Hepatitis C in Individuals of Childbearing Age and in Pregnancy

National AIDS Treatment Advocacy Project (NATAP)

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Disclosures

- Advisory and consulting for Gilead, Abbvie, Bausch
- Research support from Gilead

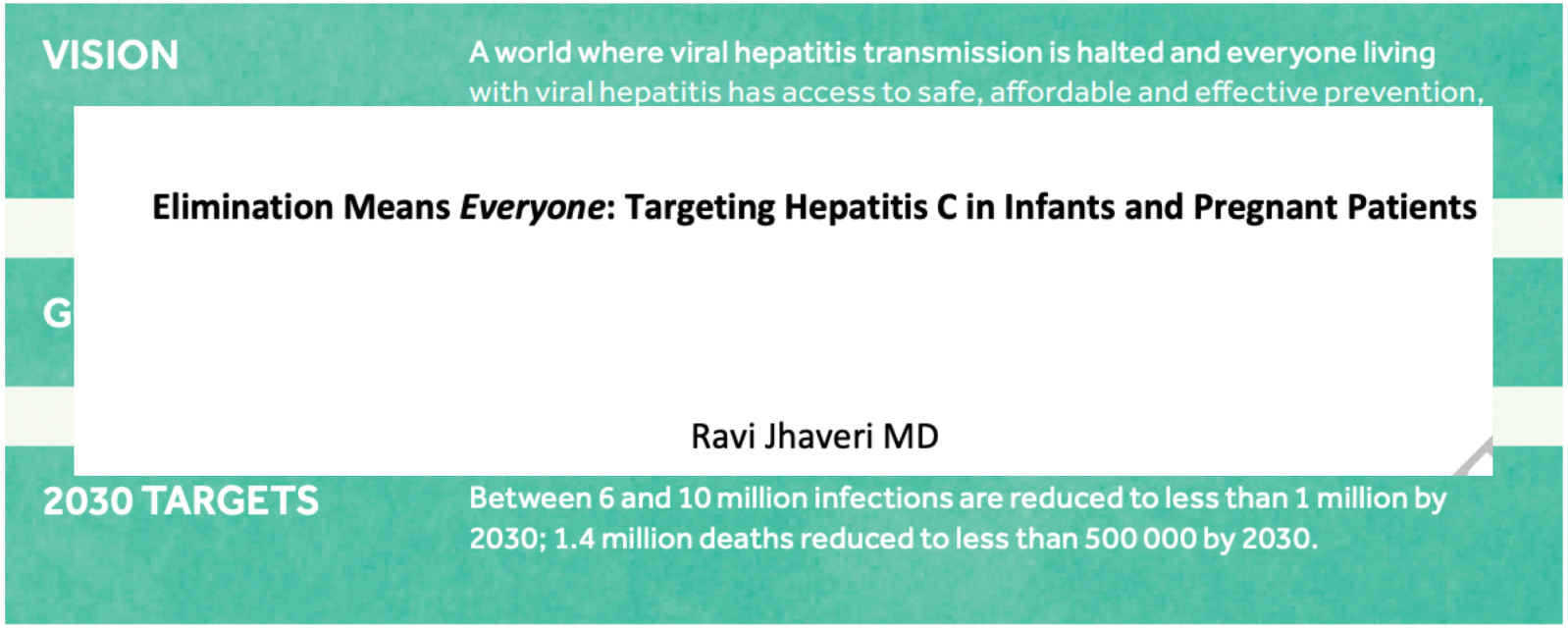
Acknowledging Statement

The word women or female may be used throughout the presentation to align with the language of the studies represented in this talk; however, we acknowledge that not all pregnant people identify as cis women and understand the importance of using gender-inclusive language in order to support all of our patients.

We have a goal for HCV elimination in 2030..

Global Health Strategy on Viral Hepatitis

World Health Organization



"Achieving these targets will require a radical change in the hepatitis response, and will mean that hepatitis is elevated to a higher priority in public health responses."

Hepatitis C (HCV) in women of childbearing age and pregnancy: What are the relevant issues?

- Changing Epidemiology of HCV
- Effect of HCV on pregnancy outcomes
- Mother-to-child transmission
- Screening and monitoring of HCV during pregnancy?
- Timing of Antiviral therapy
  - Role of antiviral therapy in pregnancy

Changing Epidemiology of HCV

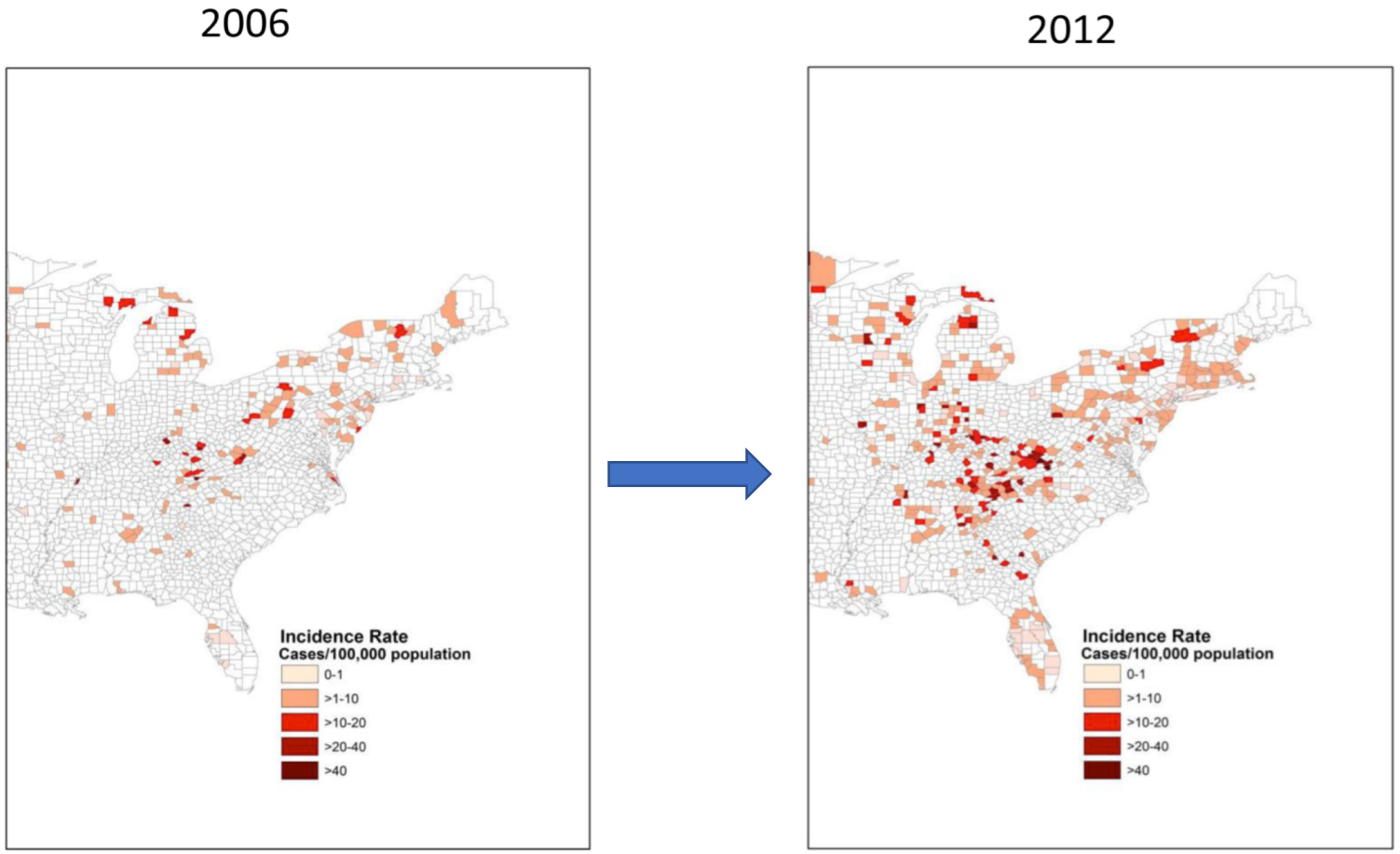
HCV in the United States

- > 2 million estimated cases of chronic HCV
  - Most common bloodborne infection in the country

- Among young individuals with new hepatitis C infections, over 50% are female

Rosenberg ES, et al. *JAMA Network Open 2018.*
Zibbell et al. *MMWR Morb Mortal Wkly Rep 2015.*

New HCV in the US: Emerging Epidemic Among Young Heroin Users (< 30 y/o)

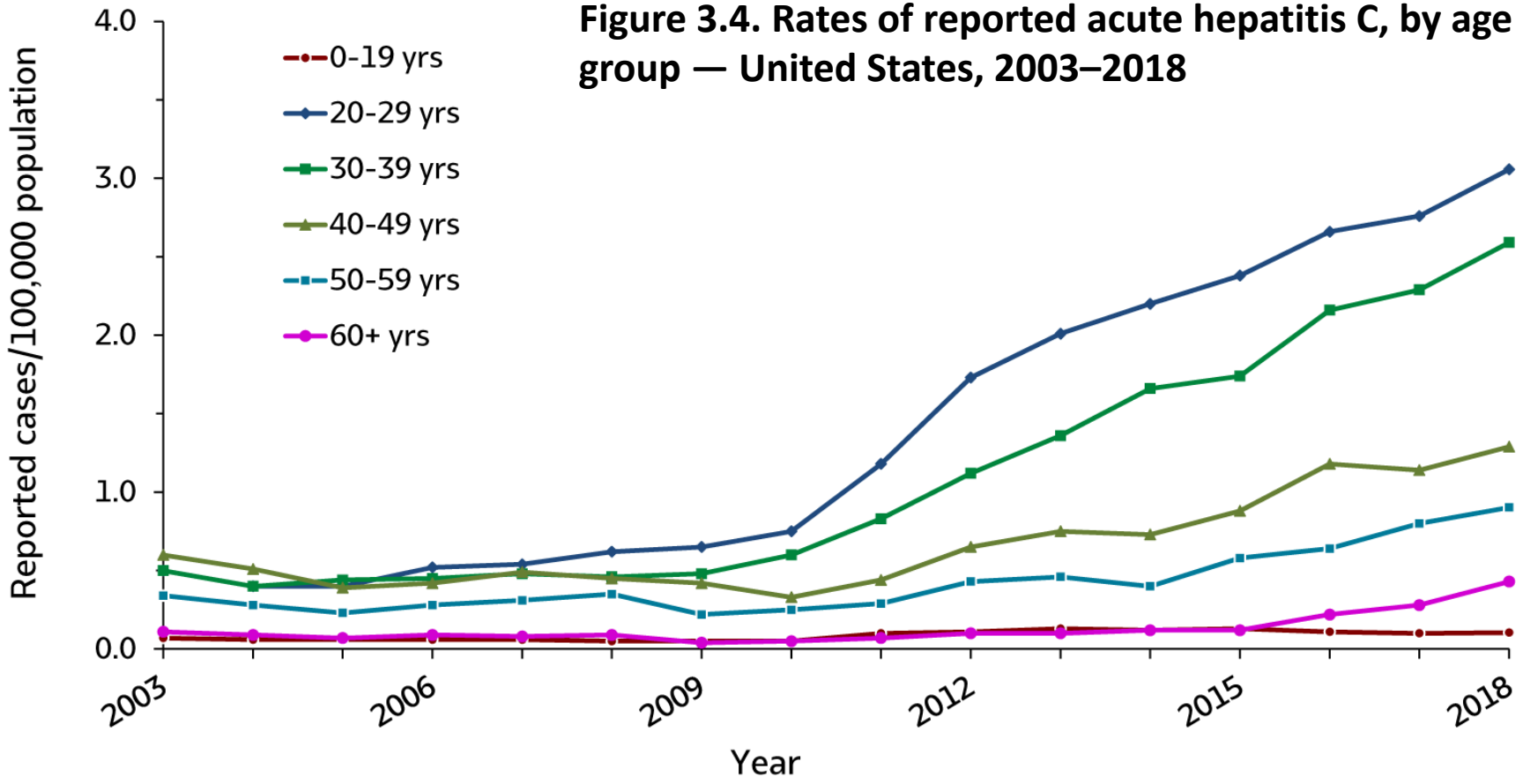


- HCV: 13% annual increase rural; 5% annual increase urban
- Regional doubling of first-time heroin users
- 3 of 4 with HCV had history of prescription opioid abuse
- 97% initiated drug use before age 20

Suryaprasad AG. *Clin Infect Dis 2014.*

The Epidemiology Of HCV Is Changing

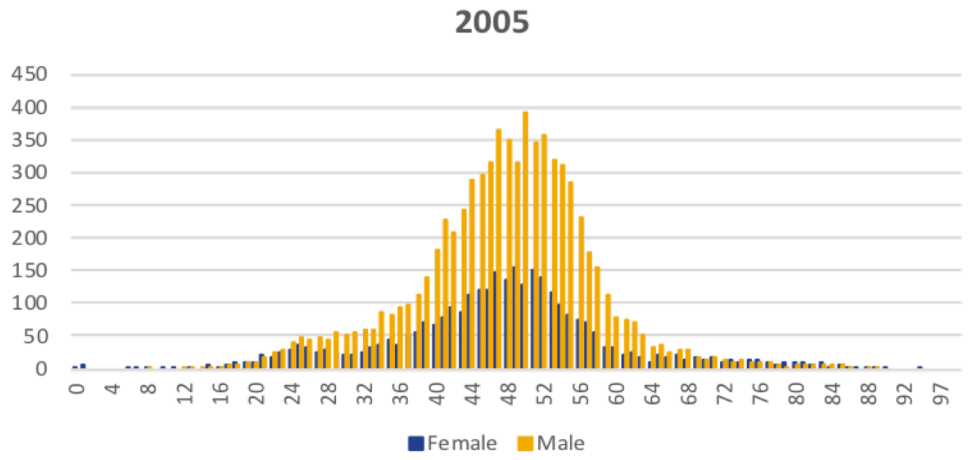
Figure 3.4. Rates of reported acute hepatitis C, by age group — United States, 2003–2018

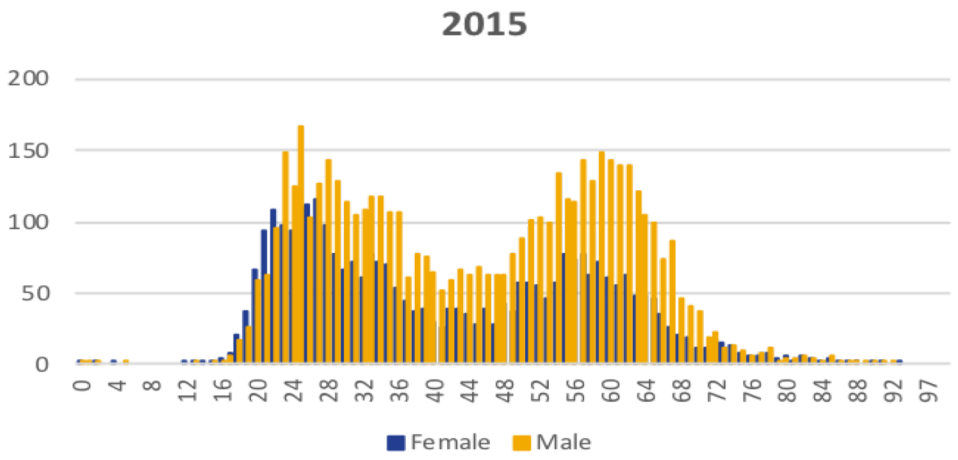


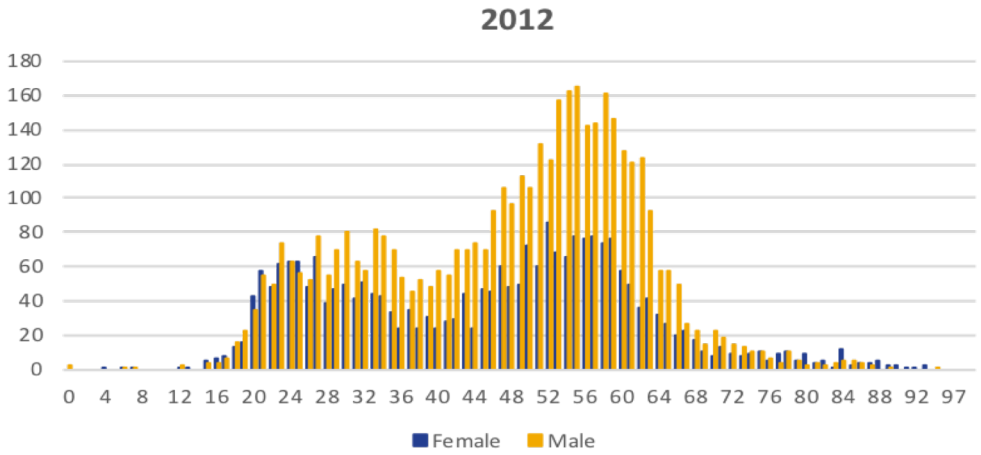
Highest incidence in 20-29 age group

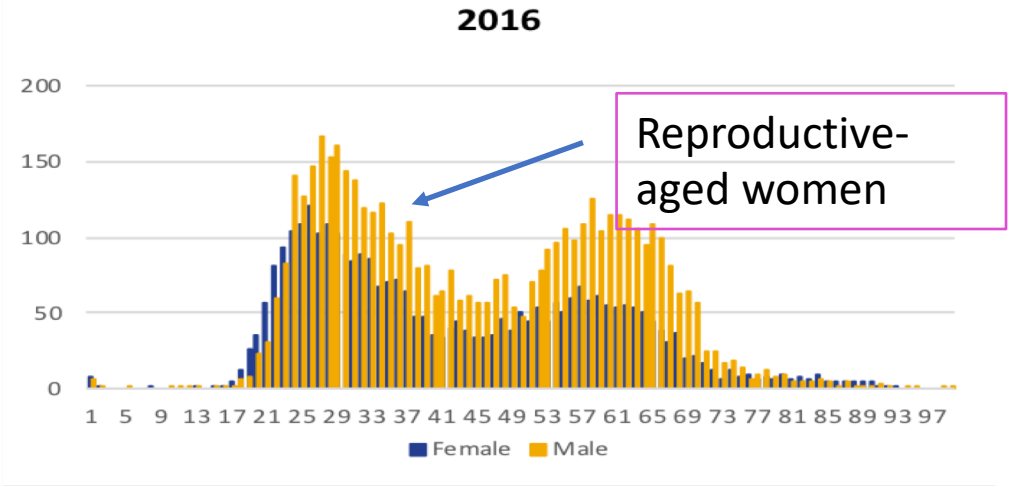
https://www.cdc.gov/hepatitis/statistics/2018surveillance/HepC.htm#Figure3.4

Bimodal HCV Distribution in New York State: Newer Peak Includes Reproductive-aged Women





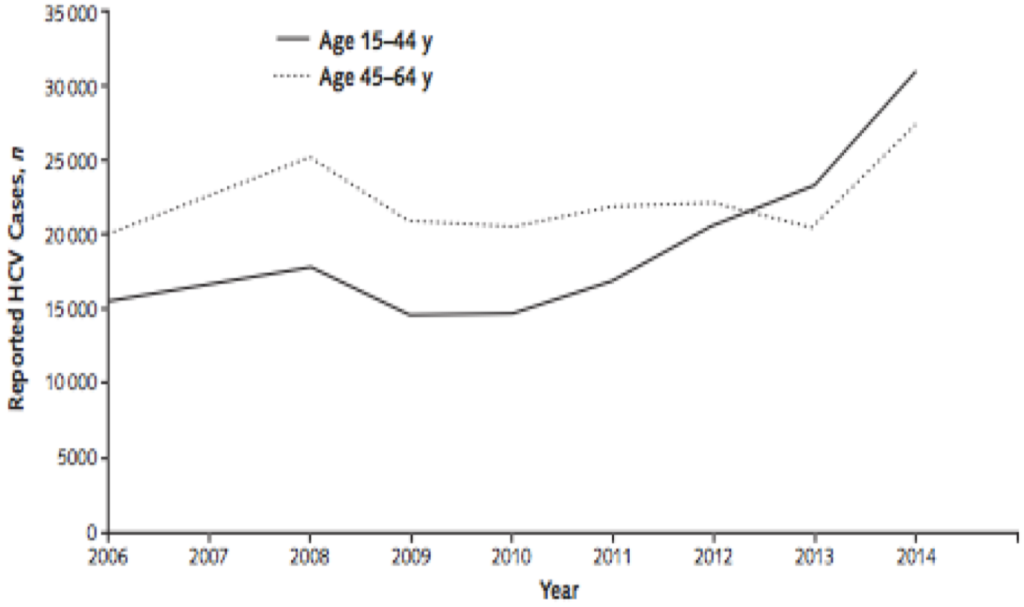




Slide courtesy of NYS DOH Bureau of Viral Hepatitis.

HCV in Women

- Among women of childbearing age:
  - # of acute cases increased 3.4-fold
  - # of past or present cases doubled
  - Rate higher than in older women since 2013

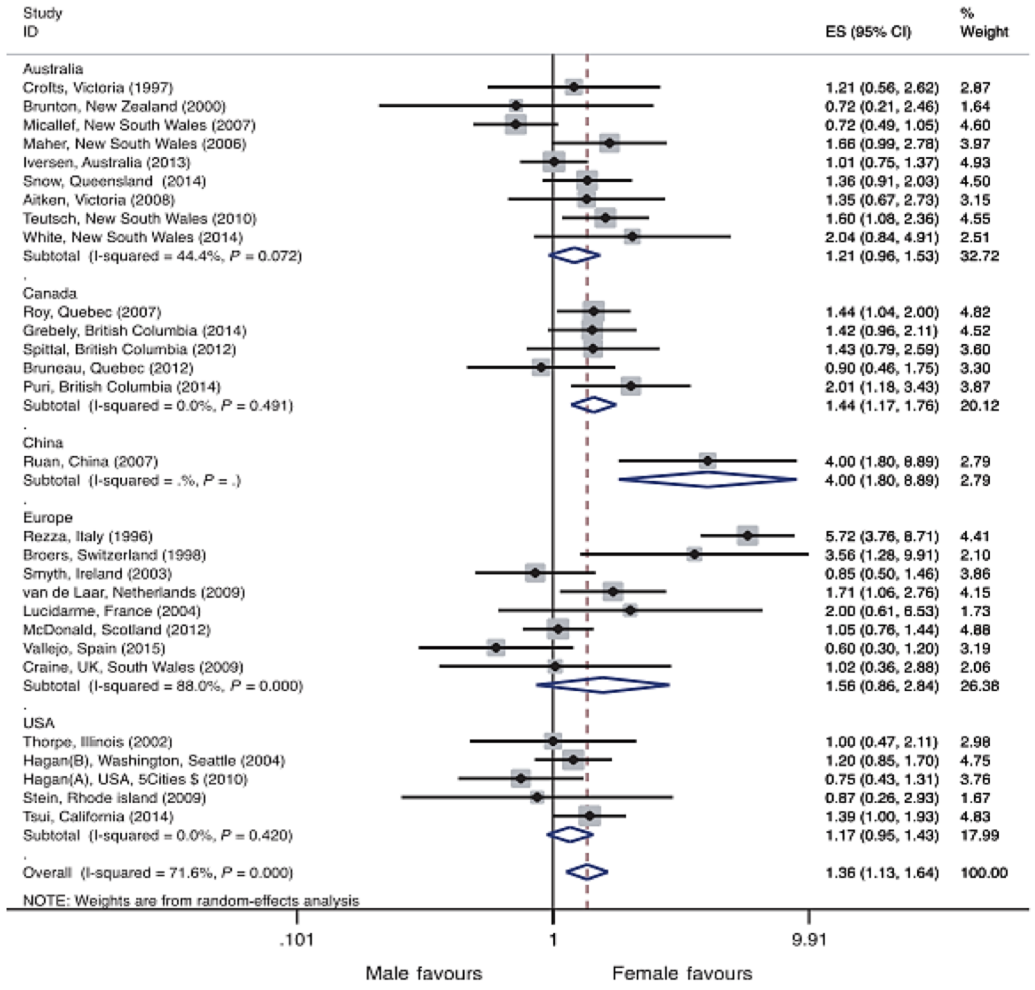


Source: NNDSS HCV case reports and Quest laboratory data

Ly K et al, *Annals Internal Medicine 2017*

Incidence of HCV Higher in Women Than Men Who Inject Drugs

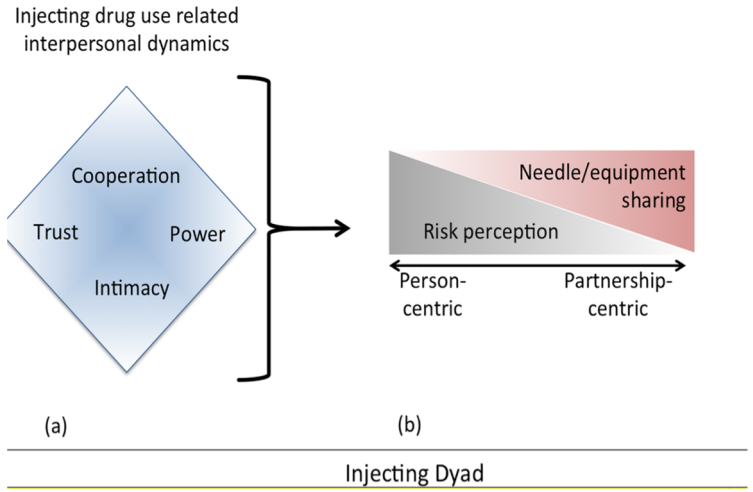
- Meta-analysis of 28 studies with 9,325 persons who inject drugs (PWID)
- Women were **36%** more likely to be anti-HCV positive than males
- Varies by country:
  - Highest in China and Europe
  - **17%** higher in US cohorts



Esmaeili A, et al. *Viral Hepat 2017.*

Women PWID may be at Higher Risk for HCV?

- Higher incidence of HIV and injection-related risk behaviors
  - Equipment and syringe sharing
  - Using injection equipment after male partners
  - More women being injected by others
- More likely than males to have IDU sex partners
  - Overlapping sexual and injection partnerships → increased injection risk
- More stigma – less likely to participate in harm reduction services
- Gendered power accompanies sexual injection behaviors



It is critical to counsel women on harm reduction services and safe injection practices!

Esmaeili A, et al. *J Viral Hepat 2017.* Morris M, et al. *Plos One 2019*
Evans J, et al. *J Urban Health 2003*

Sexual transmission of HCV in Women

- Multiple sexual partners significantly increases risk of HCV (aOR 2.2-2.9)
  - Pregnant women with unprotected sex with 2-4 partners were 3 times more likely to acquire HCV than women with one partner (aOR 2.8)
  - May be correlated with increased injection drug use

- Women with HIV are more than twice as likely to acquire HCV (aOR 1.9) – *Womens Interagency HIV Study (WIHS)*

- Presence of activities/ conditions that disrupt anal mucosal integrity (traumatic sex, genital ulcerative disease, etc) increase transmission

- **Women engaging in very high-risk sexual behavior* were 14.2 times more likely to have HCV than other women**

*Defined as anonymous sex, no protection or use of contraception, anal intercourse, unfamiliar partners, sex while using drugs, or sex for drugs or money

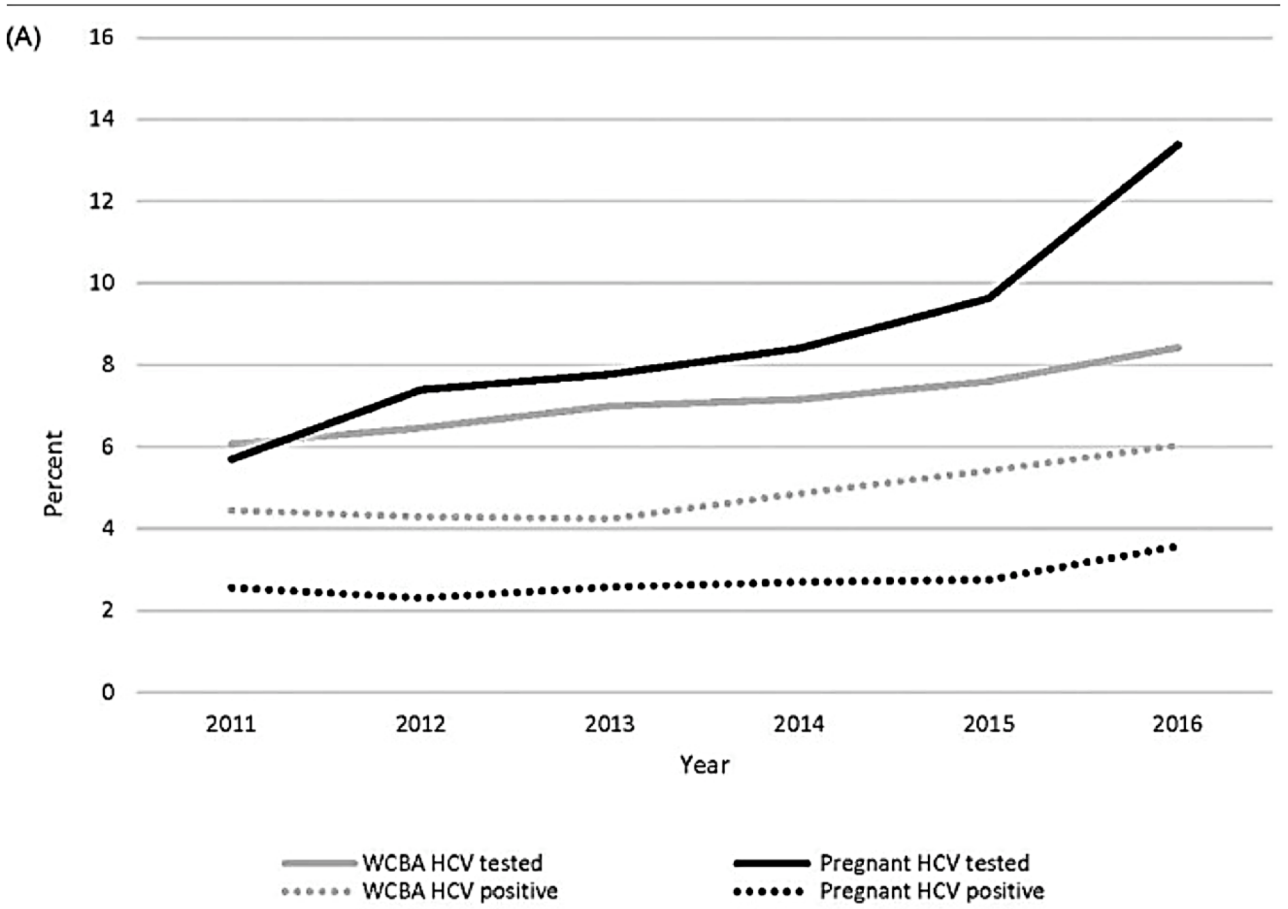
Tohme, et al. *Hepatology 2010*
Feldman J, et al. *Sexually Tranmitted Diseases 2000.*

Hepatitis C prevalence in pregnant people

HCV in Pregnant Women, 2011-2016

- National Center for Health Statistics birth certificate data; 2011-2016
- 2015: 0.38% (14,417) of live births delivered by HCV-infected women
  - Age 20-29
  - White, non-Hispanic
  - Covered by Medicaid
  - Had rural residence
- **Among pregnant women**, HCV testing increased from 5.7% to 13.4% (by 135%); **positivity increased from 2.6% to 3.6%** (by 39%)

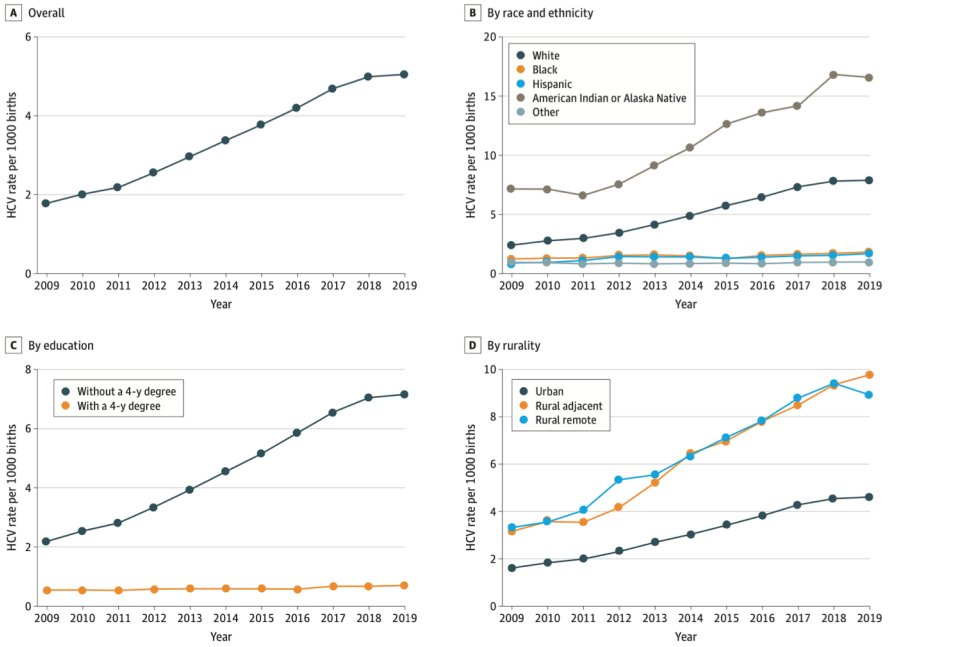
Percentage of U.S. women tested for and tested positive for HCV from 2011-2016 (n=14,417)

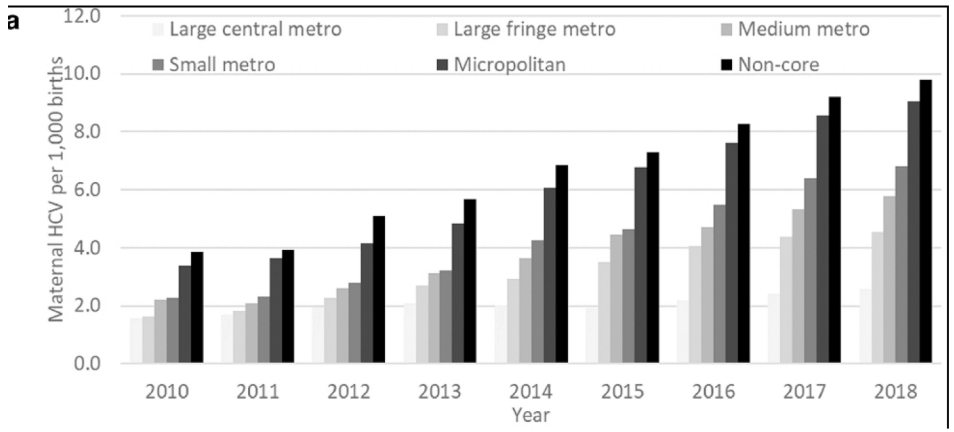


Schillie S, et al. *Am J Preventive Medicine 2018.*

HCV in pregnant people in US 2009-2019

- All US births from 2009-2019 using data from National Center for Health Statistics (CDC) and Area Health Resource File
  - 39 380 122 pregnant people
    - 138343 **(0.4%)** with HCV
- Rate increased from 1.8 to 5.1 per 1000 births
- Higher rates in:
  - White people
  - Less than 4-year degree
  - Medicaid/ Self pay
  - Rural/ Lower density of obstetricians
  - Unemployment





Patrick S et al. JAMA Health Forum October 2021.
Ahrens AK et al. Am J Prev Med 2021.

Effect of HCV on Pregnancy Outcomes

What is the impact of HCV on Pregnancy?

There is likely a negative impact on pregnancy of having HCV, but difficult to tease apart from effect of associated factors (such as injection drug use)

- **Meta-analysis of >4m women and >5000 HCV infection cases**
  - Preterm birth - OR 1.62 (95% CI 1.48-1.76)[1,]
  - IUGR - OR 1.53 (95% CI 1.40-1.68)[2]
  - Low birth weight – OR 1.97 (95% CI 1.43-2.71) [2]

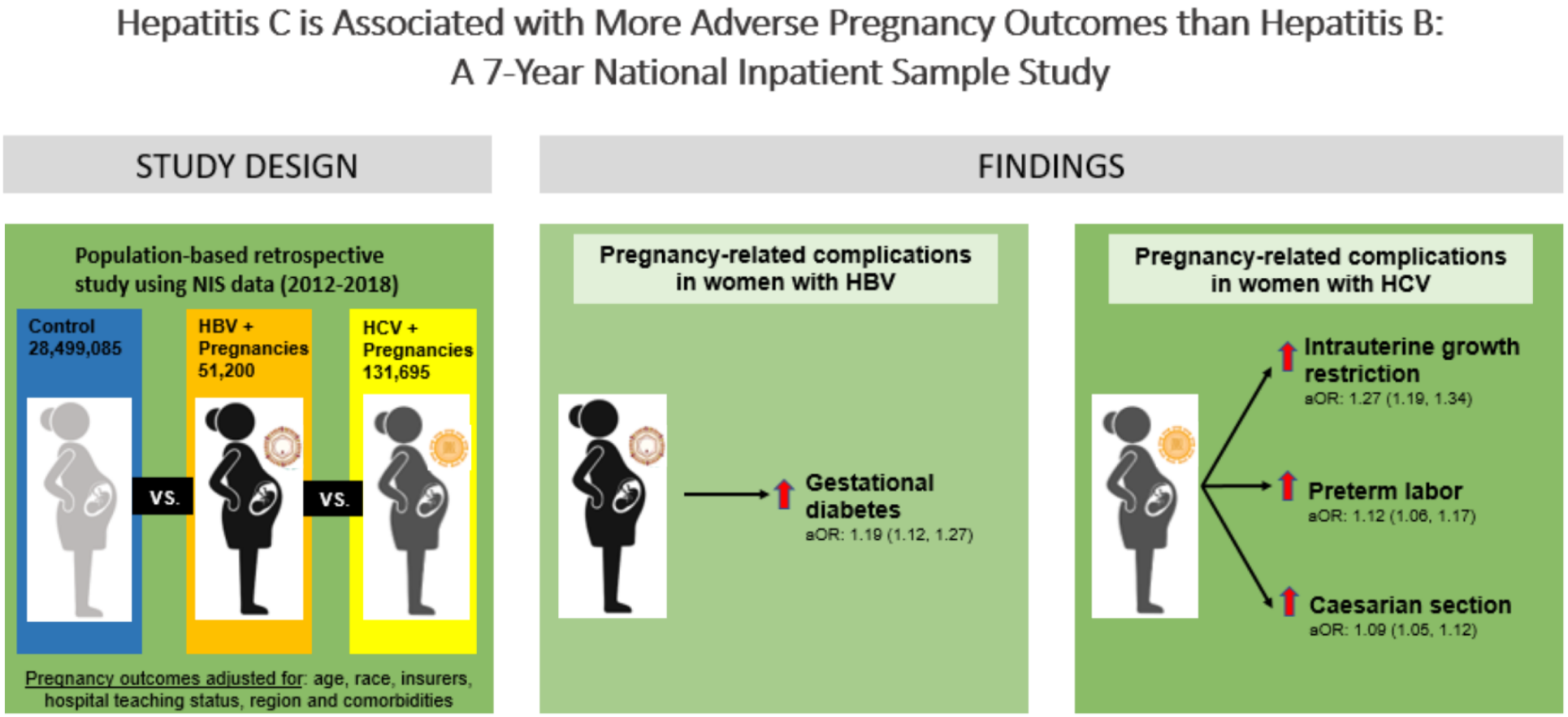
- **Swedish birth registry of >1 m women, >2000 HCV births births, 2001-2011**
  - Preterm birth (aRR 1.32 (95% CI 1.08-1.60)
  - Late neonatal death (aRR 3.79 (95% CI:1.07-13.79)

- **Italian study of >45k pregnant women screened for HCV, 2009-2018[3]**
  - Cholestasis of pregnancy **10x** higher; Gestational DM 2x higher in HCV positive

[1]Huang Q, et al. *J of Viral Hepatitis 2015.*
[2]Huang Q, et al. *Medicine 2016.*

[3]Stokkeland K, et al. *Eur J Epidemiol 2017.*
Piffer S, et al. *European Journal of Obstetrics & Gynecology 2021.*

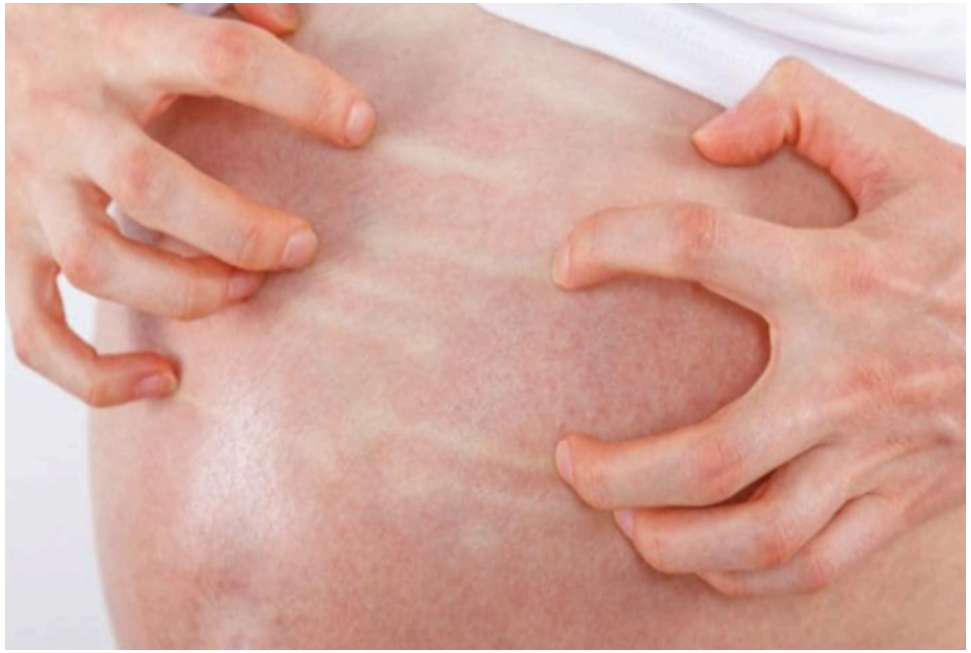
Evaluation of HCV in Nationwide Inpatient Sample



Chen B, Kushner T, et al. *Hepatol Communications*, 2022

Impact of HCV on Pregnancy

- Cholestasis of pregnancy (ICP):
  - Population-based cohort study in Sweden (11,000 ICP women; 11,000 healthy women) → HR 4.16 association of HCV with ICP
  - Meta-analysis of ICP studies in pregnancy → Pooled OR 20.4 compared to non-HCV women



Counsel women with HCV on the increased risk of cholestasis of pregnancy!

Marschall, et al. *Hepatology 2013.*
Wijarnpreecha K, et al. *Clin Res Hepatol Gastroenterol 2017.*

Recent data from Ontario Database with maternal-infant linkage

- ICES Ontario Database 2000-2016
  - 2170 HCV Ab positive pregnancies; 1780 RNA+ pregnancies

Effect of maternal HCV Viremia on probability of peripartum outcomes in infants born to mothers HCV.

	Multivariate		
Outcomes	OR	95% CI	p-value
Gestational diabetes[1]	**0.71**	**0.47 - 1.06**	**0.0958**
Intrahepatic cholestasis of pregnancy[2]	**4.55**	**1.64 - 12.64**	**0.0036**
Small for gestational age[3]	1.10	0.80 - 1.51	0.5716
Large for gestational age[4]	1.25	0.81 - 1.93	0.3153
Postpartum or antepartum hemorrhage[5]	**1.78**	**1.11 - 2.87**	**0.0173**
Preterm delivery[3]	**1.84**	**1.27 - 2.67**	**0.0013**

Kushner T, et al. *Journal of Hepatology* 2022.

Monitoring Women with HCV During Pregnancy

What Should A Provider Know About Monitoring A Woman With HCV?

AASLD guidelines:

Recommendations for Monitoring HCV-Infected Women During Pregnancy	
RECOMMENDED	RATING
HCV RNA and routine liver function tests are recommended at initiation of prenatal care for HCV-antibody–positive pregnant women to assess the risk of mother-to-child transmission (MTCT) and degree of liver disease.	I, B
All pregnant women with HCV infection should receive prenatal and intrapartum care that is appropriate for their individual obstetric risk(s) as there is no currently known intervention to reduce MTCT.	I, B
In HCV-infected pregnant women with pruritus or jaundice, there should be a high index of suspicion for intrahepatic cholestasis of pregnancy (ICP) with subsequent assessment of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and serum bile acids.	I, B
HCV-infected women with cirrhosis should be counseled about the increased risk of adverse maternal and perinatal outcomes. Antenatal and perinatal care should be coordinated with a maternal-fetal medicine (ie, high-risk pregnancy) obstetrician.	I, B

Linkage to HCV Care

- *"HCV-infected pregnant women should be linked to care so that antiviral treatment can be initiated at the appropriate time"*

- **Huge** challenge to ensure linkage to care
  - Women with HCV experience longer delays to HCV treatment than men
  - African Americans experience longer delays (280 *vs*. 165 days in non-Hispanic whites, $P < 0.05$)
    - HCV treatment uptake lower in African Americans (70.4% *vs*. 74.4%, $P < 0.05$).
  - Postpartum period – very high rates of loss to follow up

Gomes C et al. *J Transl Int Med* 2020.

Postpartum care for pregnant persons with opioid use disorder and HCV

- Retrospective cohort study using Medicaid Data
  - Delaware, Kentucky, Maine, North Carolina, Pennsylvania, West Virginia
  - 23,780 births from 2016-2019 with diagnosis of OUD

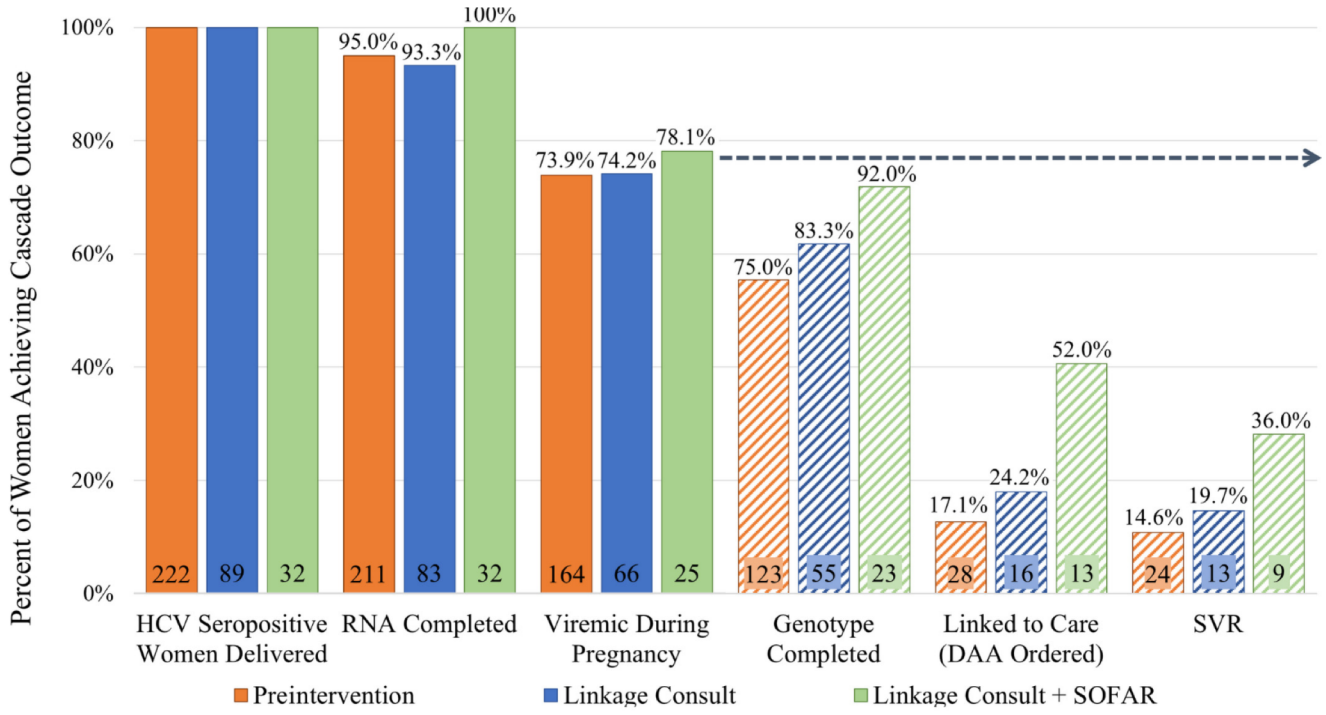
Postpartum Follow-up Period	Outcome	Pooled Average Predicted Probability*†	95% CI†	90% PI‡	I^2 (%)§
60 d	HCV infection testing	70.3	61.5–79.1	52.2–88.4	99.3
	HCV infection diagnosis	30.9	23.8–38.1	16.2–45.7	98.9
	Any follow-up visit or medication	3.2	2.6–3.8	2.1–4.3	76.3
6 mo	HCV infection testing	70.0	60.4–79.5	50.2–89.7	99.2
	HCV infection diagnosis	30.9	23.6–38.2	16.0–45.8	98.7
	Any follow-up visit or medication	5.9	4.9–6.9	4.0–7.8	80.6

Only 6% Medicaid-Enrolled Pregnant persons with OUD had postpartum follow up or treatment

Jarlenski M et al. *Obstetrics and Gynecology* 2022.

How can we enhance linkage to care following pregnancy?

- Maternal-infant linkage to care program + multidisciplinary collocated care clinic created for women with substance use in New England
  - Measured adherence to HCV cascade of care from 2014 to 2018 (pre-and post-intervention)

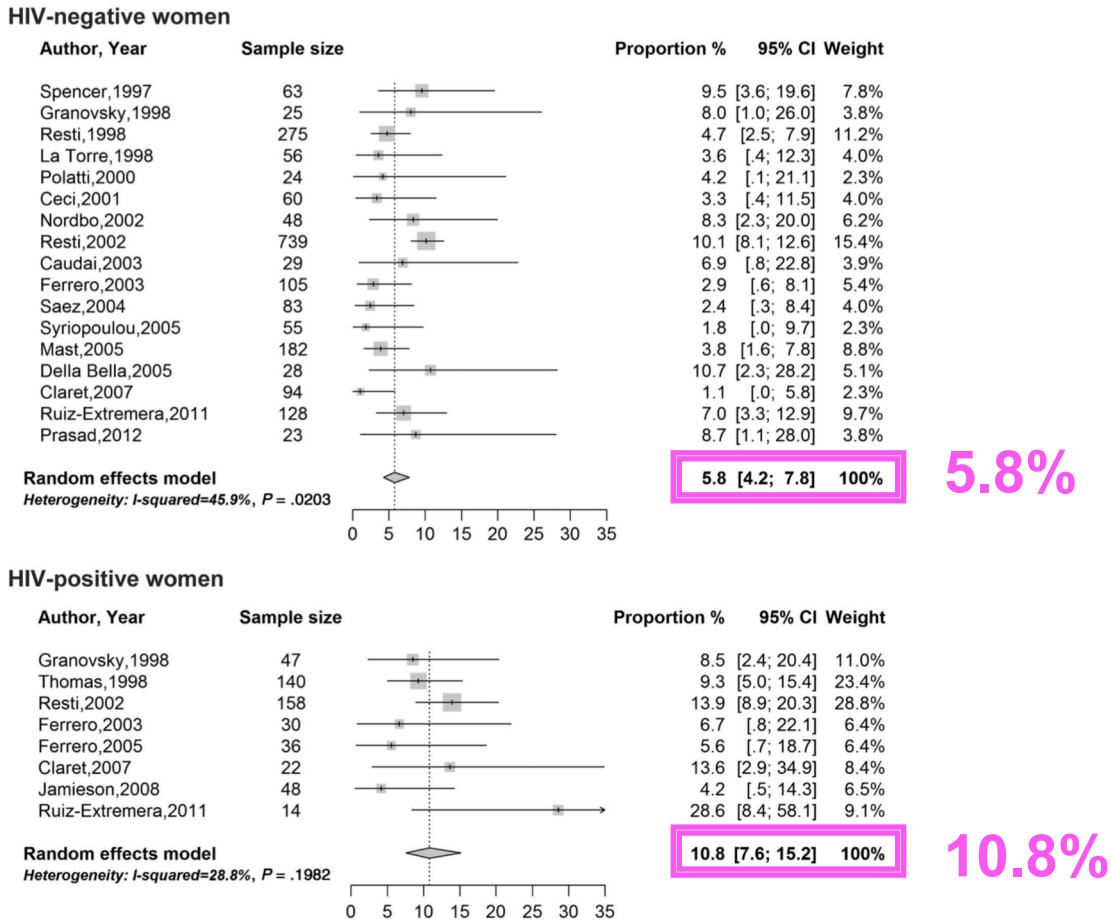


Epstein RL et al. *Hepatology Communications* 2021.

Mother-to-Child Transmission of HCV

How common is Mother-to-Child Transmission of HCV?

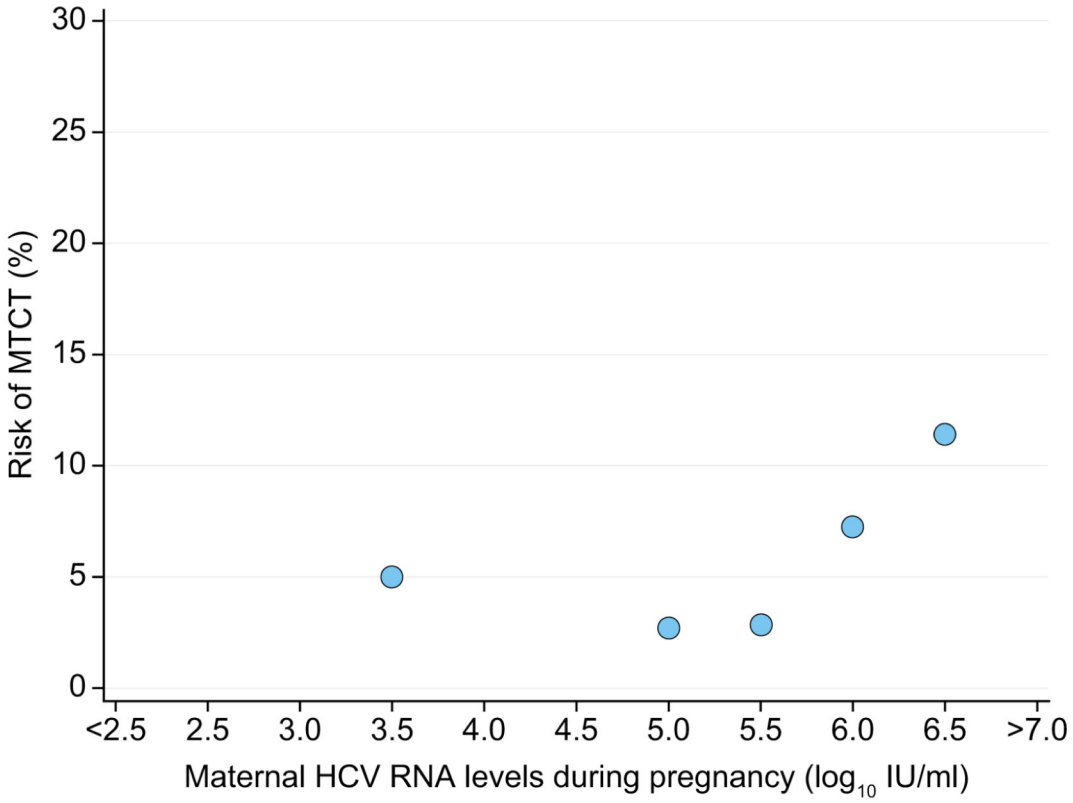
Systematic review and meta-analysis of 109 studies with HCV Ab+, RNA + mothers



Benova, et al. *Clinical Infectious Diseases*, 2014.

Is there an HCV RNA cutoff that predicts transmission?

Retrospective cohort study of 2170 HCV + pregnancies in Ontario



Multivariable predictors of MTCT in screened infants (n=451)

	eOR (95% CI)	P value
Maternal HCV RNA (log_{10}IU/mL) ≥6.0	3.38 (1.07-11.74)	0.04
HIV coinfection	3.43 (0.33-18.65)	0.32
Maternal HCV genotype Type 1	2.33 (0.62-13.06)	0.29

Kushner T, et al. *Journal of Hepatology* 2022.

Is there any way to prevent vertical transmission?

Variable	Studies; # women	Strength of Evidence	Summary of findings
Elective C/S vs. vaginal delivery	4 cohort studies; N=2080	Low	No differences, but trends in opposite directions in highest quality studies
All C/S vs. vaginal delivery	11 cohort studies; N=2308	Moderate	No association
Invasive fetal monitoring vs. none	3 cohort studies; N=928	Insufficient	Inconsistent but one good quality study OR=6.7 (95% CI 1.1-36)
Prolonged rupture of membranes vs. no	2 cohort studies; N=245	Low	Yes with > 6 hours having OR=9.3 (95% CI 1.5-18)
Breastfeeding	14 cohort studies; 2971 patients	High	No association

Cottrell, et al. *Ann Intern Med*, 2013.
Rac, et al. *Obstet Gynecol Clin North Am*, 2014.
Hughes, et al. *Society for Maternal Fetal Medicine*, 2017.

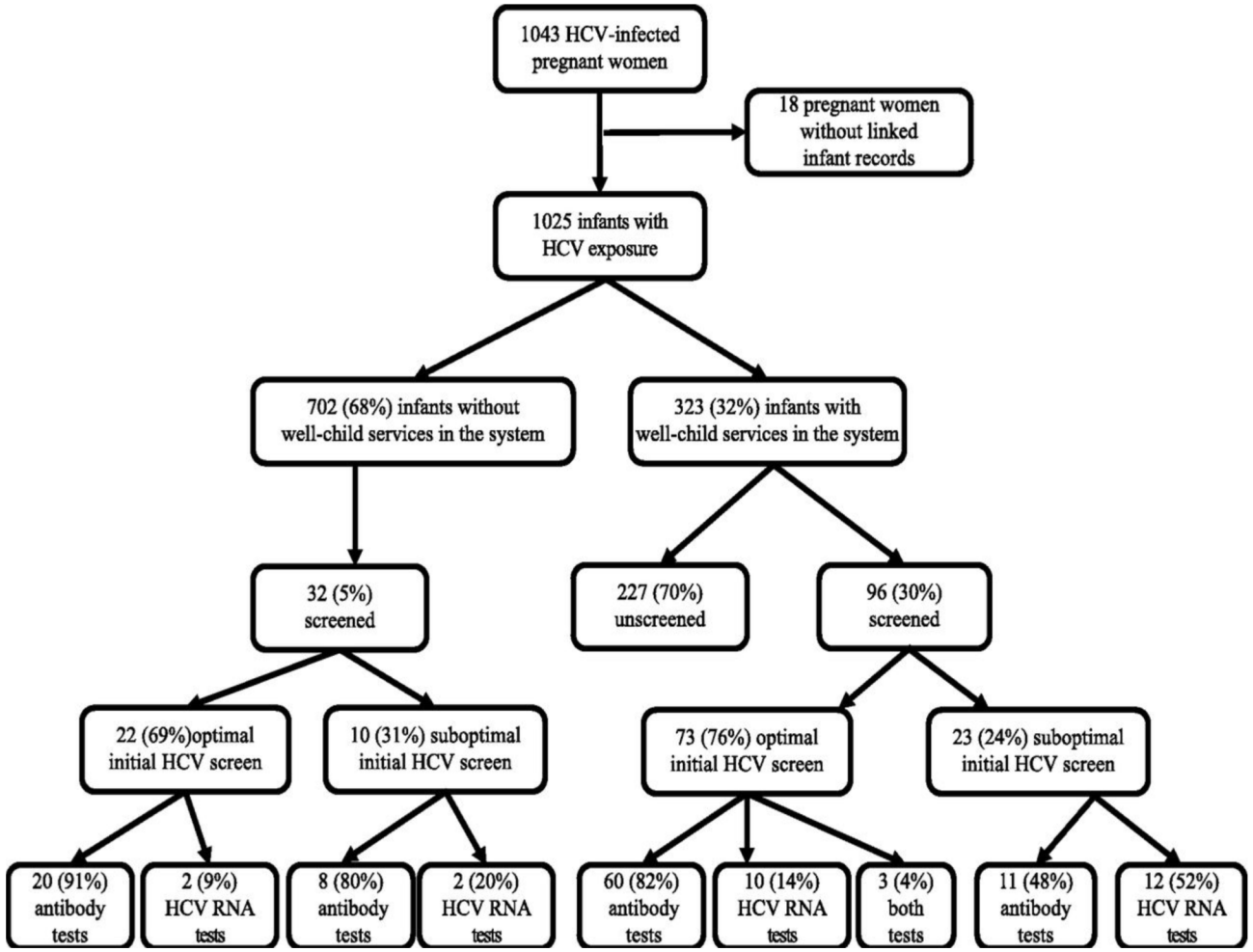
Impact of MTCT on Children

- MTCT is the most common cause of HCV in children
- 25-40% of infants clear HCV by 2-3 years
- Impact on children:
  - Quality of life
    - Reduced physical functioning
    - Executive function impairment in 20% of infected children
    - Worse cognitive functioning than uninfected children
    - Parental emotional impact and decrement in parental quality of life
  - Higher rates of cirrhosis in children who acquire HCV through MTCT
  - Hepatocellular carcinoma – 2nd most common hepatic malignancy in children

Murray, et al. *Diseases of the Liver in Children.* Springer 2014.
Modin et al. *Journal of Hepatology* 2018.
Younossi, et al. *Hepatology* 2007.

Are We Actually Testing Children to evaluate for MTCT?

- Population-based, retrospective cohort of pregnant women who delivered between 2006 and 2014
- Identified as HCV infected or HCV uninfected by billing codes
- Infant records linked to HCV-infected pregnant women queried for HCV tests and the receipt of well-child services
- Among **1025 HCV-exposed infants** with available pediatric records, 323 (31%) received well-child services, and among these, **only 96 (30%) were screened for HCV.**



Chappell C, et al. *Pediatrics*, 2018.

What Is The OB/GYN's Role In Ensuring Pediatric Testing?

- Important to communicate with pediatrician about maternal HCV infection
  - Transfer of care to pediatrician to alert them about maternal HCV status
  - Need for interventions to increase screening in infants who are at risk for perinatal HCV acquisition by including technology to improve the transfer of maternal HCV status to the pediatric record
  - Need to increase pediatric provider awareness regarding HCV screening guidelines

Chappell C, et al. *Pediatrics*, 2018.

Do we need to adjust our screening strategy for children?

"Compared with adults, there has been little attention paid to HCV screening in children and adolescents. Injection drug use and other risky behaviour that increases the chances for HCV infection do not start at 18 years of age. In fact, recent data indicate a worrisome increase in HCV infection among young persons who inject drugs. As DAAs are effective in most children and adolescents with chronic HCV infection, they could be screened as part of school physicals and promptly referred for HCV treatment."

Garrido I, et al. *Alimentary Pharmacology and Therapeutics*, 2021.

HCV Treatment in Children

Recommendations for Whom and When to Treat Among Children and Adolescents With HCV Infection	
RECOMMENDED	RATING
Direct-acting antiviral (DAA) treatment with an approved regimen is recommended for all children and adolescents with HCV infection aged ≥3 years as they will benefit from antiviral therapy, regardless of disease severity.	I, B
The presence of extrahepatic manifestations—such as cryoglobulinemia, rashes, and glomerulonephritis—as well as advanced fibrosis should lead to early antiviral therapy to minimize future morbidity and mortality.	I, C

AASLD

AASLD/ IDSA HCV Guidance. *Accessed on 2/2020.*

Approvals for HCV in Children

June 10, 2021

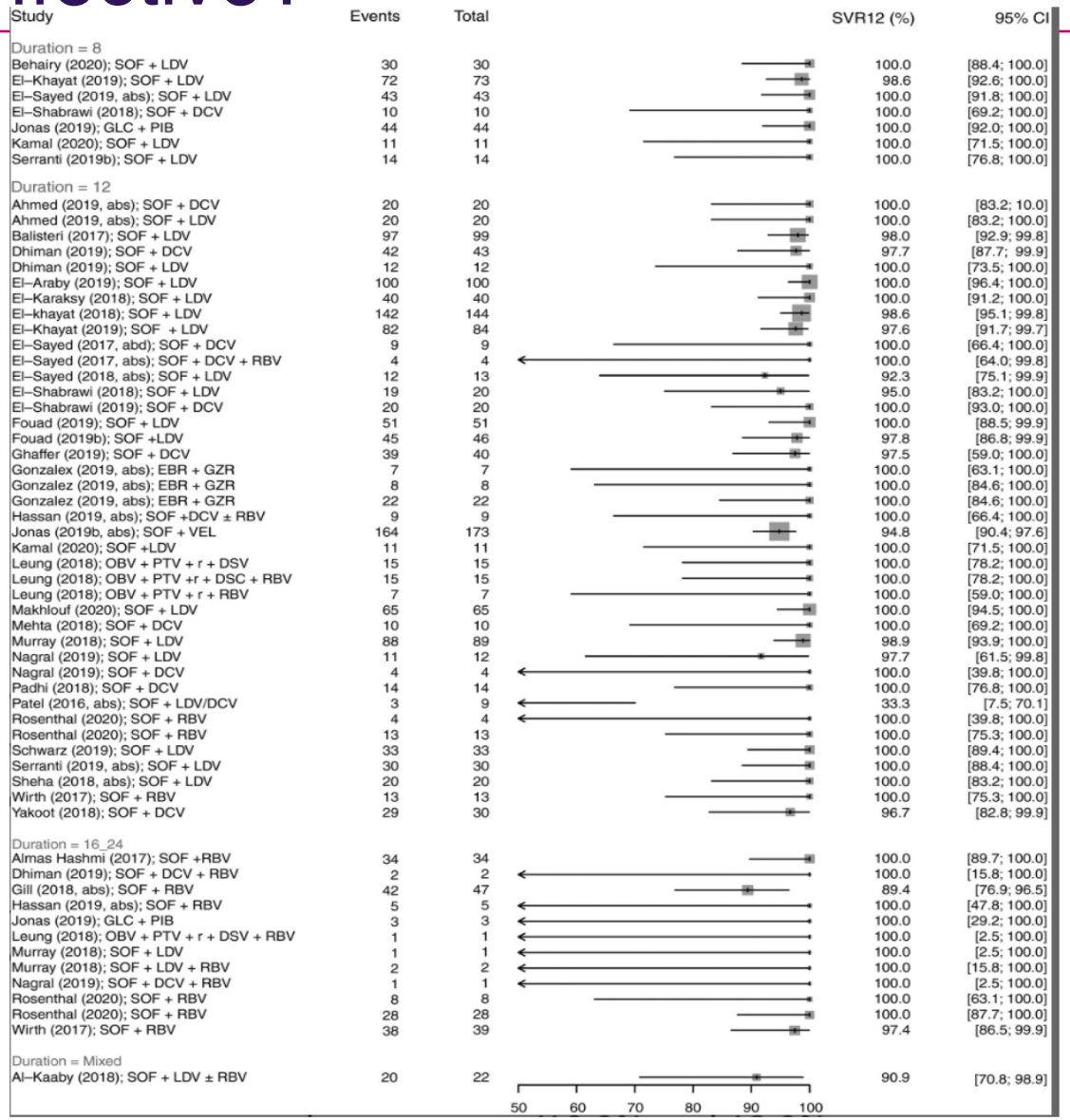
U.S. Food and Drug Administration Approves New Formulation of Epclusa®, Expanding Pediatric Indication to Treat Children Ages 3 and Older With Chronic Hepatitis C

FDA Approves Mavyret (G/P, glecaprevir and pibrentasvir) for Pediatric HCV Treatment 3 Years & Older

On June 10, 2021, the Food and Drug Administration (FDA) approved the use of glecaprevir and pibrentasvir ("G/P") or MAVYRET®, for the treatment of HCV in pediatric patients 3 years and older without cirrhosis or with compensated cirrhosis. With this pediatric approval MAVYRET® provides oral pellet formulation option for patients 3 years to less than 12 years old.

Is HCV treatment in children effective?

- Systematic review/ meta-analysis of 39 studies; 1796 patients age 0-18 y/o
  - Efficacy lower in age 3-6 overall, but same if they completed course of treatment
  - Efficacy/ safety overall does not differ from adults



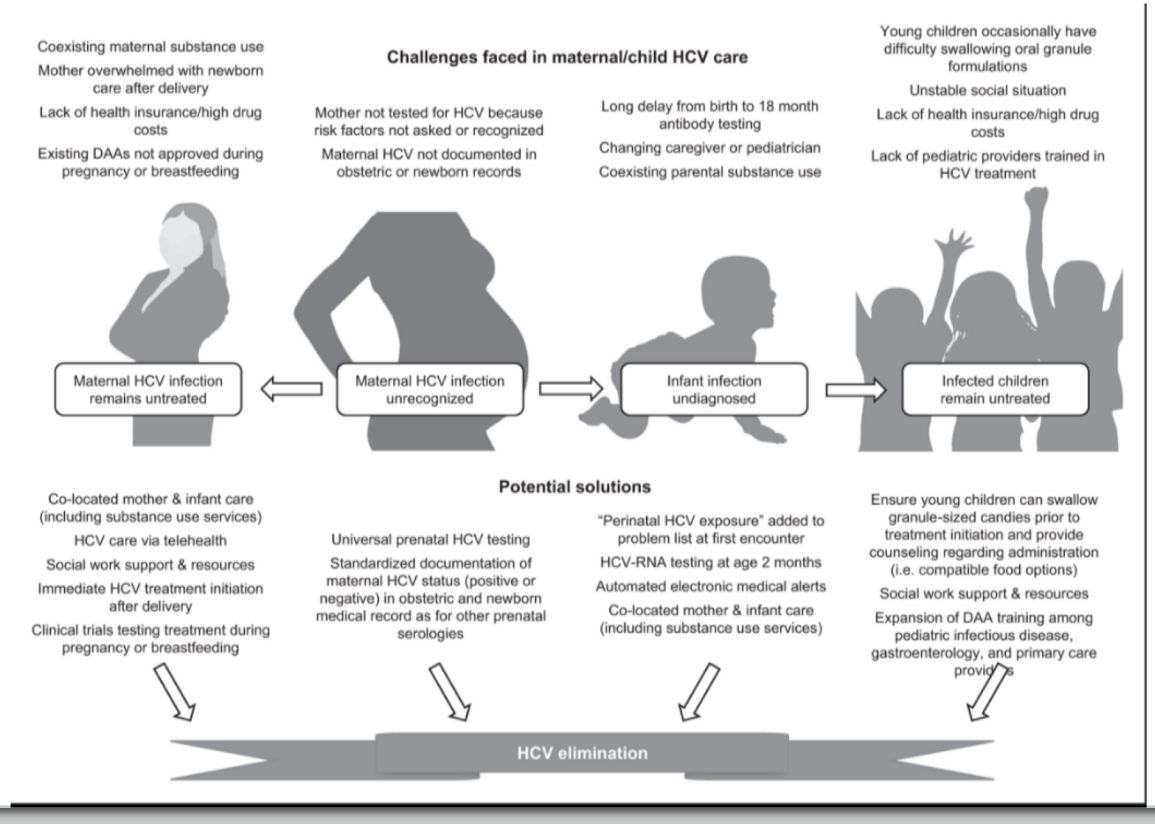
Study	Events	Total	SVR12 (%)	95% CI
Duration = 8				
Behairy (2020); SOF + LDV	30	30	100.0	[88.4; 100.0]
El–Khayat (2019); SOF + LDV	72	73	98.6	[92.6; 100.0]
El–Sayed (2019, abs); SOF + LDV	43	43	100.0	[91.8; 100.0]
El–Shabrawi (2018); SOF + DCV	10	10	100.0	[69.2; 100.0]
Jonas (2019); GLC + PIB	44	44	100.0	[92.0; 100.0]
Kamal (2020); SOF + LDV	11	11	100.0	[71.5; 100.0]
Serranti (2019b); SOF + LDV	14	14	100.0	[76.8; 100.0]
Duration = 12				
Ahmed (2019, abs); SOF + DCV	20	20	100.0	[83.2; 10.0]
Ahmed (2019, abs); SOF + LDV	20	20	100.0	[83.2; 100.0]
Balisteri (2017); SOF + LDV	97	99	98.0	[92.9; 99.8]
Dhiman (2019); SOF + DCV	42	43	97.7	[87.7; 99.9]
Dhiman (2019); SOF + LDV	12	12	100.0	[73.5; 100.0]
El–Araby (2019); SOF + LDV	100	100	100.0	[96.4; 100.0]
El–Karaksy (2018); SOF + LDV	40	40	100.0	[91.2; 100.0]
El–khayat (2018); SOF + LDV	142	144	98.6	[95.1; 99.8]
El–Khayat (2019); SOF + LDV	82	84	97.6	[91.7; 99.7]
El–Sayed (2017, abd); SOF + DCV	9	9	100.0	[66.4; 100.0]
El–Sayed (2017, abs); SOF + DCV + RBV	4	4	100.0	[64.0; 99.8]
El–Sayed (2018, abs); SOF + LDV	12	13	92.3	[75.1; 99.9]
El–Shabrawi (2018); SOF + LDV	19	20	95.0	[83.2; 100.0]
El–Shabrawi (2019); SOF + DCV	20	20	100.0	[93.0; 100.0]
Fouad (2019); SOF + LDV	51	51	100.0	[88.5; 99.9]
Fouad (2019b); SOF +LDV	45	46	97.8	[86.8; 99.9]
Ghaffer (2019); SOF + DCV	39	40	97.5	[59.0; 100.0]
Gonzalex (2019, abs); EBR + GZR	7	7	100.0	[63.1; 100.0]
Gonzalez (2019, abs); EBR + GZR	8	8	100.0	[84.6; 100.0]
Gonzalez (2019, abs); EBR + GZR	22	22	100.0	[84.6; 100.0]
Hassan (2019, abs); SOF +DCV ± RBV	9	9	100.0	[66.4; 100.0]
Jonas (2019b, abs); SOF + VEL	164	173	94.8	[90.4; 97.6]
Kamal (2020); SOF +LDV	11	11	100.0	[71.5; 100.0]
Leung (2018); OBV + PTV + r + DSV	15	15	100.0	[78.2; 100.0]
Leung (2018); OBV + PTV +r + DSC + RBV	15	15	100.0	[78.2; 100.0]
Leung (2018); OBV + PTV + r + RBV	7	7	100.0	[59.0; 100.0]
Makhlouf (2020); SOF + LDV	65	65	100.0	[94.5; 100.0]
Mehta (2018); SOF + DCV	10	10	100.0	[69.2; 100.0]
Murray (2018); SOF + LDV	88	89	98.9	[93.9; 100.0]
Nagral (2019); SOF + LDV	11	12	97.7	[61.5; 99.8]
Nagral (2019); SOF + DCV	4	4	100.0	[39.8; 100.0]
Padhi (2018); SOF + DCV	14	14	100.0	[76.8; 100.0]
Patel (2016, abs); SOF + LDV/DCV	3	9	33.3	[7.5; 70.1]
Rosenthal (2020); SOF + RBV	4	4	100.0	[39.8; 100.0]
Rosenthal (2020); SOF + RBV	13	13	100.0	[75.3; 100.0]
Schwarz (2019); SOF + LDV	33	33	100.0	[89.4; 100.0]
Serranti (2019, abs); SOF + LDV	30	30	100.0	[88.4; 100.0]
Sheha (2018, abs); SOF + LDV	20	20	100.0	[83.2; 100.0]
Wirth (2017); SOF + RBV	13	13	100.0	[75.3; 100.0]
Yakoot (2018); SOF + DCV	29	30	96.7	[82.8; 99.9]
Duration = 16_24				
Almas Hashmi (2017); SOF +RBV	34	34	100.0	[89.7; 100.0]
Dhiman (2019); SOF + DCV + RBV	2	2	100.0	[15.8; 100.0]
Gill (2018, abs); SOF + RBV	42	47	89.4	[76.9; 96.5]
Hassan (2019, abs); SOF + RBV	5	5	100.0	[47.8; 100.0]
Jonas (2019); GLC + PIB	3	3	100.0	[29.2; 100.0]
Leung (2018); OBV + PTV + r + DSV + RBV	1	1	100.0	[2.5; 100.0]
Murray (2018); SOF + LDV	1	1	100.0	[2.5; 100.0]
Murray (2018); SOF + LDV + RBV	2	2	100.0	[15.8; 100.0]
Nagral (2019); SOF + DCV + RBV	1	1	100.0	[2.5; 100.0]
Rosenthal (2020); SOF + RBV	8	8	100.0	[63.1; 100.0]
Rosenthal (2020); SOF + RBV	28	28	100.0	[87.7; 100.0]
Wirth (2017); SOF + RBV	38	39	97.4	[86.5; 99.9]
Duration = Mixed				
Al–Kaaby (2018); SOF + LDV ± RBV	20	22	90.9	[70.8; 98.9]

50 60 70 80 90 100

Indolfi G et al. *AP & T* 2020.

Defer no more: advances in the treatment and prevention of chronic hepatitis C virus infection in children

Honegger, Jonathan R.[a,b,c]; Gowda, Charitha[a,b,d]



- Addressing HCV in the youngest is needed for HCV elimination.
- Over 3.2 million children worldwide are chronically infected with HCV [2].
- MTCT accounts for most paediatric HCV infections, with iatrogenic transmission in some low-middle income countries (LMICs) and adolescent IDU also contributing
- Perinatally acquired HCV infection establishes chronicity in 60–75% of cases [8,9]. Cirrhosis reported in only 1–2% by age 20 [8–11], but if left untreated, the risk of advanced fibrosis accelerates substantially in adulthood [12].
- Successful treatment of HCV during childhood can avert long-term consequences and further transmission.

Honegger, J al. *Current opinion Infectious Diseases 2022*.

What are recommendations for Screening During Pregnancy?

The history of viral hepatitis screening recommendations in pregnancy..

- **1984** – High risk screening for hepatitis B (HBV) recommended – Ineffective
- **1991** – Universal screening for HBV recommended
- **1998 – 2011** - Cross-sectional analysis of deliveries using Nationwide Inpatient Sample: HBV rate in pregnant women increased from 57.8 in 1998 to 105.0/ 100,000 deliveries in 2011 (*annual increase of 5.5%)*
- ***Prior to 2018:*** **Risk based screening for HCV during pregnancy recommended by all societies (ACOG, AASLD, CDC)**

What do the experts say now?

Guideline (Year)	Recommendation
AASLD/ IDSA (2018)	***All pregnant women*** *should be tested for HCV infection*
USPSTF (2020)	Test **all asymptomatic adults (including pregnant persons),** aged 18-79 years
CDC (2020)	*Hepatitis C screening is recommended for* ***all pregnant women*** *during each pregnancy* ***except in settings where the prevalence of HCV infection is < 0.1%"***
ACOG (5/2021)	Hepatitis C screening during the first prenatal blood assessment obtained in **every pregnancy** is recommended to identify pregnant individuals with HCV infection and infants who should receive testing at a pediatric visit.
SMFM (9/2021)	*We recommend that obstetric providers* ***screen all pregnant patients for HCV*** *in every pregnancy*

Summary of recommendations for viral hepatitis Screening in pregnancy

- Screen all patients for HCV with HCV Ab and reflex HCV RNA
- Screen all patients for HBV with HBsAg
  - If positive, check HBV DNA
  - If positive, screen for delta hepatitis with HDV Ab
- Counsel patients that screen positive:
  - Known association with pregnancy outcomes
  - Risk of mother-to-child transmission
  - Treatment recommendations
  - Linkage to care postpartum

But is HCV screening actually being done during prenatal care?

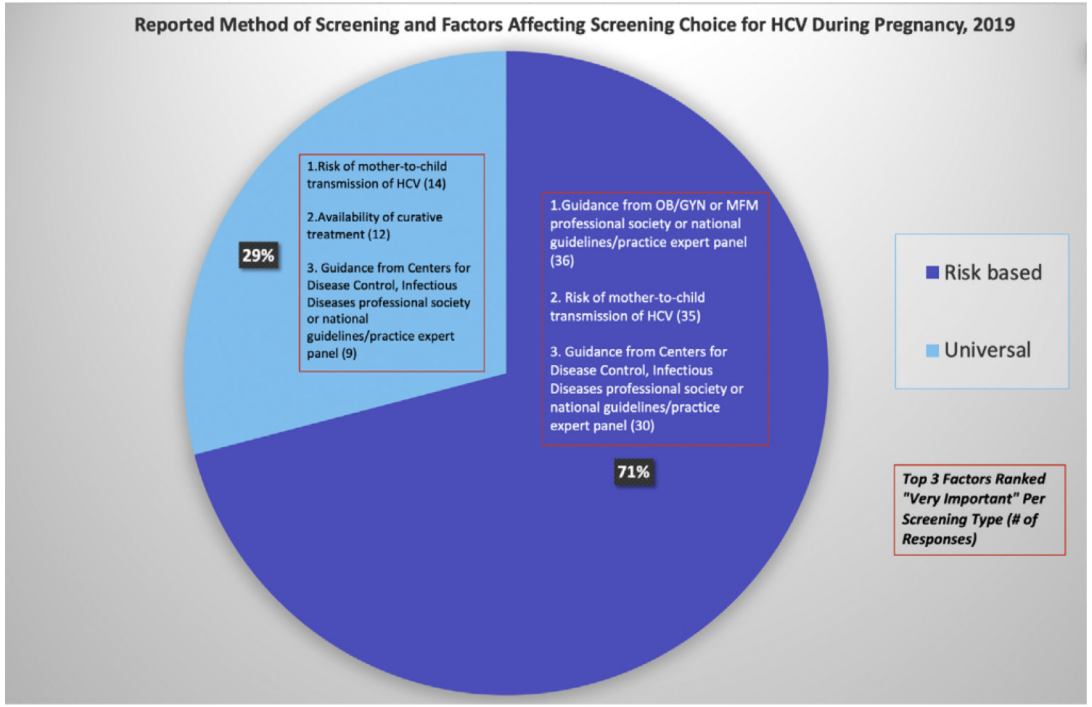
Clinical Therapeutics/Volume xxx, Number xxx, xxxx

A Survey of Practices in the United States Regarding Hepatitis C Screening in Pregnant Women

Elizabeth A. Godar, MD[1]; and Ravi Jhaveri, MD[2]

Division of Infectious Diseases, Department of Pediatrics, School of Medicine, University of North Carolina, Chapel Hill, NC, USA

- Survey distributed to Prenatal Care providers in the US
  - 86 completed surveys (1% response rate)



Godar EA and Jhaveri R. *Clinical Therapeutics* 2021.

Have the universal screening recommendations changed practice?

- Retrospective study using Quest laboratory data, 2011-2021

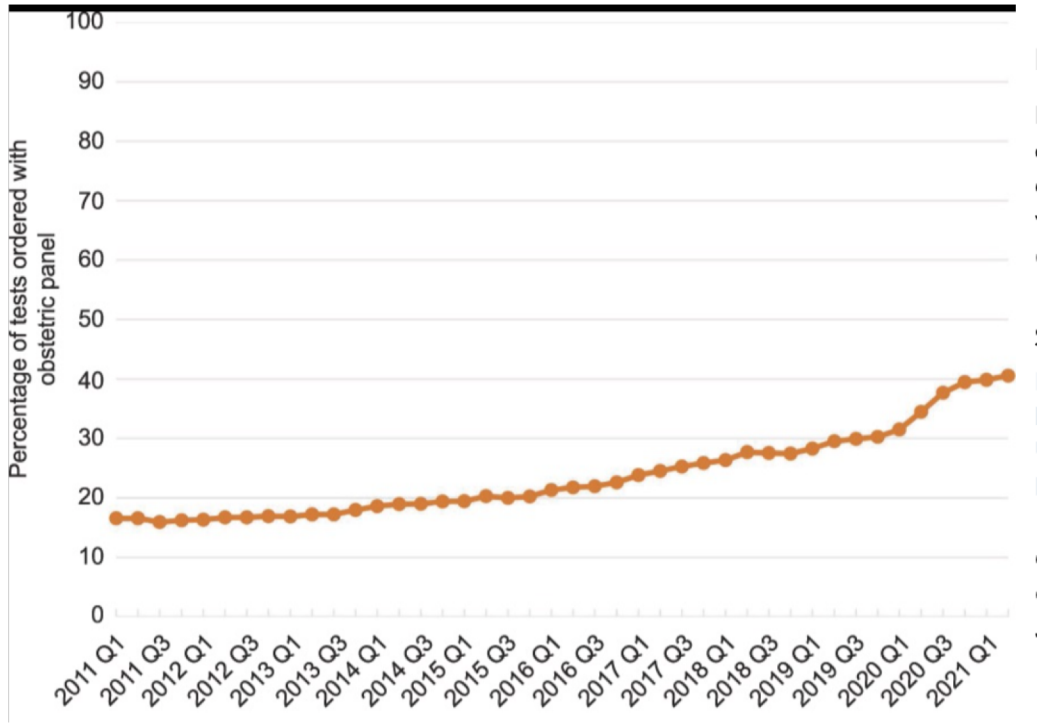
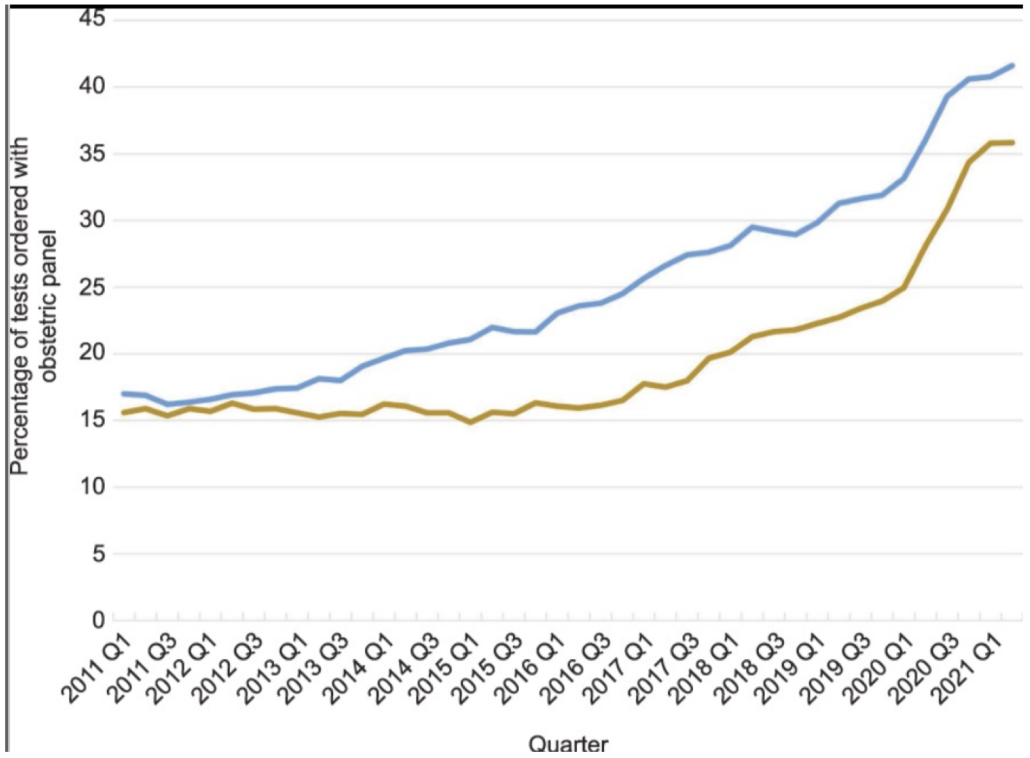


Fig. 1.
Pregnant persons with an obstetric panel test combined with hepatitis C virus antibody screens (percentage): quarter (Q) 1 2011 through Q2 2021.



Pregnant persons with an obstetric panel test combined with hepatitis C virus antibody screens (percentage), by commercial insurance (*blue line*) and Medicaid insurance (*brown line*).

Kaufman H et al. *Obstetrics and Gynecology* 2022.

Patient-level barriers may also exist..

- Compared with whites, women of Latina (OR 0.45 [95% CI 0.37-0.55]; $P < 0.001$) and Asian (OR 0.74 [95% CI 0.58-0.94]; $P = 0.01$) race were less likely to receive HCV screening.
- African American (AA) → less likely to receive quality prenatal care and preventative services
  - Pregnancy morbidity and mortality disproportionately affect AA women

Programs designed to address individual-level, interpersonal-level, community-level, and system-level factors are needed to improve uptake of HCV screening

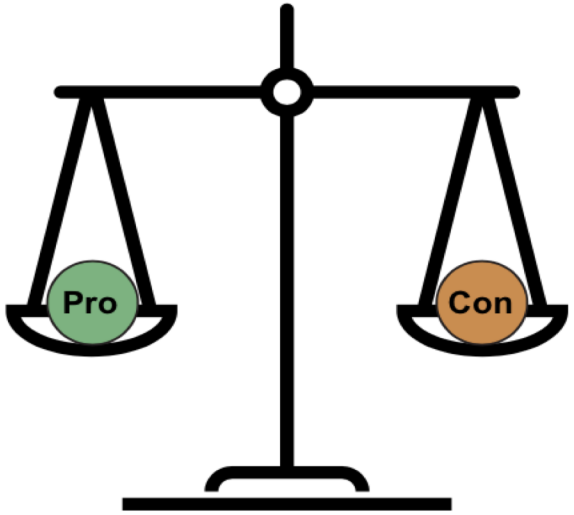
Kim N et al. *Hepatology Communications* 2019.

Prater C et al. *Health Equity* 2018.

Is there a role for Antiviral Therapy During Pregnancy?

How About Antiviral Therapy During Pregnancy?

Treatment with DAAs during pregnancy



1. Maternal cure while engaged in pregnancy care
2. Possible decrease in MTCT
3. Maternal treatment while under insurance coverage
4. Decrease in community transmission
5. Potential decrease in HCV-associated adverse pregnancy outcomes?

1. Human safety in pregnancy not established
2. Safety during breastfeeding not established
3. More established data for treatment prior to pregnancy or children starting at age 3
4. Difficulty in accessing DAA therapy in time (prior to delivery)
5. Cost-effectiveness not established

Kushner T & Reau N. *Journal of Hepatology* 2021.

What are the experts saying?

AASLD
AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C

IDSA
Infectious Diseases Society of America

"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."

AASLD/ IDSA HCV Guidance 2020.

"Women who become pregnant while on DAA therapy (with or without ribavirin) should discuss the risks versus benefits of continuing treatment with their physicians."

AASLD/ IDSA HCV Guidance 2021.

Society for Maternal-Fetal Medicine
High-risk pregnancy experts

SMFM Consult Series

smfm.org

"We recommend that DAA regimens only be initiated in the setting of a clinical trial during pregnancy and that people who become pregnant while taking a DAA should be counseled in a shared decision-making framework about the risks and benefits of continuation"

Am J Obstet Gynecol 2021

Are direct acting antivirals safe in pregnancy?

DAA therapy		Prenatal and postnatal development		Placental transfer		Lactation
DAA combination	Drug	Safety concerns?	Tested animal species (Dose and duration)	Transfer across placenta	Tested animal species (% of maternal plasma levels)	Transfer into milk[a] (% of maternal plasma levels)
SOF/DAC	SOF[b]	No	Rats: 10x RHD, GD6-18, GD6-LD20 Rabbits: 28x RHD, GD6-19	Yes	Rats	Yes (80%)
	DAC	Yes[c]	Rats: 4x RHD, GD7-19 Rabbits: 16x RHD, GD6-15	Yes	Rats	Yes (170%-200%)
SOF/LDV	SOF[b]	No	Rats: 10x RHD, GD6-18, GD6-LD20 Rabbits: 28x RHD, GD6-19	Yes	Rats	Yes (80%)
	LDV	Possible[c]	Rats: 4x RHD, GD6-18 Rabbits: 2x RHD, GD7-20	Unknown	Not tested	Yes
SOF/VEL SOF/VEL/VOX	SOF[b]	No	Rats: 10x RHD, GD6-18, GD6-LD20 Rabbits: 28x RHD, GD6-19	Yes	Rats	Yes (80%)
	VEL	Possible[d]	Rats: 6x RHD, GD6-17, GD6-LD20 Rabbits: 0.5-0.7x RHD, GD7-20 Mice: 31x RHD, GD6-15	Not evident	Rats	Yes (173%)
	VOX	No	Rats: 141x RDH, GD6-LD20 Rabbits: 4x RHD, GD7-19	Unknown	Not tested	Yes
GZR/ELB	GZR	No	Rats: 117x RHD, GD6-20, GD6-LD20 Rabbits: 41x RHD, GD7-20	Yes	Rats (89%) Rabbits (7%)	Yes (400%)
	ELB	No	Rats: 10x RHD, GD6-20, GD6-LD20 Rabbits: 18x RHD, GD7-20	Yes	Rabbits (0.8%) Rats (2.2%)	Yes (87%)
GLE/PIB	GLE	Possible[e]	Rats: 53x RHD, GD6-18, GD6-LD20 Rabbits: 0.07x RHD, GD7-19	Yes	Rats	Yes (<8%)
	PIB	No	Rabbits: 1.5x RHD GD7-19 Mice: 51x RHD GD6-15, GD6-LD20	Yes	Mice	Yes (150%)

Freriksen, et al. *AP&T, 2019.*

Would women consider HCV treatment during pregnancy?

- Survey of 141 women with HCV at UCSF and WIHS
  - 60% of women said they would take DAA if it lowered risk of MTCT
  - 21% they would take during pregnancy for self-cure; 20% said they would consider it if there was more data

Kushner T, et al. *Hepatology Communications*, 2018.

HEPATOLOGY

AASLD
AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

SPECIAL ARTICLE | HEPATOLOGY, VOL. 74, NO. 3, 2021

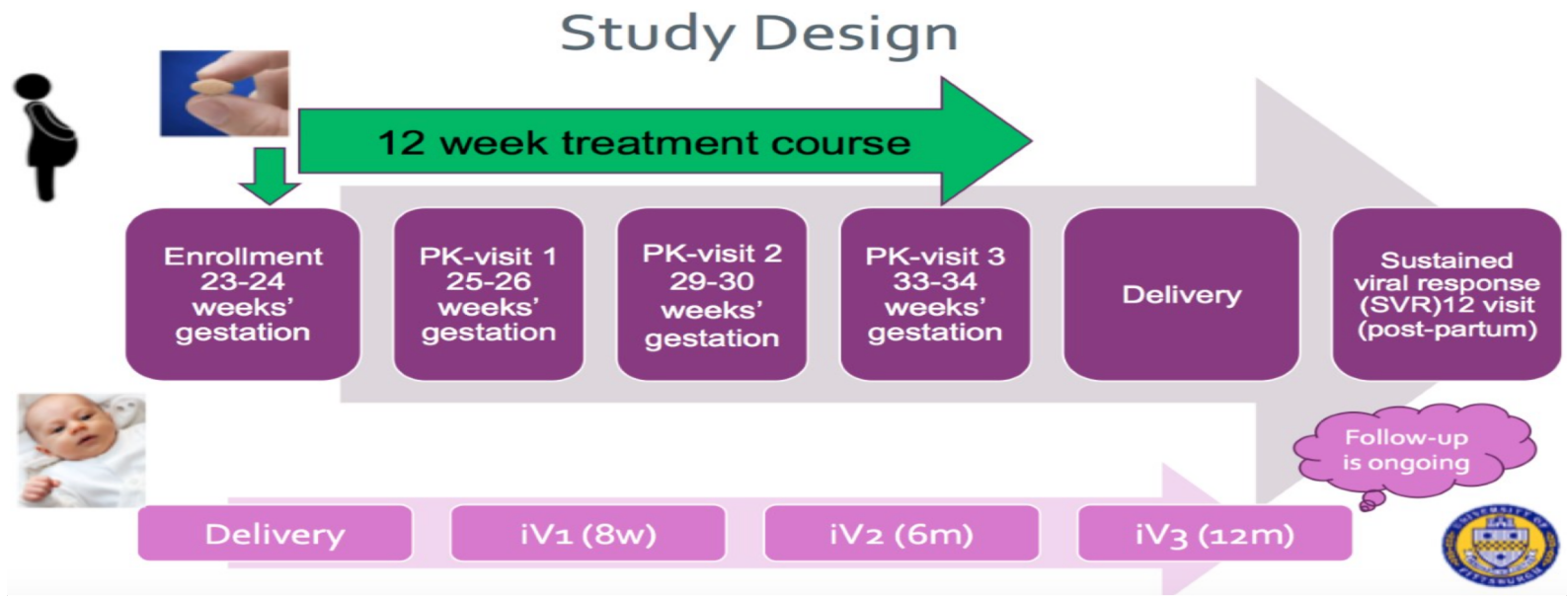
Responsible Inclusion of Pregnant Individuals in Eradicating HCV

Ravi Jhaveri [1,2] Lynn M. Yee,[3] Swati Antala,[1,4] Margaret Murphy,[1,5] William A. Grobman,[3] and Seema K. Shah[1,6]

- Recent guidelines recommend that research with pregnant individuals be “promoted”
  - US Federal regulations governing research removed pregnant individuals from list of “vulnerable populations”
- Exclusion without justification denies pregnant individuals and fetuses access to potential health benefits
- There are critical evidence gaps in treatment of pregnant individuals
- There are clear benefits to initiate HCV treatment during pregnancy

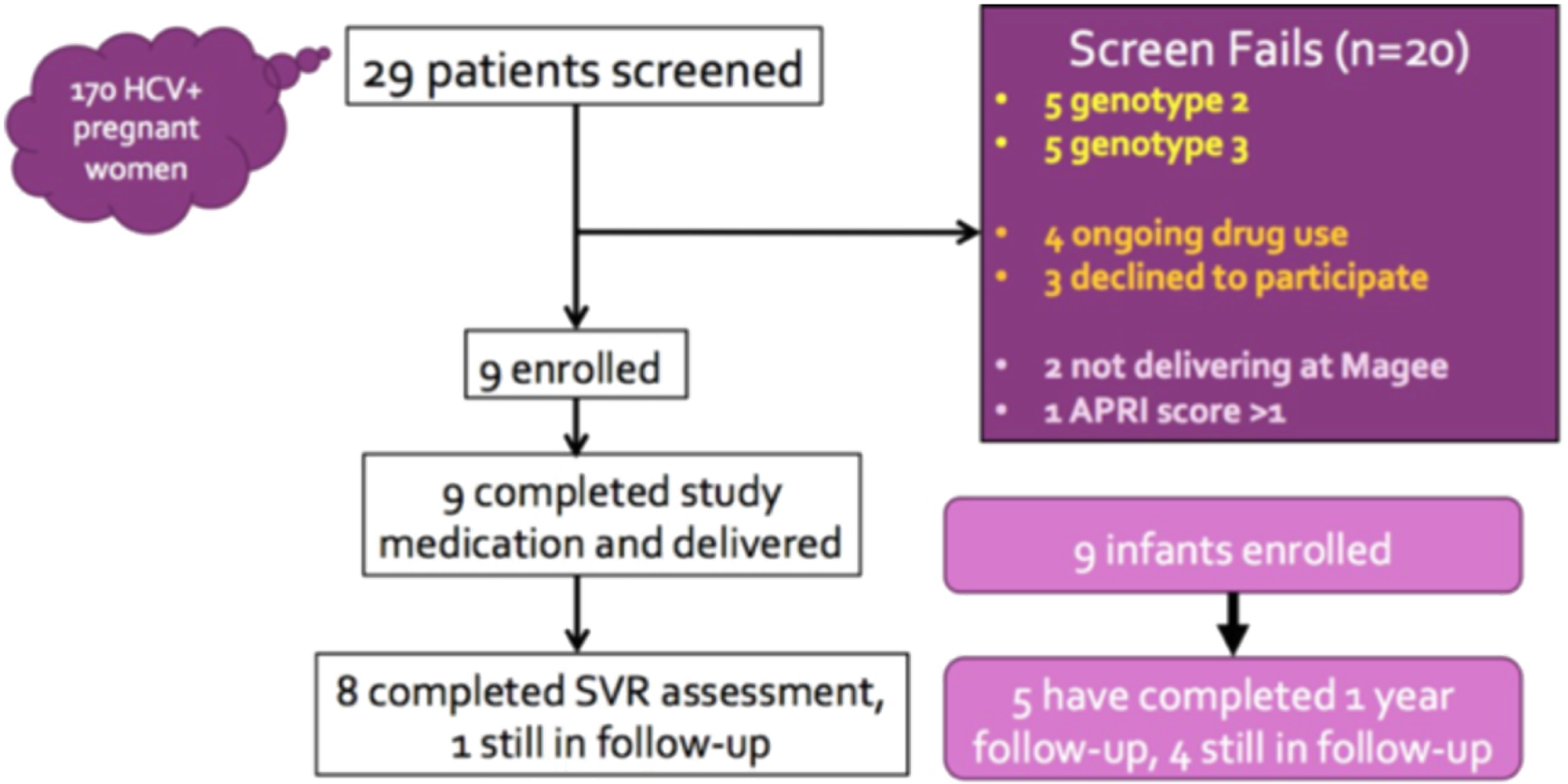
First Trial of HCV Treatment During Pregnancy

- Phase 1 Study of Ledipasvir/ Sofosbuvir in Pregnant Women with HCV Virus
  - Primary Objective
    - To define the safety and virologic response to ledipasvir/ sofosbuvir in pregnancy



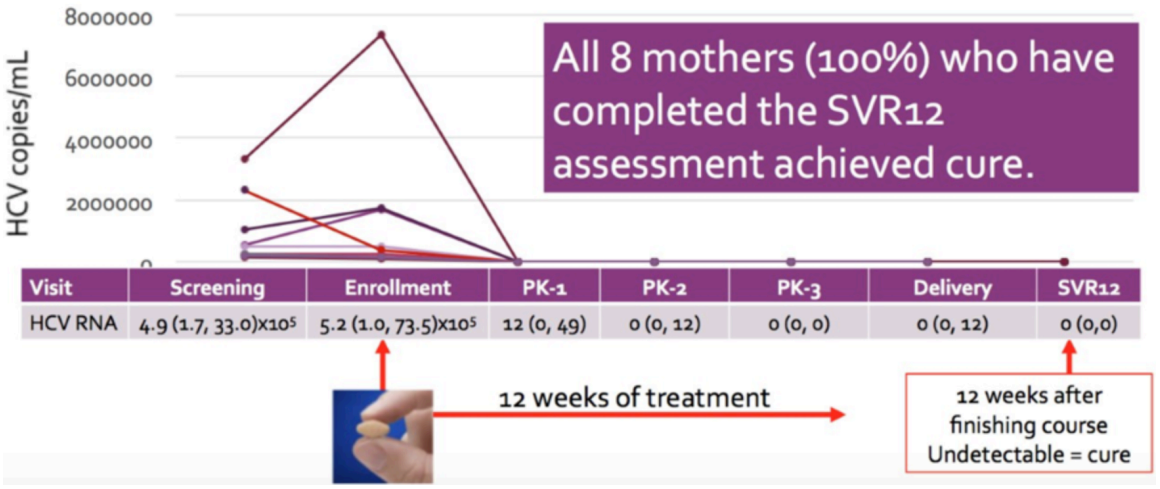
Chappell C, et al. *CROI*, March 2019.

Trial of HCV Treatment During Pregnancy



Trial of HCV Treatment during Pregnancy

Results



Pregnancy and Delivery Outcomes

Outcome	N (%) or Median (Range)
Maternal Related Adverse Events	5 (56%)
Maternal Related Adverse Events >Grade 2	0 (0%)
Vaginal Delivery	5 (56%)
Gestational age at delivery (weeks + days)	39+2 (36+6, 41+0)
Birth weight (g)	3,290 (2,600, 4,160)
Infant Length of Hospital Stay (days)	3 (2, 12)
Infant Related Adverse Events	0 (0%)
Infant HCV RNA at Last Visit (copies/mL)	0 (0, 0)

Chappell C, et al. *Lancet Microbe 2020*.

Our experience with treatment of HCV in pregnant people..

- 23 pregnant women with active HCV infection were referred to our Women's Liver Clinic for consideration for HCV treatment

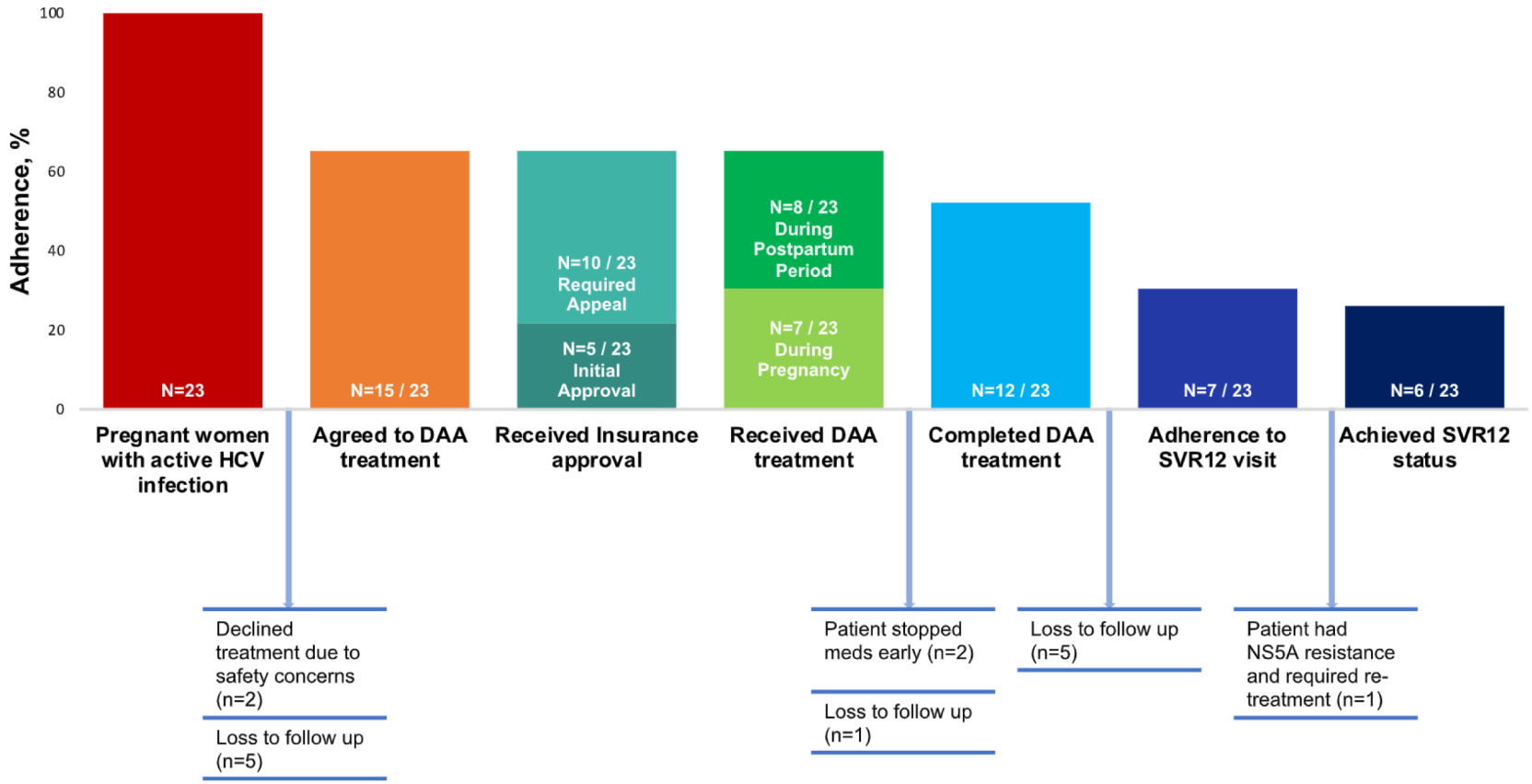


Figure 1. Compliance with steps in the HCV pregnancy cascade of care.

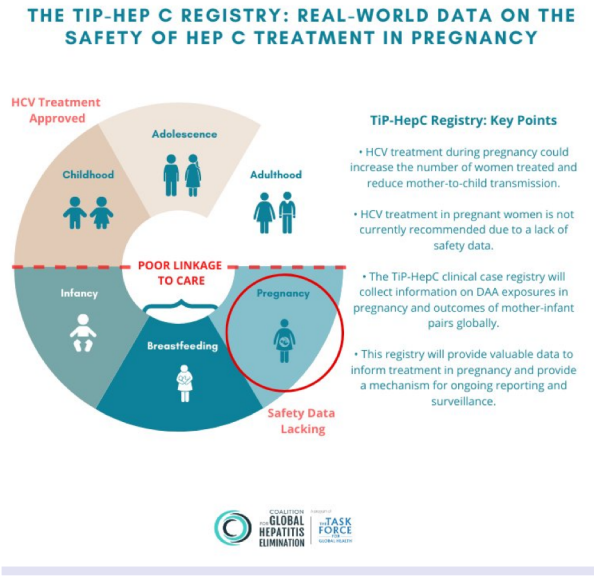
Kushner T, et al. *Gastroenterology 2022*.

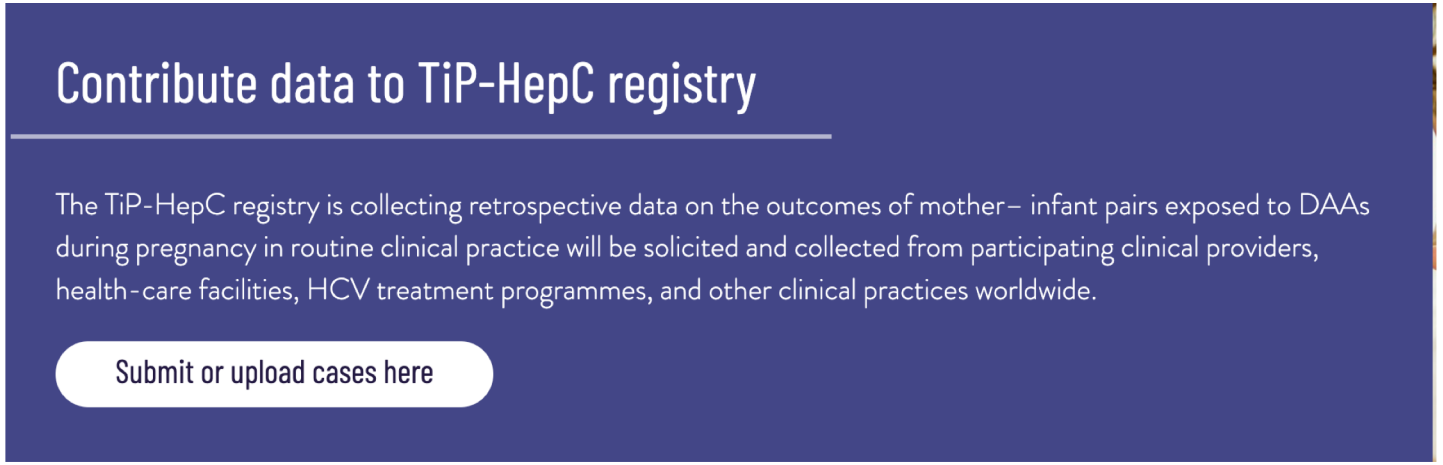
Sofosbuvir/Velpatasvir Treatment of Chronic Hepatitis C During Pregnancy (STORC)

- Phase 4, multicenter study, single arm study of Sofosbuvir/Velpatasvir (SOF/VEL) for treatment of chronic hepatitis C infection during pregnancy (NCT05140941)
  - Goal to recruit 100 patients
  - Treatment during 2nd and 3rd trimester of pregnancy with Sof/ Vel for 12 weeks
  - Efficacy and safety evaluated
  - Seven sites in the country: University of Pittsburgh , The Christ Hospital (Cincinnati), Denver Health, Mount Sinai (New York), University Health Network (Toronto), University of Utah
  - **Recruitment is under way!**

Treatment in Pregnancy for Hepatitis C (TiP-HepC-registry)

- Established by the CDC and Coalition for Global Hepatitis Elimination- publicly launched in June 2022
  - Collects clinical information and case reports about DAAs use in pregnancy
  - https://www.globalhep.org/evidence-base/treatment-pregnancy-hepatitis-c-tip-hepc-registry





Summary

- HCV among women of childbearing potential and during pregnancy is on the rise as a result of the opioid epidemic
- Universal screening for HCV recommended in pregnancy
- HCV increases the risk of cholestasis of pregnancy and other adverse pregnancy outcomes
- Mother-to-child transmission rates range from 6-11%
- All children of mothers with HCV should be tested at 18 months of age and referred to specialty care as needed
- Treatment is currently recommended in children ≥3 years of age
- Studies of HCV treatment during pregnancy are under way – will also need to find ways to maintain engagement during the vulnerable pregnancy period

Thank you!

Questions?

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