosure instead of fibroscan (one visit)?
- Virtual OV
- Pre-auth issues addressed

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Labs needed for HCV treatment

Definite

- HCV VL
- HCV genotype
- CBC
- CMP
- Hepatitis B core antibody total
- Fibrosis assessement
  - HCV fibrosure
  - Elastography
  - imaging

Should order

- HIV antibody
- Hepatitis B surface antigen
- Hep A antibody total
- Hep B surface antibody
- US
- AFP

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Hepatitis C treatment – 3 drug targets

- "**asvir**" – **ns5a inhibitor**
  - Non-enzymatic replication inhibitor
- "**previr**" – **protease inhibitor**
  - cleaves the HCV polyprotein
  - Potent
  - Low barrier to resistance
- "**buvir**" – **ns5b inhibitor**
  - which truncates RNA polymerization
  - High barrier to resistance

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HCV treatment options

MAVYRET

Glecaprevir/Pibrentasvir

- 8 weeks
- 3 pills per day
- Hepatic clearance (of PI)
- Contraindicated in Child's B/C cirrhosis or with any history of decompensation
- PPI OK
- Use down to age 3
- Paxlovid incompatible
- ESRD OK

EPCLUSA

Sofosbuvir/Velpatasvir

- 12 weeks
- One pill per day
- Renal clearance
- OK for decompensated cirrhosis
- PPI incompatible
- Use down to age 6
- OK with Paxlovid
- ESRD OK

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Glecaprevir/Pibrentasvir efficacy

Table 13. ENDURANCE-1: Efficacy in Treatment-Naïve and PRS Treatment-Experienced Adults with HCV Genotype 1 Infection without Cirrhosis

	MAVYRET 8 Weeks
	GT1 N=351
SVR12	99% (348/351)
Outcome for Subjects without SVR12	
On-treatment VF	<1% (1/351)
Relapse	0/349
Other*	<1% (2/351)

VF= virologic failure
* Includes subjects who discontinued due to adverse event, lost to follow-up, or subject withdrawal.

Table 15. EXPEDITION-8: Efficacy in Treatment-Naïve Adults with HCV Genotype 1, 2, 3, 4, 5 or 6 Infection with Compensated Cirrhosis

	MAVYRET 8 Weeks (N=343)						
	Total (all GTs) (N=343)	GT1 (N=231)	GT2 (N=26)	GT3 (N=63)	GT4 (N=13)	GT5 (N=1)	GT6 (N=9)
SVR12	98% (335/343)	98% (226/231)	100% (26/26)	95% (60/63)	100% (13/13)	100% (1/1)	100% (9/9)
Outcome for Subjects without SVR12							
On-treatment VF	0/343	0/231	0/26	0/63	0/13	0/1	0/9
Relapse	<1% (1/336)	0/225	0/26	2% (1/62)	0/13	0/1	0/9
Other*	2% (7/343)	2% (5/231)	0/26	3% (2/63)	0/13	0/1	0/9

GT = genotype; VF = virologic failure
* Includes subjects who discontinued due to lost to follow-up or subject withdrawal.

Abbvie prescribing information

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Sofosbuvir/Ledipasvir efficacy

Table 13 **Study ASTRAL-1: Virologic Outcomes by HCV Genotype in EPCLUSA-Treated Subjects without Cirrhosis or with Compensated Cirrhosis (12 Weeks After Treatment)**

	EPCLUSA 12 Weeks (N=624)							
	Total (all GTs) (N=624)	GT-1			GT-2 (N=104)	GT-4 (N=116)	GT-5 (N=35)	GT-6 (N=41)
		GT-1a (N=210)	GT-1b (N=118)	Total (N=328)				
SVR12	99% (618/624)	98% (206/210)	99% (117/118)	98% (323/328)	100% (104/104)	100% (116/116)	97% (34/35)	100% (41/41)

Gilead prescribing information

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Dealing with previous treatment failures

- Why are there DAA treatment failures:
  - Noncompliance
    - SVR is high even in non-compliant patients
  - HCC
  - Decompensation
  - Multiple RAS?

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Dealing with previous DAA treatment failures

Original regimen	Retreatment I	Retreatment II
Glecaprevir/pibrentasvir	Sof/vel/vox*	G/P 16 weeks with ribavirin
Sofosbuvir based	Sof/vel /vox* - with ribavirin for G3/cirrhosis	G/P 16 weeks but not G3 or PI experienced patient

* Sofosbuvir/velpatasvir/voxilaprevir (Vosevi)

Acute Hepatitis C

- Up to 40% spontaneously clear
- ALF extremely rare
- Do not wait for clearance to treat - same regimens as for chronic HCV – same SVR rates *
- Drug treatment, harm reduction, reinfection education in the right setting*
- No role for exposure prophylaxis*

* www.hcvguidelines.org

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HBV and HCV coinfection

- Hepatitis B coinfection present in 1.4 percent of US HCV patients *
- HCV and HBV replication is reciprocal –HCV typically dominates
  - replication "interference"
  - HCV activation of innate immune response which ebbs with eradication

- Hepatitis C eradication can lead to Hepatitis B reactivation
  - Defined by HBV DNA turning (+) from (-) or one log increase in HBV DNA
  - 1/200 HBV surface antigen (-) and core AB (+)
  - 21% reactivation in HBV surface antigen (+) **

* Kruse et al, Hepatology, 2014

** Jiang et al, World J Gastroenterol, 2018

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Treatment recommendations in HCV/HBV coinfection

- Check HBV surface antigen, HBV core AB **total**, Hep B surface antibody and (?) HBV DNA prior to treatment
- No prophylactic NUC for resolved HBV infection
- Consider prophylactic NUC (entecavir/TAF) if HBV surface antigen (+)
- Start NUC tx for HBV DNA (+)
- Measure LFTS and HBV DNA before, during, and after treatment on a regular basis (?monthly)

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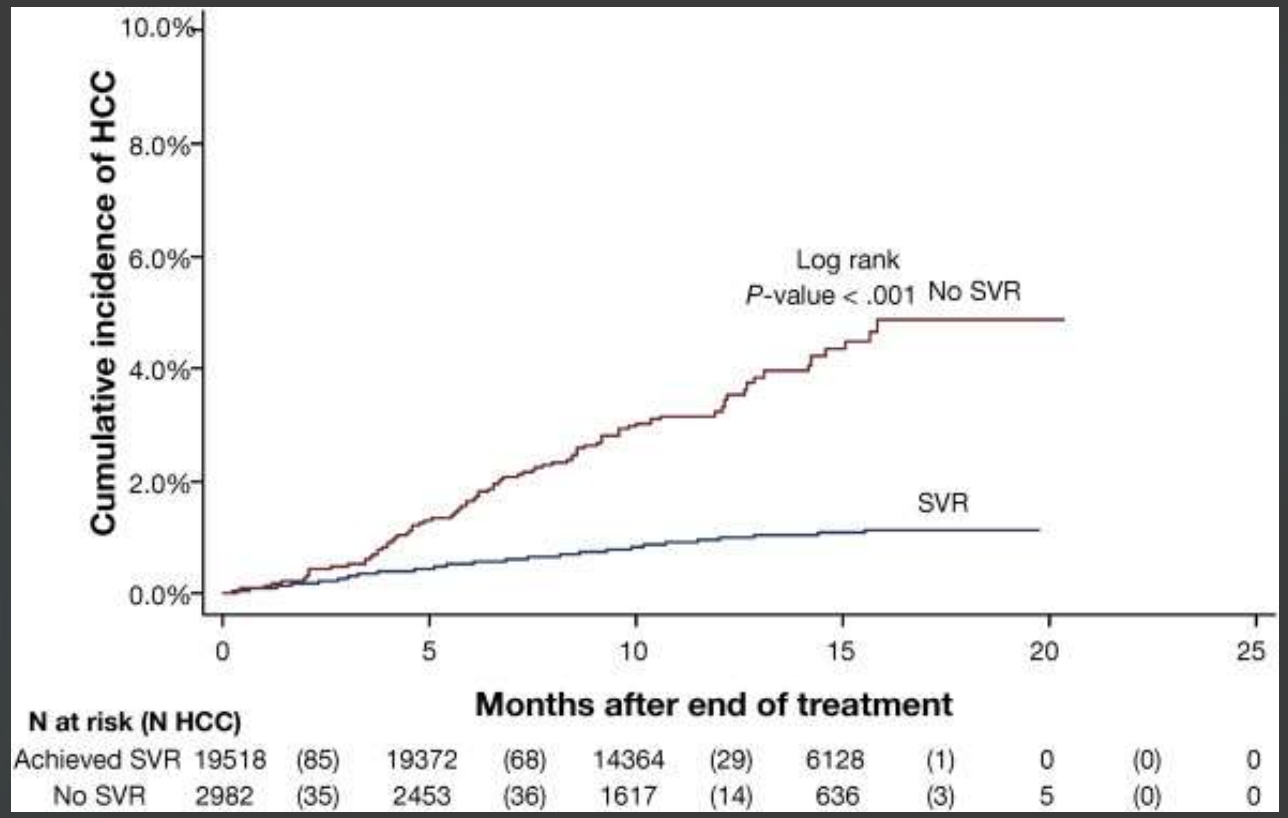
Cirrhosis					<.0001
No	12,769.6	44	0.34 (0.24–0.45)	1	
Yes	7645.7	139	1.82 (1.52–2.12)	4.73 (3.34–6.68)	

Risk is reduced but not eliminated



Kanwal et al, Gastroenterololgy, 2017

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Risk factors for HCC after SVR

- **Cirrhosis (FIB-4 >3.25, kPa >12.5) <u>at baseline</u>**
  - Male
  - Age
  - Liver steatosis (NAFLD, ETOH)
  - Portal hypertension
  - ?lack of regression of kPa after SVR
  - Persistent elevation of AFP after SVR
  - HBV core antibody (+)

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Follow up of HCV patients with SVR and advanced fibrosis/cirrhosis

- HCC surveillance
- Stay thin
- No ETOH
- Drink coffee
- Quit smoking
- Take statins
- Reinfection warning
- Vaccination for Hep A/B if appropriate

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Decompensated cirrhosis

- SVR rates are lower (85%)
- SVR improves status by:
  - QOL
  - Mortality
  - Portal hypertension
  - MELD
  - Avoid MELD "purgatory" in OLT candidate
- Treatment is sofosbuvir for 12 weeks with ribavirin or 24 weeks – no ribavirin

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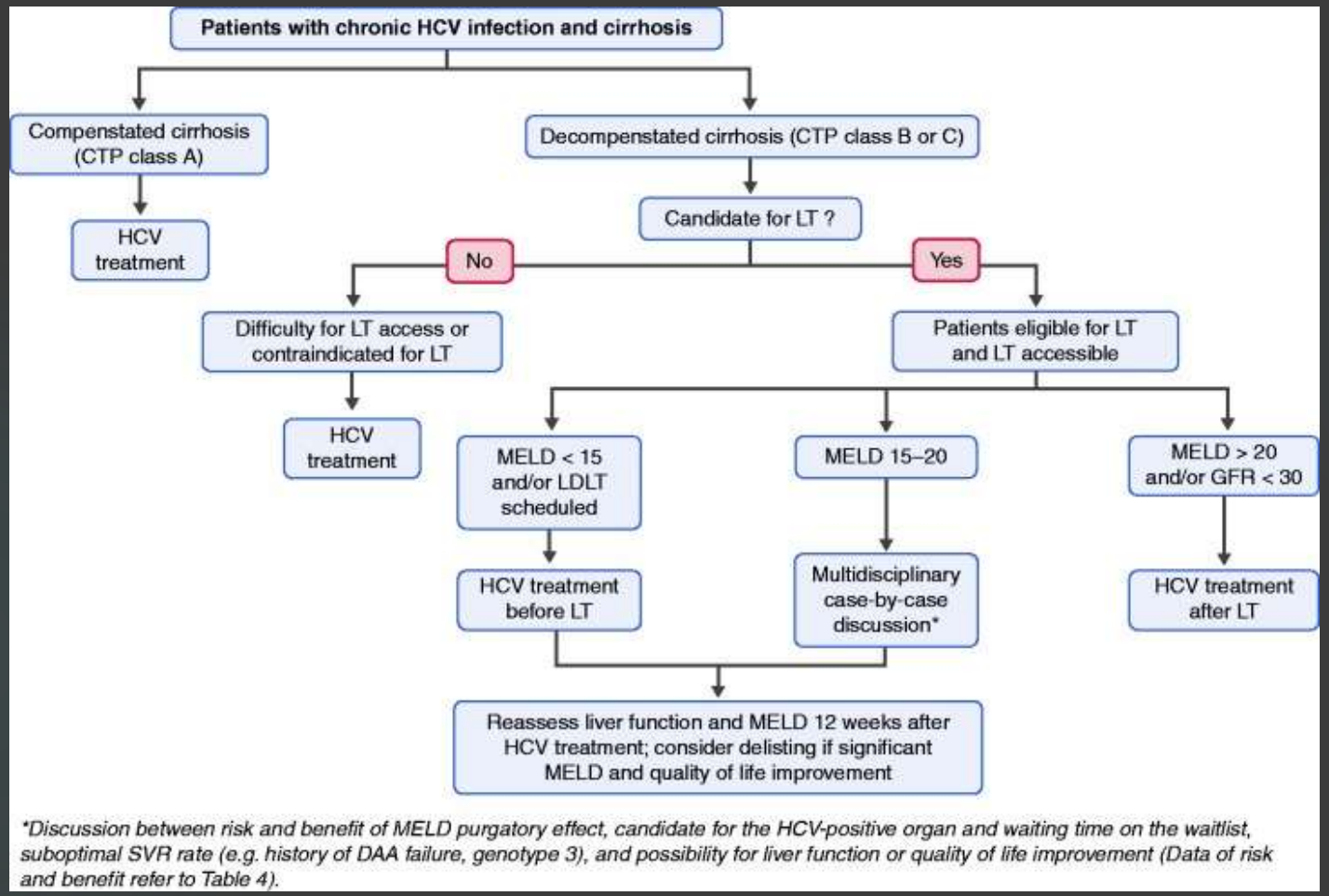
Decompensated HCV cirrhosis - ?antiviral therapy



Ekpanyapong S et al. United European Gastroenterol J. 2019

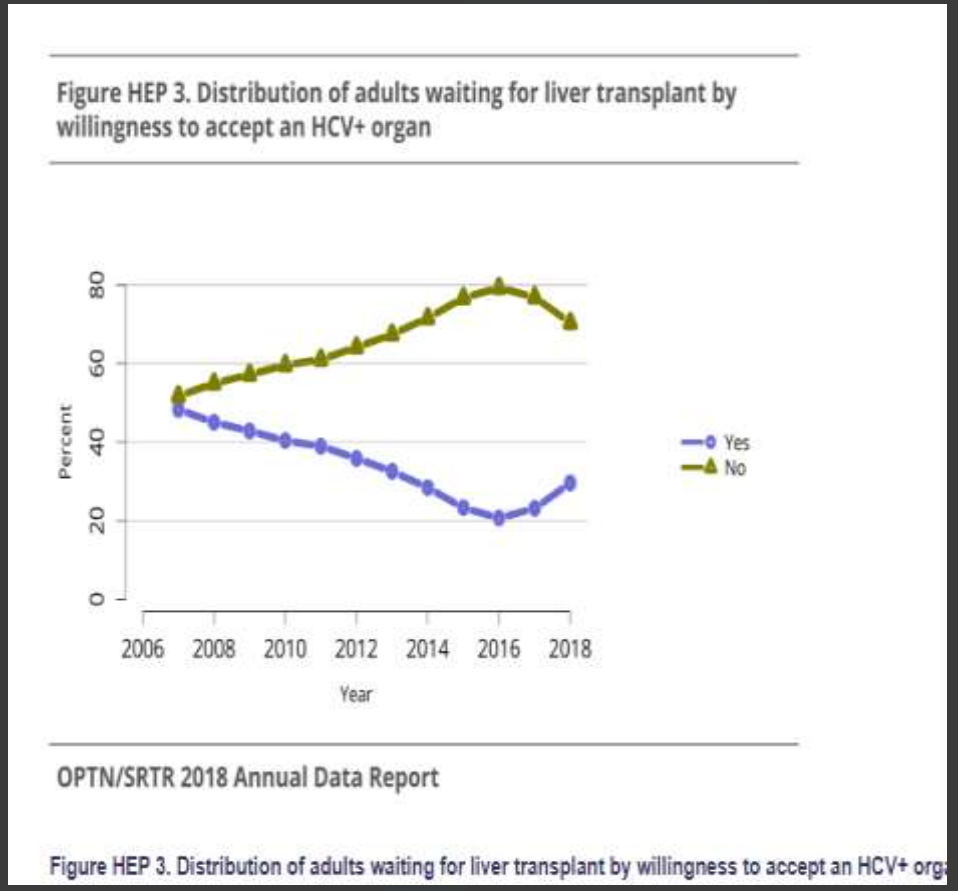
Reproductive issues in the HCV patient

- HCV patients encouraged to seek treatment prior to conception
- Not clear HCV affects pregnancy
  - ICP?
- HCV treatment during pregnancy discouraged(?)
- 10% of patients have spontaneously viremia after delivery – VL should be rechecked prior to treatment
- Breast feeding is not contraindicated
- Ethinyl estradiol containing OCP are discouraged with G/P due to risk of increased liver enzymes

HCV negative patients receiving HCV positive livers

- Treatment success is high
- Treatment should be guaranteed before liver transplant
- 12 week regimens of G/P and S/V suggested
- Treatment within two weeks of transplant
- Sofosbuvir/valpatasvir/voxileprevir (Vosevi) can be safely used to salvage DAA failure*

*Higley et al , World J Hep, 2020



Hepatitis C vaccine

- T cell and humoral components needed for clearance
- HCV is genetically highly diverse
  - Eight genotypes differing by 30% in nucleotide sequence
  - 90 subtypes with 15% sequence variation. HCV adept at avoiding host immune responses
- HCV envelope proteins (E1 and E2) are the targets of the humoral immune response
  - hypervariable region of E2 "shields" more conserved epitopes in the protein

Hepatitis C vaccine

Randomized Trial of a Vaccine Regimen to Prevent Chronic HCV Infection

Kimberly Page, Ph.D., M.P.H., Michael T. Melia, M.D., Rebecca T. Veenhuis, Ph.D., Matthew Winter, D.D.S., Kimberly E. Rousseau, B.S., Guido Massaccesi, B.S., William O. Osburn, Ph.D., Michael Forman, B.S., Elaine Thomas, M.D., Karla Thornton, M.D., M.P.H., Katherine Wagner, M.I.P.H., Ventzislav Vassilev, Ph.D., et al.

NEJM, 2021

- adenovirus 3 (ChAd3) and modified vaccinia Ankara (MVA) vectors **encoding NS proteins of HCV genotype 1b**

Table 2. Vaccine Efficacy against Chronic HCV Infection at 6 Months.*

Analysis and Population†	Vaccine (N=275)		Placebo (N=273)		Vaccine Efficacy (95% CI)‡	Hazard Ratio (95% CI)§	P Value¶
	Censored Data	Chronic Infection	Censored Data	Chronic Infection			
	number of participants				*percent*		
Primary efficacy analysis, per-protocol population	261	14	259	14	−53 (−255 to 34)	1.53 (0.66–3.55)	0.31
Secondary efficacy analysis, modified intention-to-treat population	256	19	257	17	−66 (−250 to 21)	1.66 (0.79–3.50)	0.18

↓ RNA

↑ T cell response

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