Addressing HCV across the reproductive life span in women: from data to joint decision-making

National AIDS Treatment Advocacy Project (NATAP)

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Disclosures

- Advisory and consulting for Gilead, Abbvie, Bausch, Eiger, GSK.
- Research support to institution from Gilead

Outline

1. Considerations for Screening and treatment for hepatitis C (HCV) in women of reproductive age
2. Updates and gaps in HCV screening in pregnancy
3. Influence of HCV on pregnancy outcomes and vertical transmission
4. Current data and new studies evaluating direct acting antivirals in pregnancy
5. Integrated approaches to optimize care of women with HCV after pregnancy
6. Implications of HCV exposure on children and updated approaches to their screening and treatment

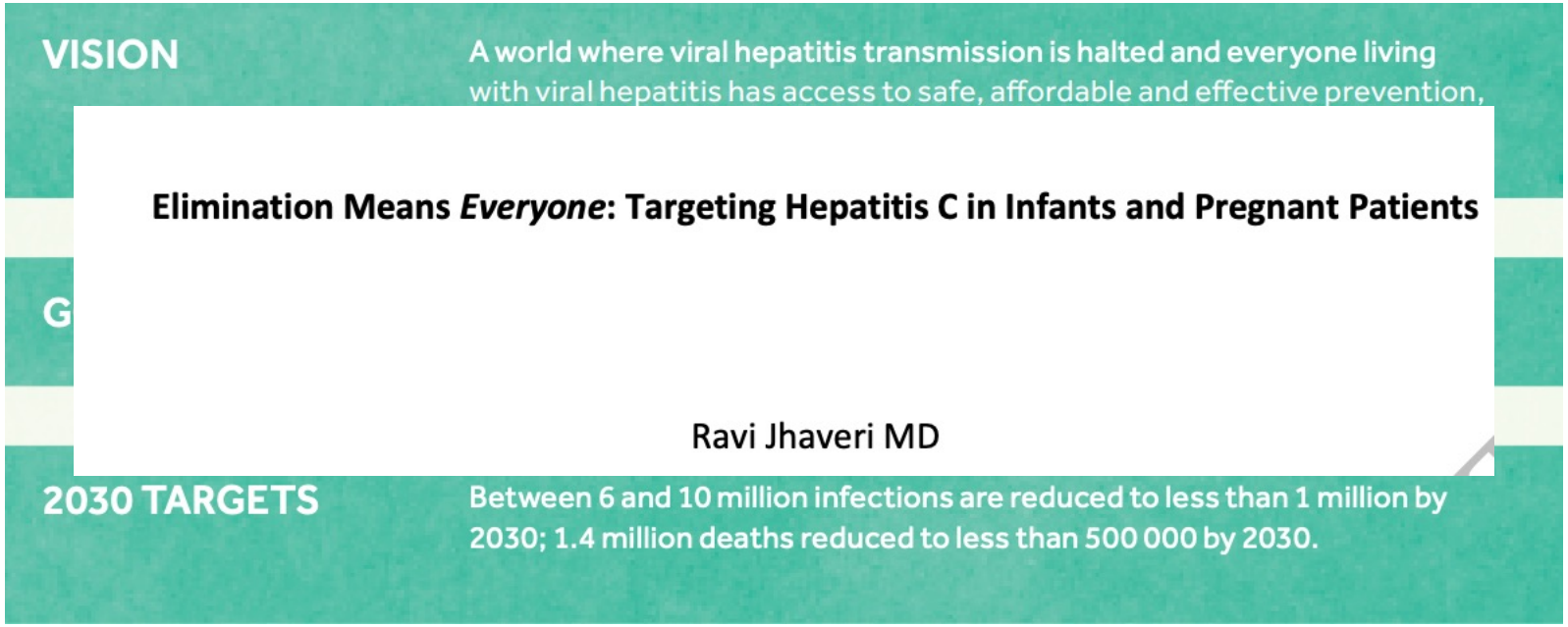
Acknowledging Statement

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..

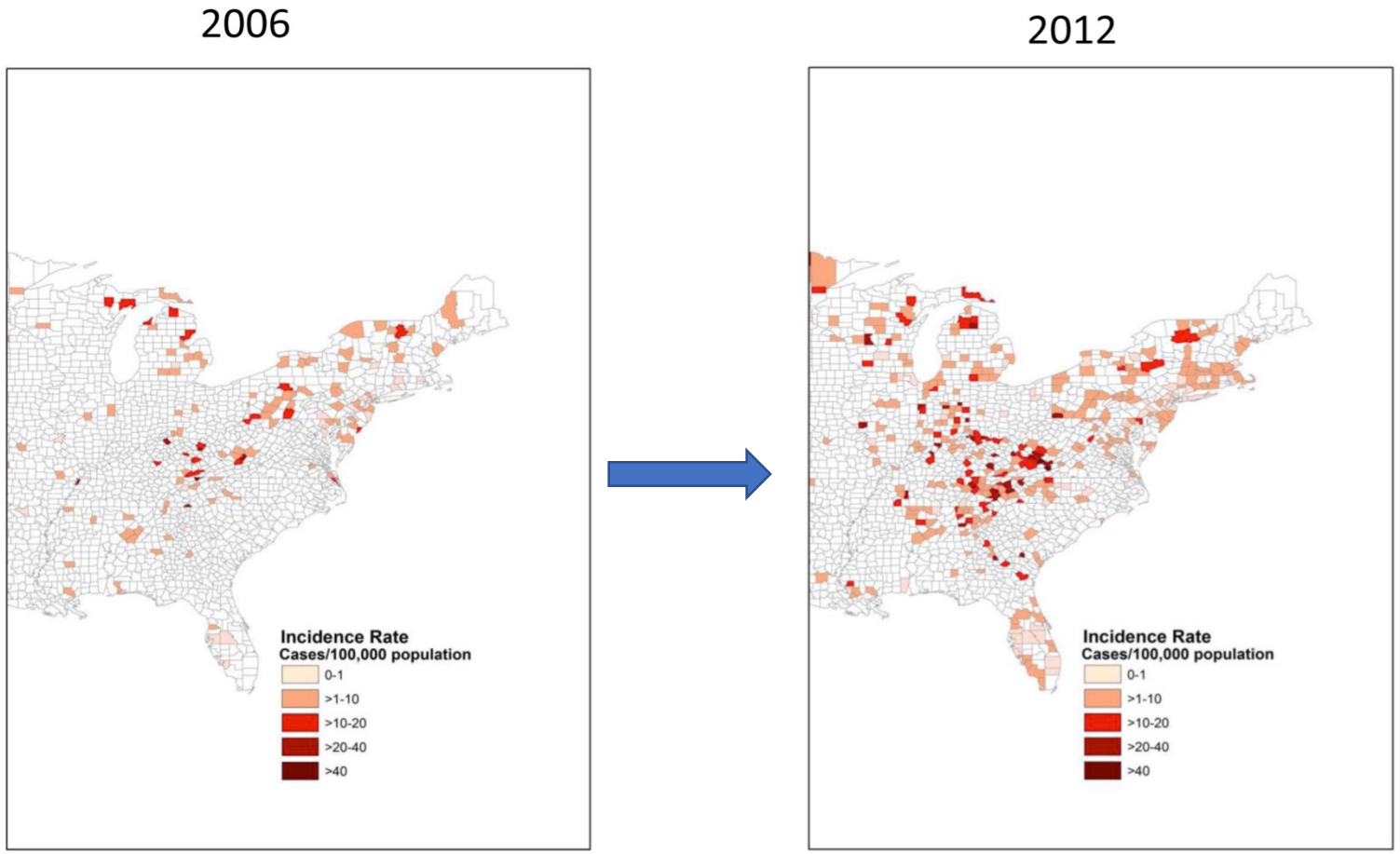
Global Health Strategy on Viral Hepatitis

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."

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

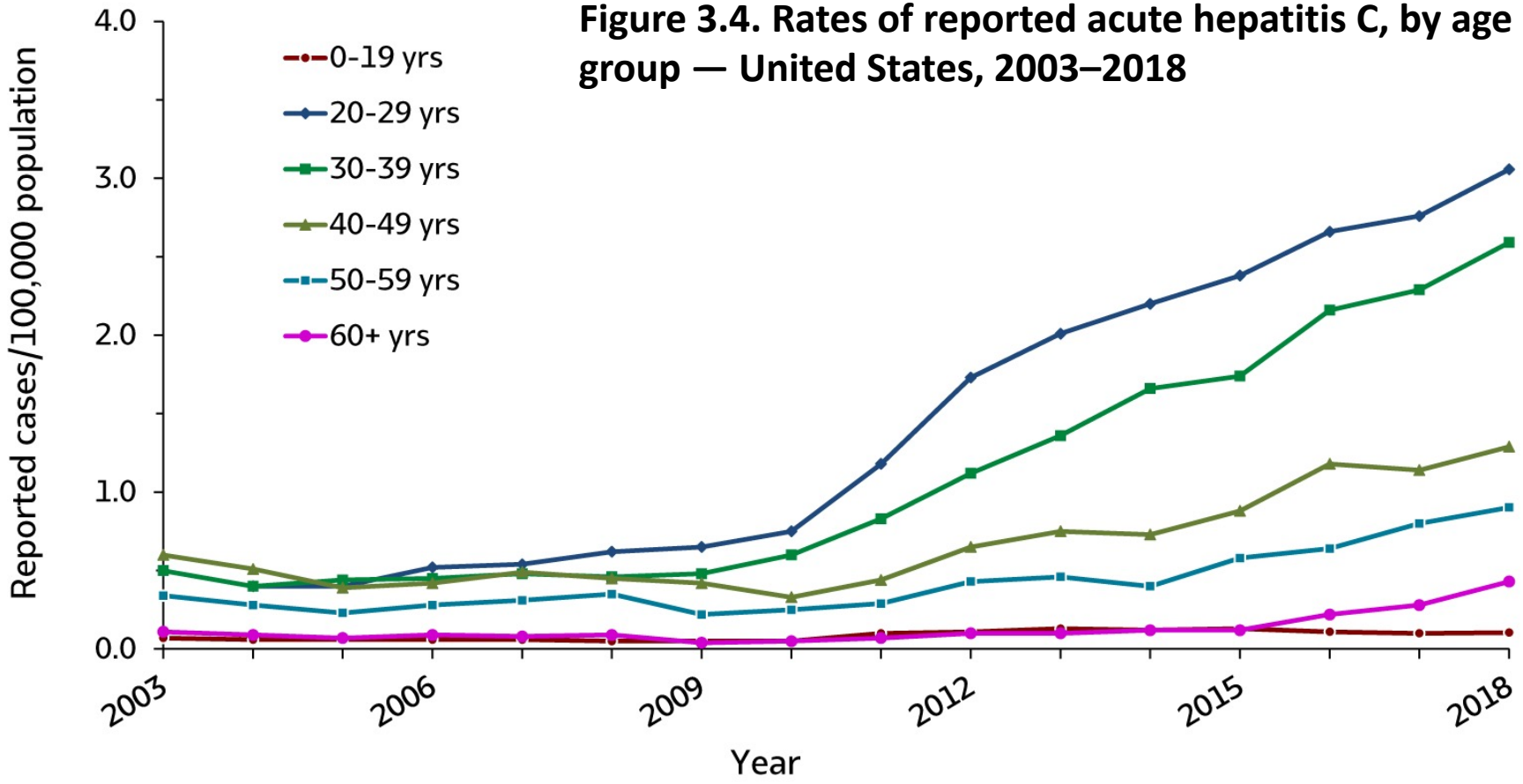


- HCV: 13% annual increase rural; 5% annual increase urban
- Regional doubling of first-time heroin users
- 3 of 4 with HCV had history of prescription opioid abuse
- 97% initiated drug use before age 20

Suryaprasad AG. *Clin Infect Dis 2014.*

The Epidemiology Of HCV Is Changing

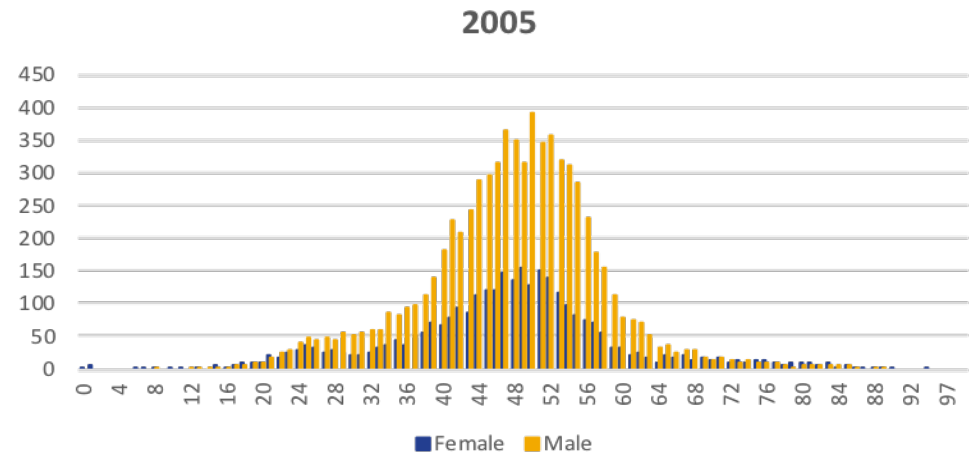
Figure 3.4. Rates of reported acute hepatitis C, by age group — United States, 2003–2018

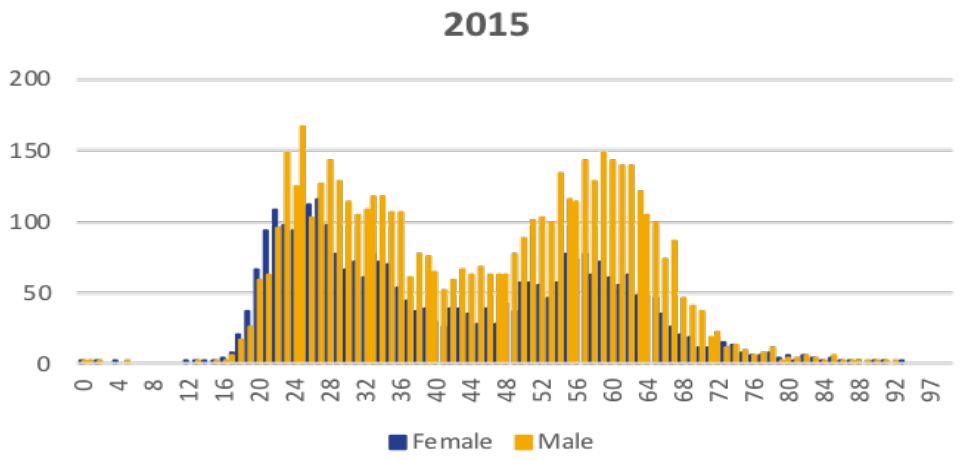


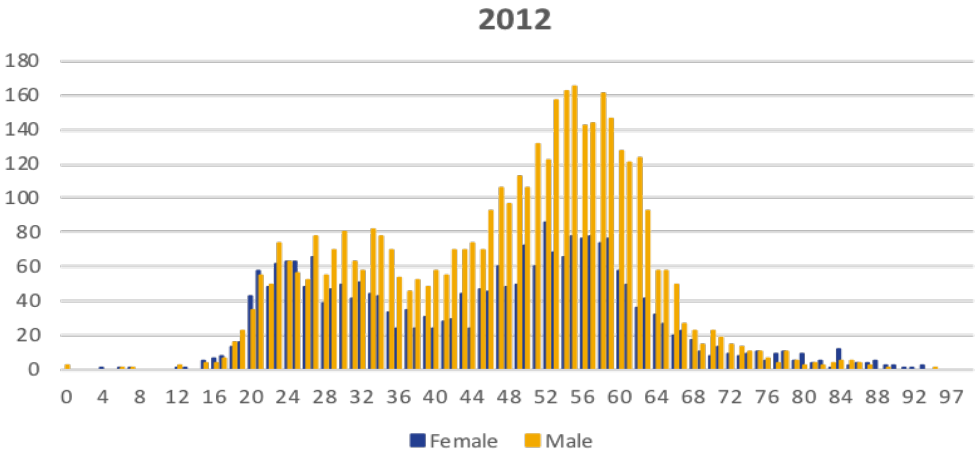
Highest incidence in 20-29 age group

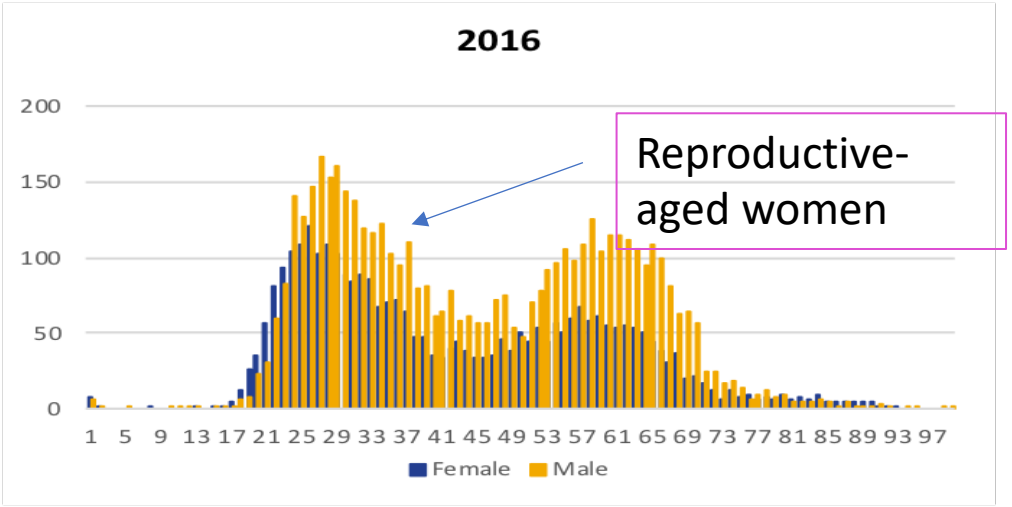
https://www.cdc.gov/hepatitis/statistics/2018surveillance/HepC.htm#Figure3.4

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







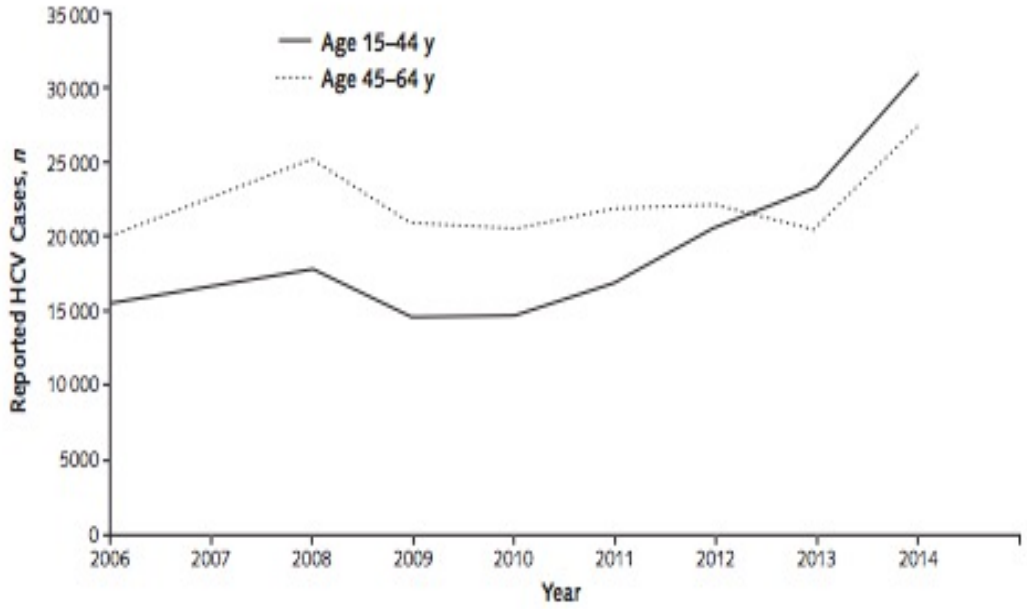


Slide courtesy of NYS DOH Bureau of Viral Hepatitis.

Hepatitis C in women

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*

Substance use in women of childbearing age

- Substance use affects 1/5 pregnant individuals; 15% with SUD
- SUD is stigmatized in women, particularly in perinatal period
- Ob/GYNs are positioned to leverage maternal motivation for change to increase the number of individuals with treated addiction in pregnancy

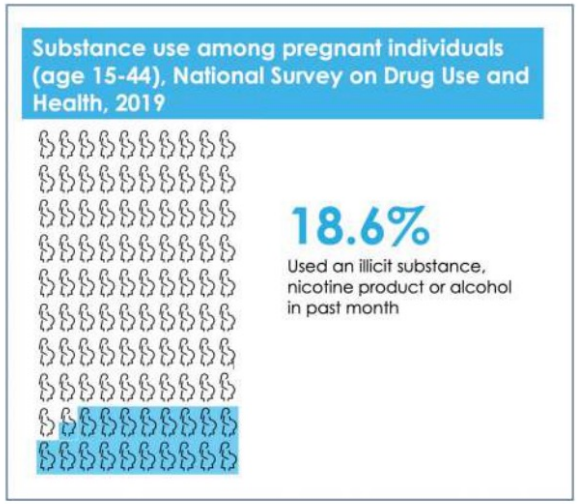


Fig. 1. Proportion of pregnant individuals with past-month substance use, National Survey on Drug Use and Health, 2019.

Overdose is a leading cause of maternal death in the United States.

Smid M, et al. Obstetrics & Gynecology 2022

Substance use across reproductive life span

Antepartum → During Pregnancy → Postpartum

64% of nonpregnant reproductive-aged individuals report past- month substance use

18% of Pregnant individuals report past- month substance use

-Use for all substances decreases by pregnancy trimesters→ remission in pregnancy

- Hormonal changes affect brain's reward-reinforcement pathways

Vulnerable period; high rates of return to use

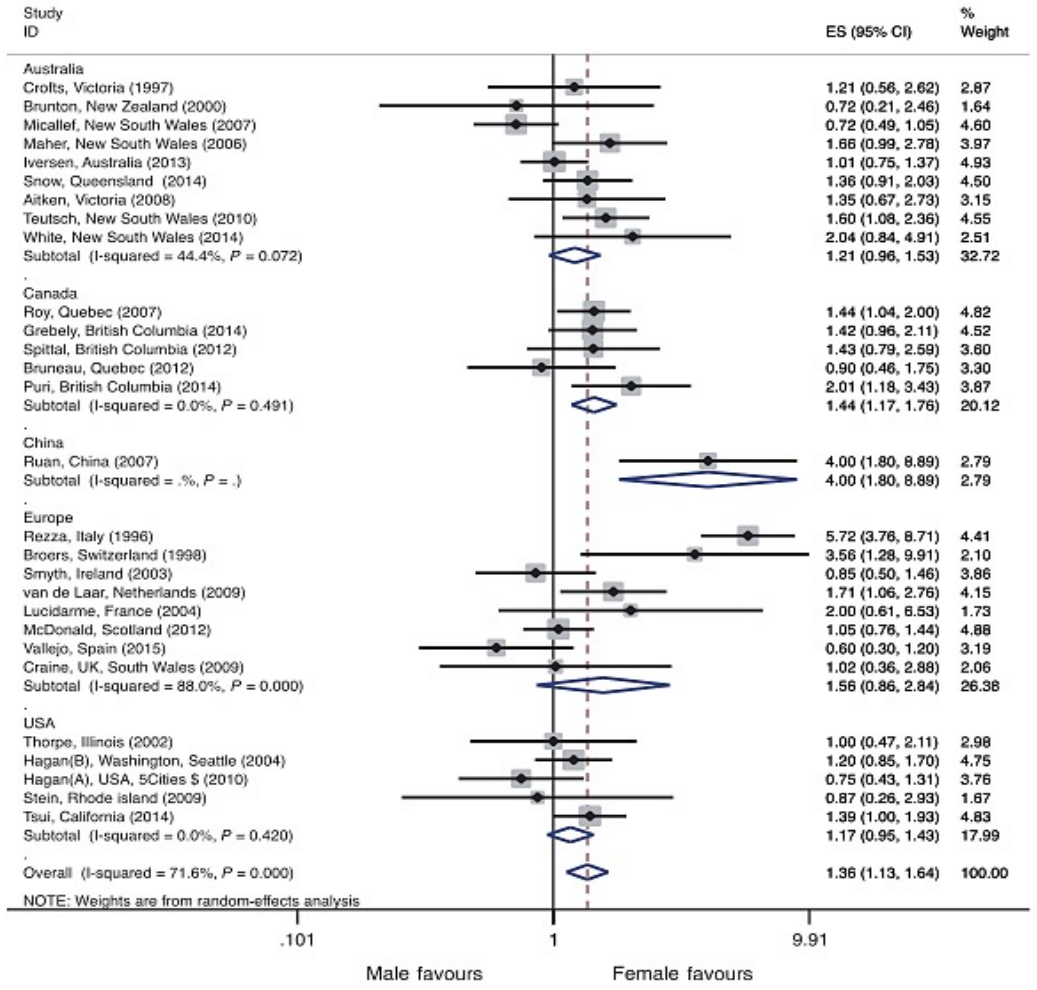
- SUD symptoms (e.g. cravings) recur
- Postpartum physiologic and mental health changes
- Demands of newborn care
- Child welfare involvement
- Strain on relationships and finances
- Grief over loss of a child
- System factors: treatment disengagements, discrimination, clinician lack of knowledge, inaccessible SUD treatment for parenting individuals, insurance change or loss

Mounting evidence suggests that for individuals with SUD, the postpartum period is frequently destabilizing

Smid M, et al. Obstetrics & Gynecology 2022

Incidence of HCV Higher in Women Than Men Who Inject Drugs

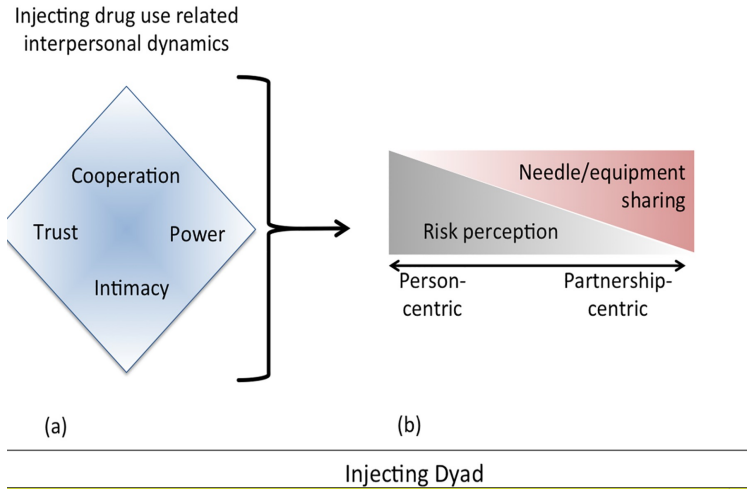
- Meta-analysis of 28 studies with 9,325 persons who inject drugs (PWID)
- Women were **36%** more likely to be anti-HCV positive than males
- Varies by country:
  - Highest in China and Europe
  - **17%** higher in US cohorts



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

Women who inject drugs 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!

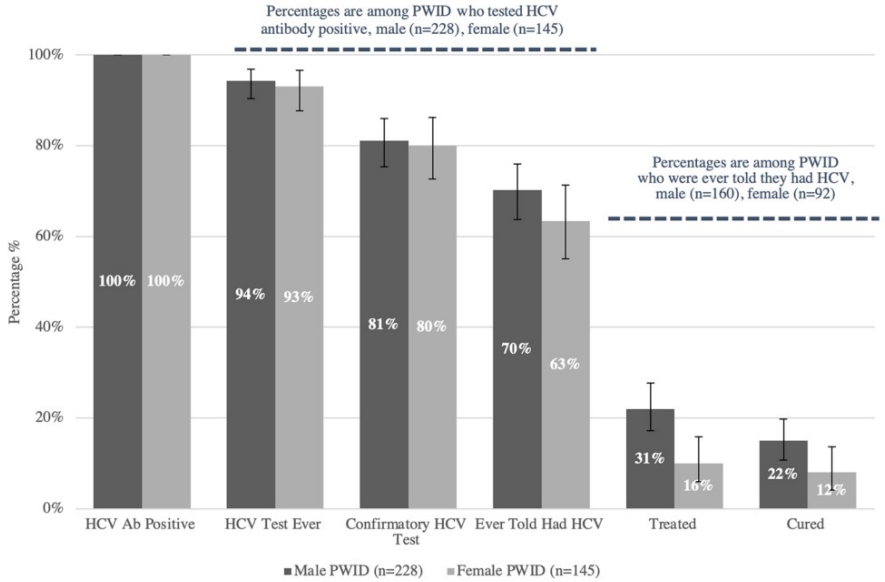
Esmaeili A, et al. *J Viral Hepat 2017.* Morris M, et al. *Plos One 2019*
Evans J, et al. *J Urban Health 2003*

Age and gender-specific hepatitis C continuum of care and predictors of direct acting antiviral treatment among persons who inject drugs in Seattle, Washington

Maria A. Corcoran [a,*], Judith I. Tsui [b], John D. Scott [a], Julia C. Dombrowski [a,c], Sara N. Glick [a,c]

- Survey of 533 PWID; 71% with HCV Ab positive →

Female gender (AOR 0.36, 0.16– 0.78) was associated with a **64 % lower odds of having received treatment with DAAs**



WHY?

- Higher competing priorities (i.e. child and elder care)
- Women PWID suffer from higher rates of depression, have higher rates of self-reported medical conditions, are less educated, and are more likely to have been the victim of physical or sexual abuse
- High rates of unintended pregnancy, transactional sex work, and unstable housing among Seattle area women who inject drugs
- Stigma associated with injection drug use, which may be particularly strong for women who have historically comprised a minority of PWID; implicit bias within the healthcare system may also be contributing

"Additional research is needed to better understand the multiple factors driving lower rates of DAA uptake among female PWID with chronic HCV infection"

Drug and Alcohol Dependence, 2021

So what are the recommendations for HCV in women of childbearing age?

Recommendations for One-Time Hepatitis C Testing	
RECOMMENDED	RATING
One-time, routine, opt out HCV testing is recommended for all individuals aged 18 years or older.	I, B
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).	I, B
Annual HCV testing is recommended for all persons who inject drugs,	

AASLD
AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

IDSA
Infectious Diseases Society of America

How about HCV treatment in women?

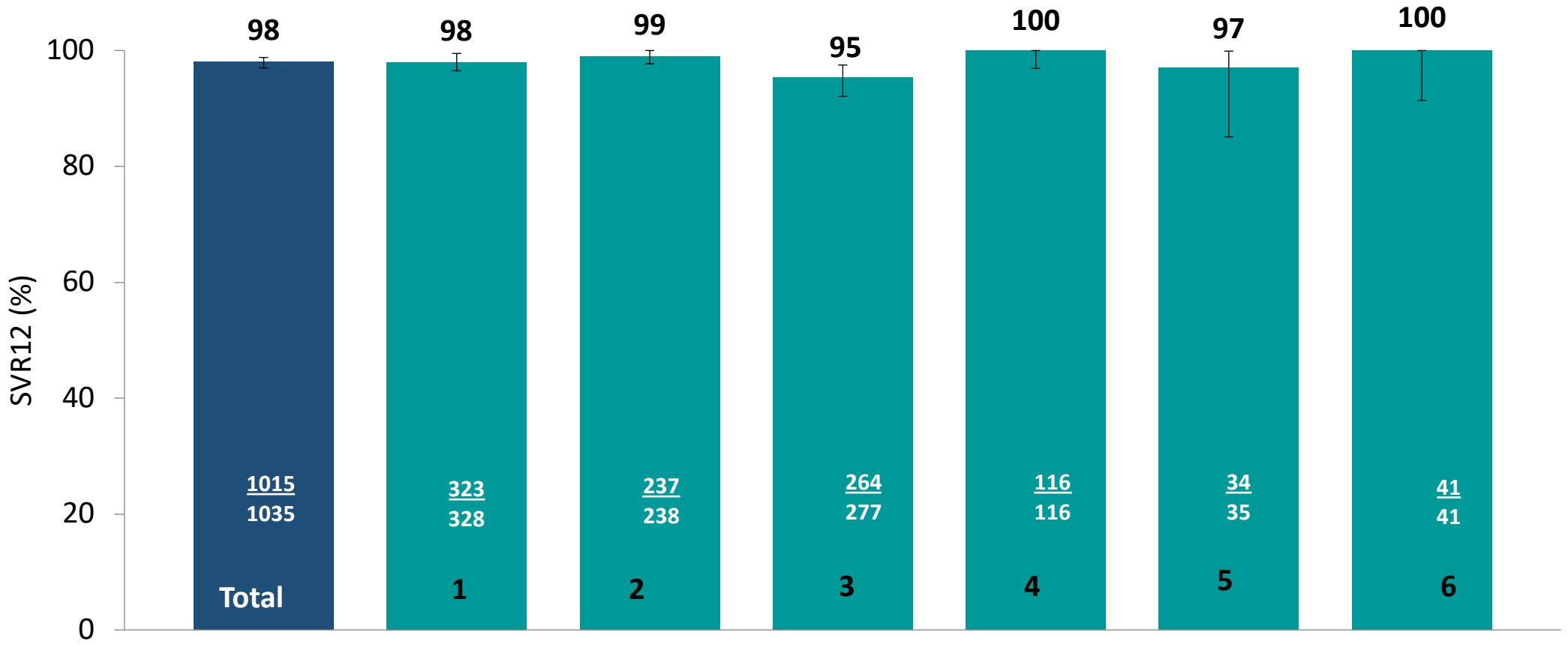
Recommendation Regarding HCV Treatment	
RECOMMENDED	RATING
For women of reproductive age with known HCV infection, antiviral therapy is recommended **before** considering pregnancy, whenever practical and feasible, to reduce the risk of HCV transmission to future offspring.	I, B

Recommended Regimens*

- Glecaprevir (300 mg) / pibrentasvir (120 mg) to be taken with food for a duration of 8 weeks
- Sofosbuvir (400 mg) / velpatasvir (100 mg) for a duration of 12 weeks

Persons with HCV genotype 1, 2, 3, 4, 5, or 6 infection can be effectively treated with 1 tablet daily for 12 weeks

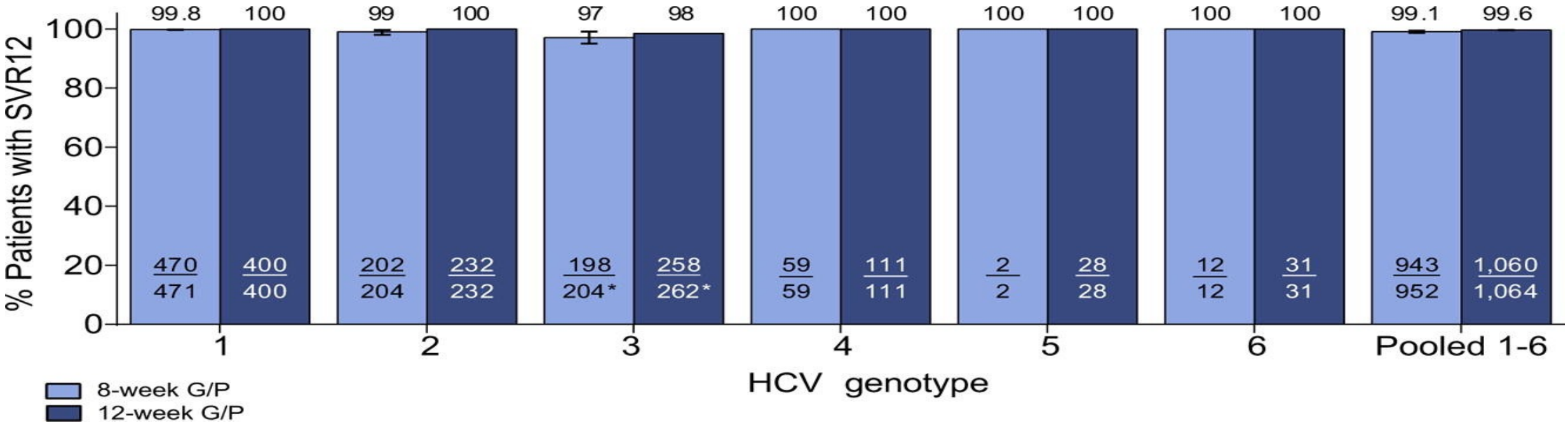
Sofosbuvir/Velpatasvir



Feld JJ et al. NEJM 2016; Foster G et al NEJM 2016

Persons with HCV genotype 1, 2, 3, 4, 5, or 6 infection can be effectively treated with 3 tablets daily for 8 weeks

Glecaprevir/Pibrentasivir



Puoti M et al. Journal of Hepatology (2018); Brown RS et al. Journal of Hepatology (2019)

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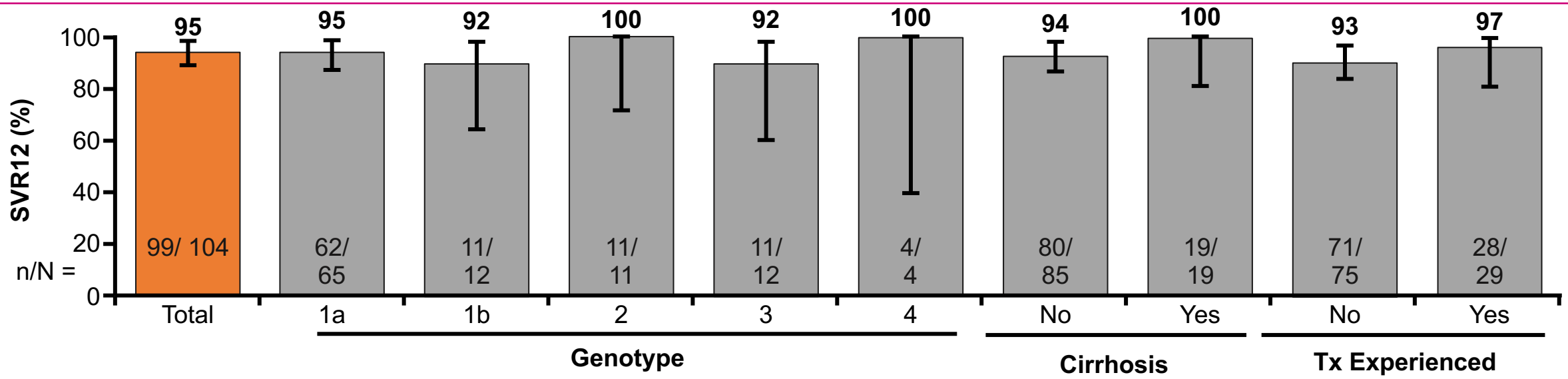
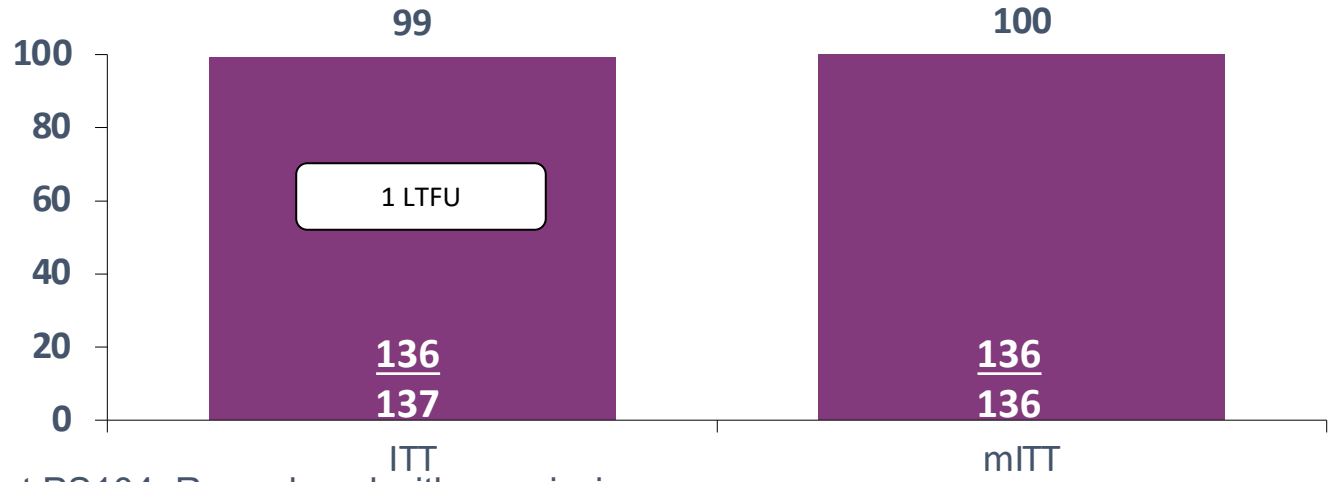
HIV/HCV Coinfected Individuals Have Similar Cure Rates

Sofosbuvir/Velpatasvir x 12 weeks



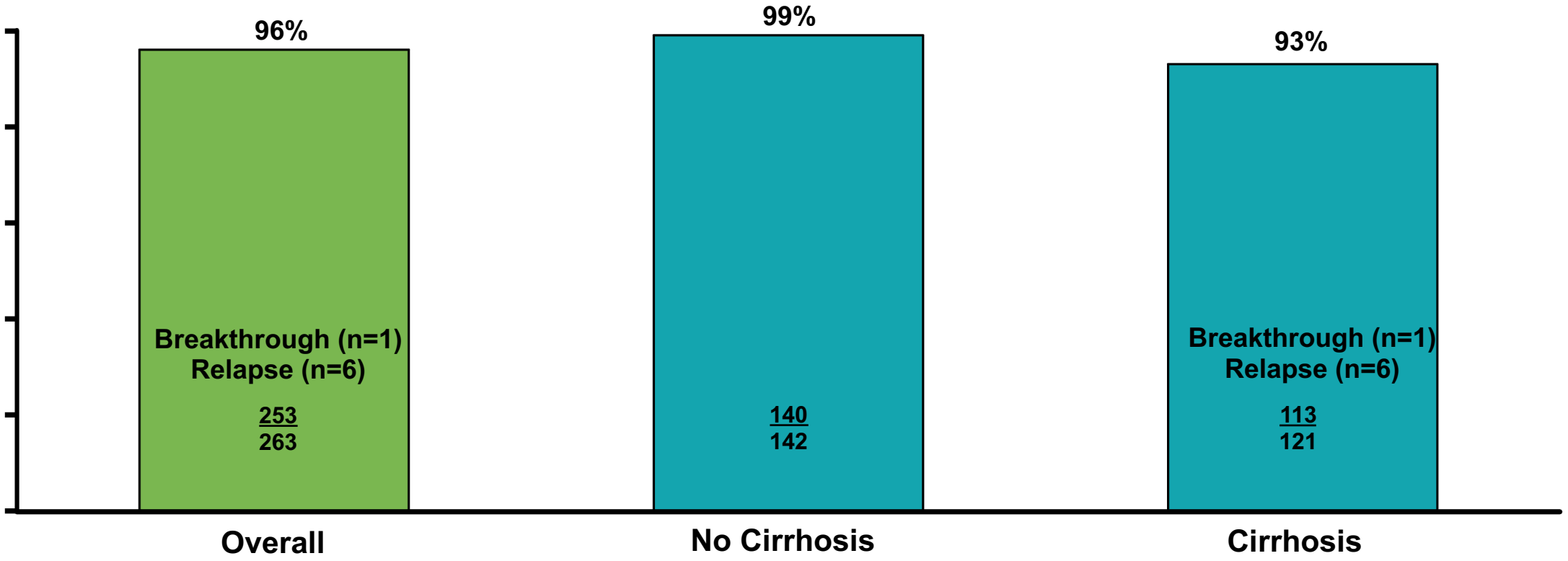
Glecaprevir/Pibrentasvir for 8 weeks



Wyles D, et al. EASL 2016. Abstract PS104. Reproduced with permission.

Overall Cure Rates in NS5A inhibitor – Experienced patients

Sofosbuvir/Velpatasvir/Voxilaprevir (Genotypes 1-6)



No placebo patients achieved an SVR12.

*$P \leq 0.001$ for superiority versus pre-specified goal of 85% for sofosbuvir/velpatasvir/voxilaprevir.

Mount Sinai

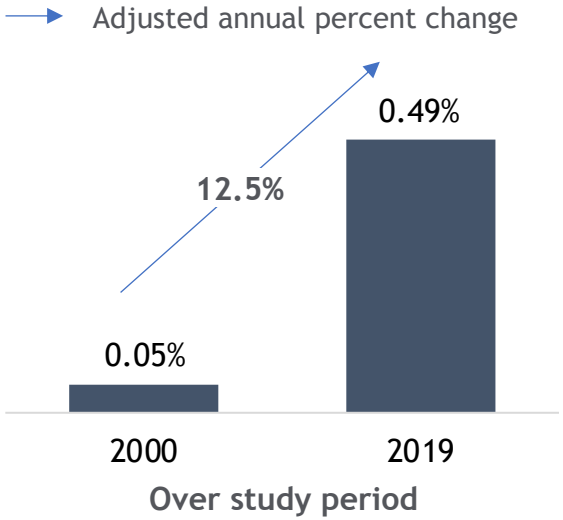
Bourlière M, et al. Hepatology. 2016;64(suppl S1):102A. Abstract 194.

Hepatitis C in pregnant people

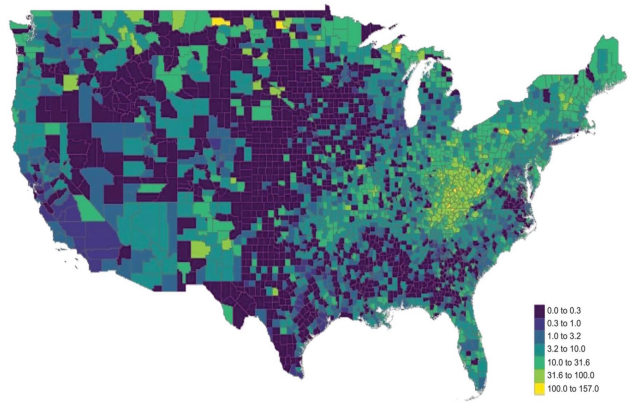
Recent Nationwide Inpatient Sample Data on HCV+ Pregnancies

Nationwide inpatient sample 76.7 million deliveries 2000-2019: 182,904 (0.24%) with HCV1

Prevalence increased 10-fold over study period from 0.05% in 2000 to 0.49% in 2019, adjusted annual percent change of 12.5%

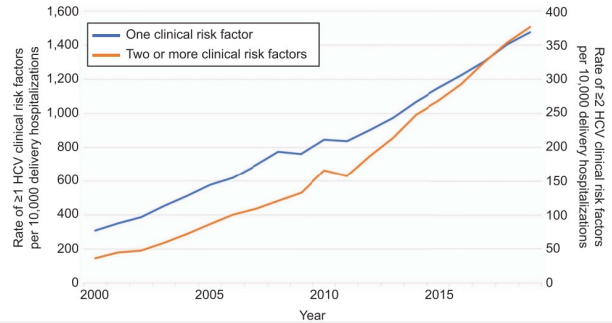


Prevalence of Maternal HCV Infection*, 2009-2017[2]

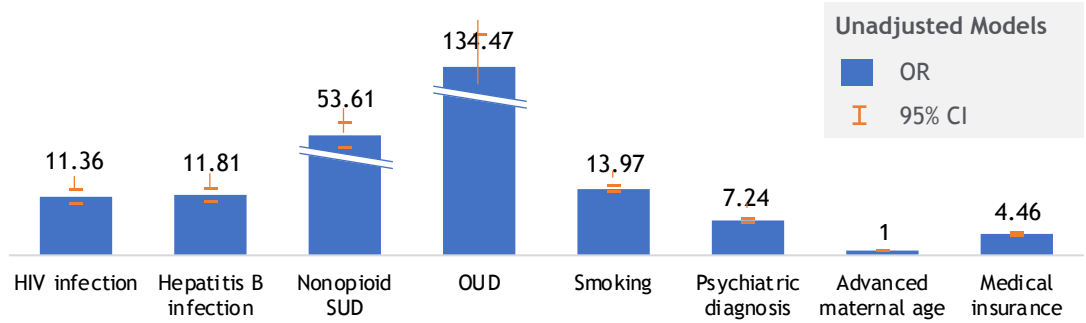


Per 1,000 live births

Rate of HCV Clinical Factors per 10,000 Delivery Hospitalizations



Clinical Factors associated with a Diagnosis of Hepatitis C Virus Infection



OR, odds ratio; HIV, human immunodeficiency virus; SUD, substance use disorder; OUD, opioid use disorder.

* By National Center for Health Statistics birth records

1. Arditi B et al. Obstetrics & Gynecology 2023 141(4);858-836; 2. Rossi et al, Obstetrics & Gynecology 2020 135(2):387-395

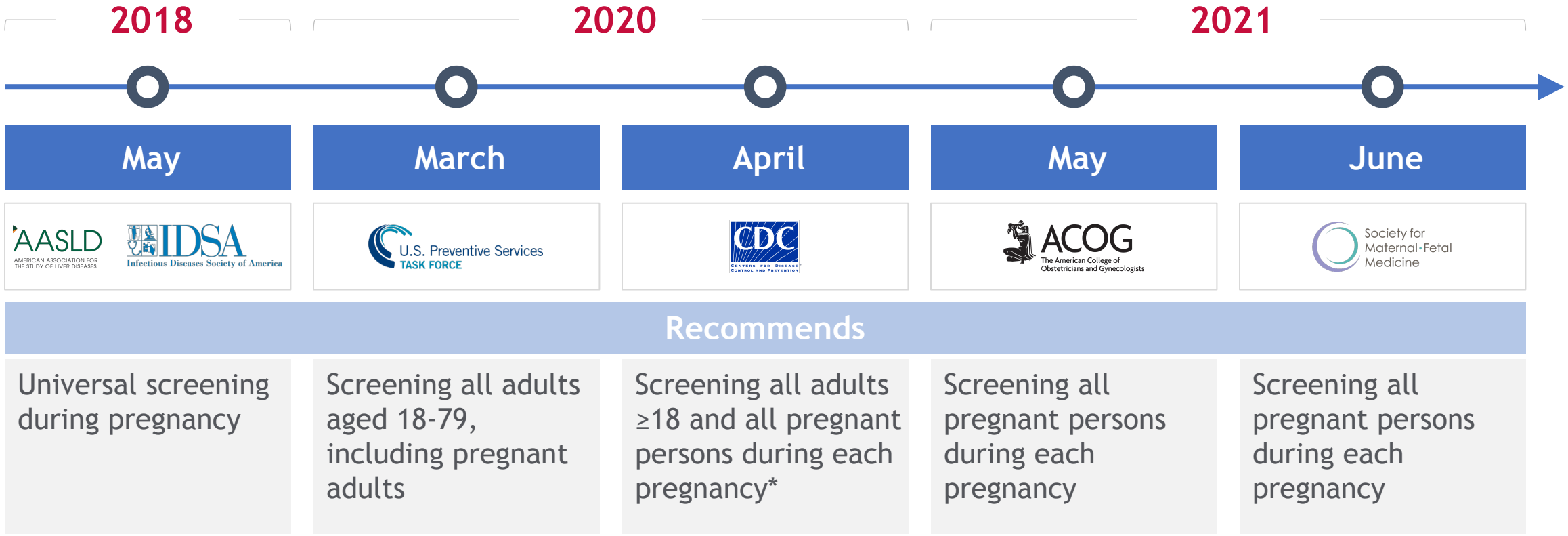
Universal HCV Screening During Pregnancy Cost Effectiveness

Table 2. Cost-effectiveness studies of universal HCV screening during pregnancy in DAA era.			
Study	Assumptions	ICER	Cost-effective?
Chaillon et al. (2019)	HCV prevalence 0.73%	<$3,000	Yes (if HCV prevalence >0.07%)
Tasilo et al. (2019)	Time to cirrhosis <70 years;	$41,000	Yes
	HCV prevalence >0.16%		
Selvapatt N et al. (2015)	HCV prevalence 0.38%	£2,400	Yes

DAA, direct-acting antiviral

Kushner and Reau; JHep 2021

Timeline of HCV Screening Recommendations During Pregnancy in the United States, 2018-2021



AASLD, American Association for the Study of Liver Disease; IDSA, Infectious Diseases Society of America; USPSTF, United States Preventative Services Task Force; CDC, Centers for Disease Control and Prevention; ACOG, American College of Obstetricians and Gynecologists; SMFM, Society for Maternal-Fetal Medicine *except in settings where the prevalence of HCV infection is <0.1%

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

HCV Testing During Pregnancy After Universal Screening Recommendations

Retrospective cohort study of 5,048,428 pregnant individuals aged 15-44 with obstetric panel testing by Quest Diagnostics from January 2011 through June 2021 were evaluated for the number of OB panels ordered with a hepatitis C antibody test.

Demographics

74.6% Commercial insurance

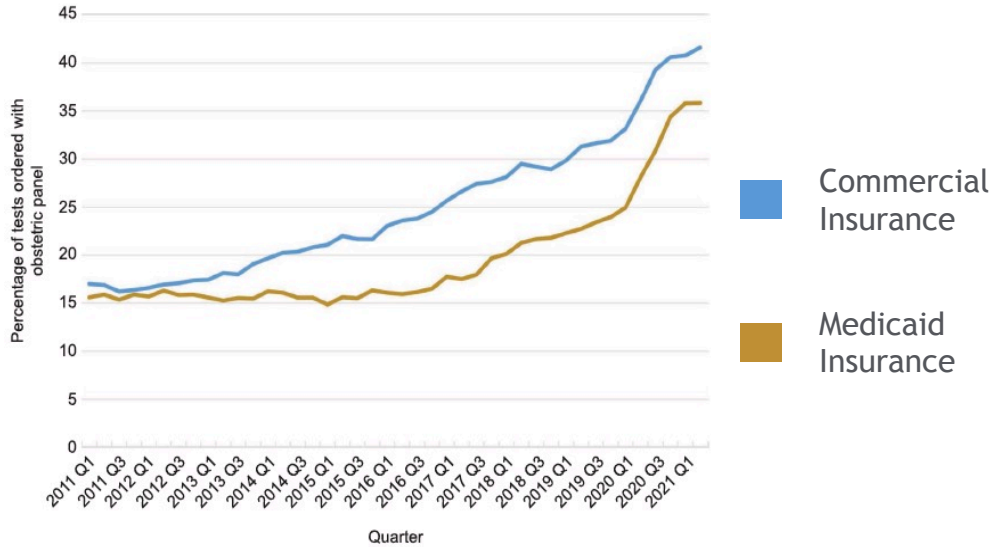
25% tested

25.4% Medicaid insurance

18.4% tested

23.3% had HCV screening test

Percentage tested increased from 16.6% to 40.6% at end of study



Universal HCV screening in pregnancy increased by 145% after the CDC and USPSTF recommendations but remains less than 50% of pregnancies

Kaufman et al, Obstet Gynecol 2022;140:99-101

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.

Effect of HCV on Pregnancy Outcomes and Perinatal transmission

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.*

Pregnancy Complications in Women with HCV

STUDY DESIGN

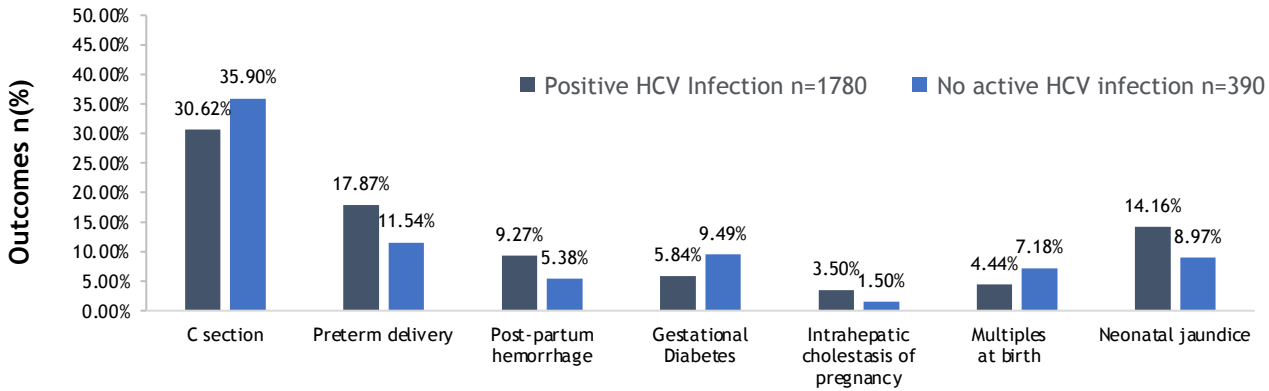
Population-based retrospective study using ICES data (2000-2018)

1,780 HCV RNA+ pregnancies	390 HCV Ab+/RNA-pregnancies

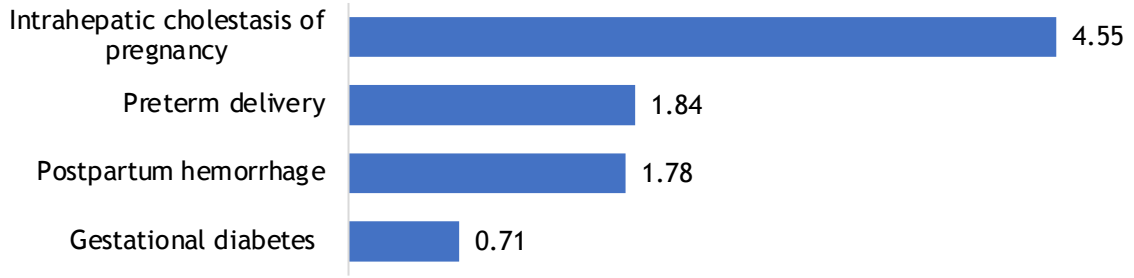
VS.

Pregnancy outcomes adjusted for: Age, parity, diabetes, multiple gestations, cirrhosis, alcohol and substance use, HIV co-infection

Pregnancy and Infant-Related Outcomes
HCV RNA + vs HCV Ab+/RNA-

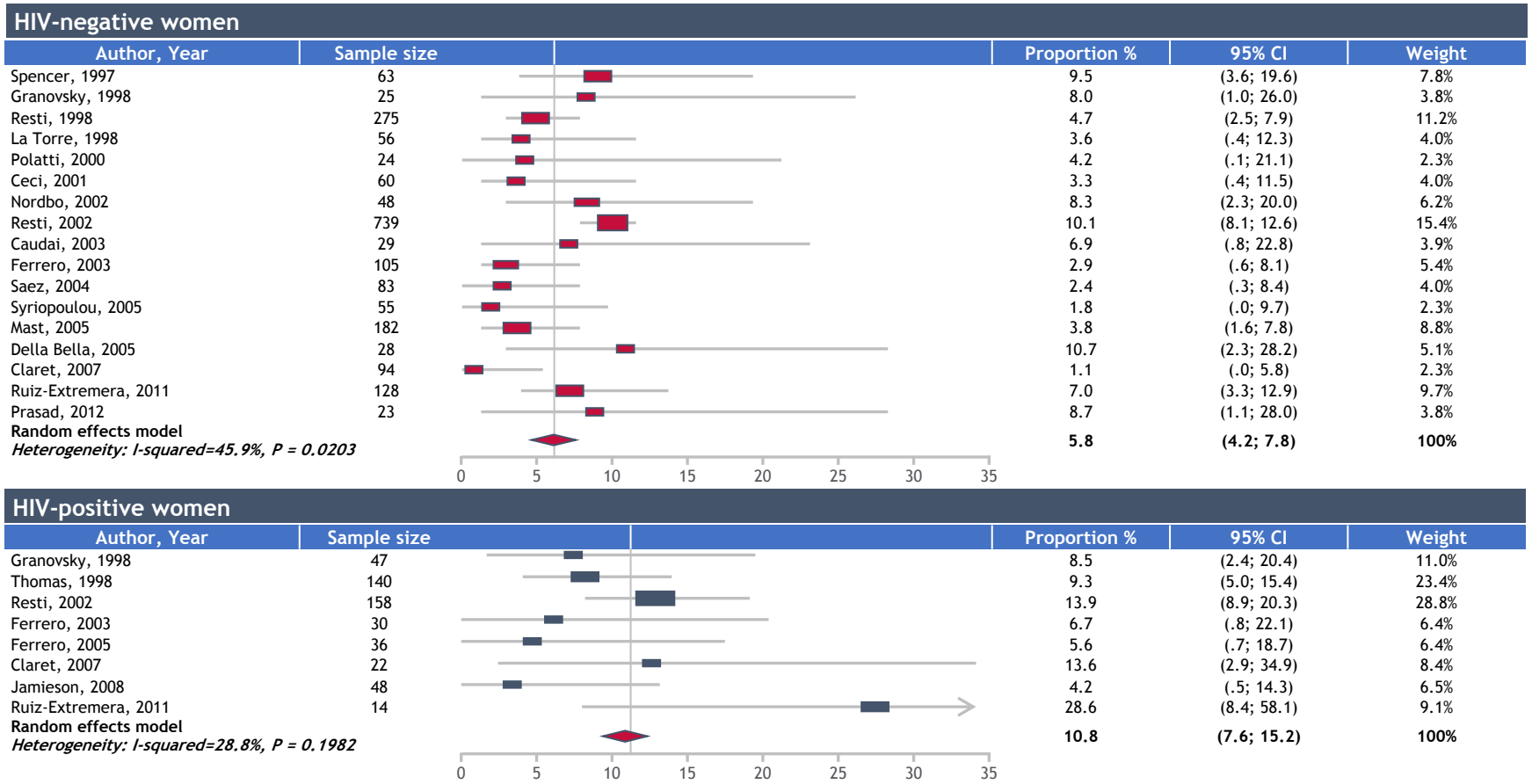


Multivariate Analysis, Odds Ratio
HCV RNA + vs HCV Ab+/RNA-



Kushner T, et al. *J Hepatol*. 2022;77(5):1256-1264. https://doi.org/10.1016/j.jhep.2022.05.016.

Rates of HCV Transmission in Pregnancy



- Meta-analysis of 17 studies of HCV vertical transmission risk in women with chronic HCV
- In HIV-negative women, the risk was 5.8%
- In viremic HIV-positive women, the risk was 10.8%

Risk of hepatitis C virus (HCV) vertical transmission in infants ≥18 months of age born to anti-HCV-positive, HCV RNA-positive women by maternal HIV serostatus: results of meta-analysis. Reprinted with permission. CI, confidence interval.
Society for Maternal-Fetal Medicine, et al. *Am J Obst Gynecol* 2017;217(5):B2-B12. https://doi.org/10.1016/j.ajog.2017.07.039.

Impact of HCV Viral Parameters on risk of MTCT

Outcomes

HCV screening performed in infants

1) HCV antibody test at 18 months of age or later **OR**
2) HCV RNA test within 2 to 24 months after delivery

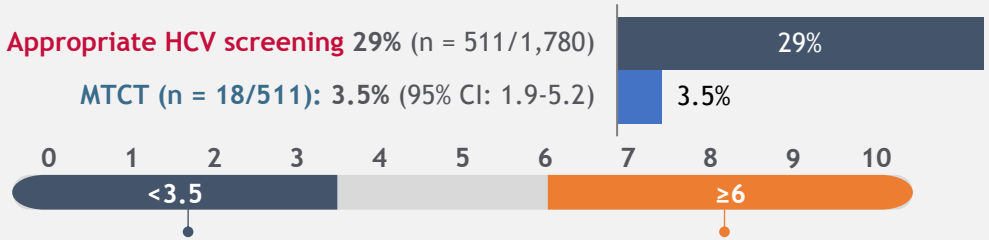
Mother-to-child transmission (MTCT)

In infants who were appropriately screened: HCV Ab+ or RNA+

Findings

Appropriate HCV screening 29% (n = 511/1,780)

MTCT (n = 18/511): 3.5% (95% CI: 1.9-5.2)



No MTCT If:

- RNA **<3.5** $\log_{10}$ IU/ml

If HCV RNA ≥6 $\log_{10}$ IU/ml

- MTCT eOR 3.38, p = 0.04

Mom's HCV RNA viral load (IU/ml), n(%)	
Mean ± SD	1,657,839.50 ± 4,203,655.76
Median (IQR)	360,000 (62,200-1,420,000)
N/A	197 (11.07)
≤1 million	1,102 (61.91)
>1 million	481 (27.02)
Mom's HCV RNA viral load ($\log_{10}$ IU/ml), n (%)	
N/A	197 (11.07)
<2.5	41 (2.30)
2.5-3.0	38 (2.13)
3.0-3.5	44 (2.47)
3.5-4.0	65 (3.65)
4.0-4.5	108 (6.07)
4.5-5.0	185 (10.39)
5.0-5.5	273 (15.34)
5.5-6.0	345 (19.38)
6.0-6.5	294 (16.52)
6.5-7.0	136 (7.64)
7.0<	54 (3.03)

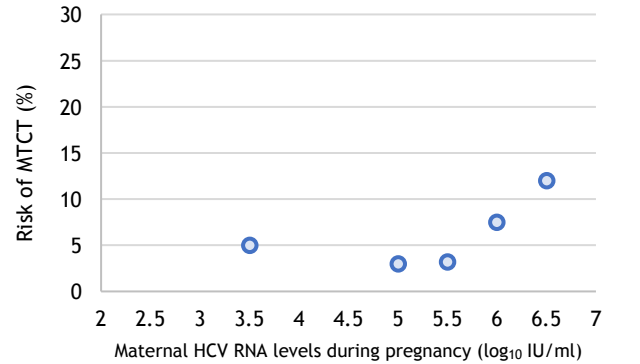


Fig. 2. MTCT risk by HCV viral load. MTCT, mother-to-child transmission

Table 6. Logistic regression analysis assessing effect of maternal HCV viral load on probability of MTCT in screened infants born to HCV+ mothers (n = 451)

	Univariate			Multivariate		
	eOR	95% CI	p value	eOR	95% CI	p value
Maternal HCV RNA viral load ($\log_{10}$ IU/ml)						
≥6.0	3.94	1.27-13.48	0.0155	3.38	1.07-11.74	0.0373
<6.0	1.00	Ref		1.00	Ref	
HIV coinfection						
Yes	4.61	0.46-23.65	0.1893	3.43	0.33-18.65	0.3174
No	1.00	Ref		1.00	Ref	
Maternal HCV genotype						
Type 1	2.72	0.73-15.11	0.1706	2.33	0.62-13.06	0.2864
Non-type 1	1.00	Ref		1.00	Ref	

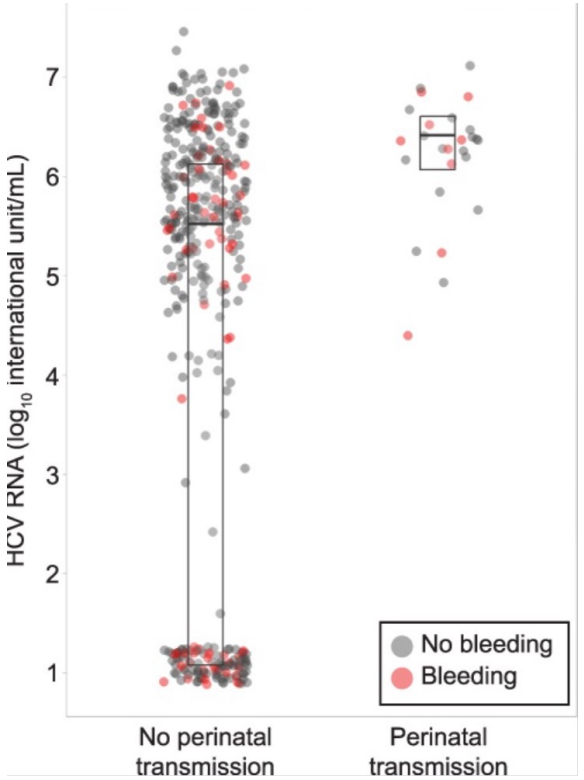
eOR, exact odds ratio; MTCT, mother-to-child transmission

Kushner T, et al. *J Hepatol*. 2022;77(5):1256-1264. https://doi.org/10.1016/j.jhep.2022.05.016.

MFMU risk factors for perinatal transmission

- Prospective observational @ 45 hospitals in Maternal-Fetal Medicine Units (MFMU) network; 2012-2018
  - 772 HCV Ab + with follow up; Outcomes available in 432
    - 26/ 432 children with transmission (6%, 95% CI 4.0-8.7%)
    - Among viremic, transmission **8% (95% CI 5.2-11.5%)**

Risk Factor	Perinatal Transmission: Yes (n=26)	Perinatal Transmission: No (n=406)	OR (95% CI)	aOR (95% CI) Final model*
HCV RNA titer greater than 10^6 international units/mL[†]	20 (76.9)	128 (31.7)	7.19 (2.82–18.33)	8.22 (3.16–21.39)
Antepartum bleeding	9 (34.6)	72 (17.7)	2.46 (1.05–5.73)	3.26 (1.32–8.03)
Any self-reported injection drug use during current pregnancy	6 (23.1)	108 (26.6)	0.83 (0.32–2.12)	
Premature rupture of membranes[†]	9 (34.6)	108 (27.1)	1.43 (0.62–3.30)	
Duration of membrane rupture 6 h or longer[†]	9 (36.0)	131 (33.9)	1.10 (0.47–2.55)	
Internal fetal monitoring[†]	6 (23.1)	79 (19.5)	1.24 (0.48–3.18)	
Breastfeeding[†]	13 (52.0)	219 (57.3)	0.81 (0.36–1.81)	



1. Prasad M. et al. *Obstetrics & Gynecology September 2023.*

Prevalence of HCV in Children and Adolescents in the United States

Statistical model using prevalence rates among women, given the assumption that most HCV cases in children are vertically transmitted (2001-2017)

Maternal HCV

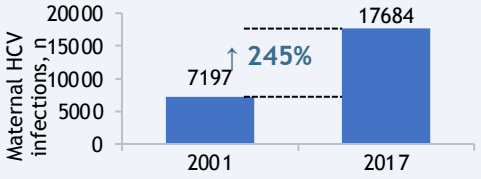
Total Cases

154,016

% of Total Live Births

0.24%

Number of Maternal HCV Infections Over Time



Pediatric HCV

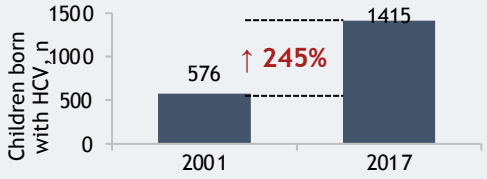
Total Born with HCV

8,649

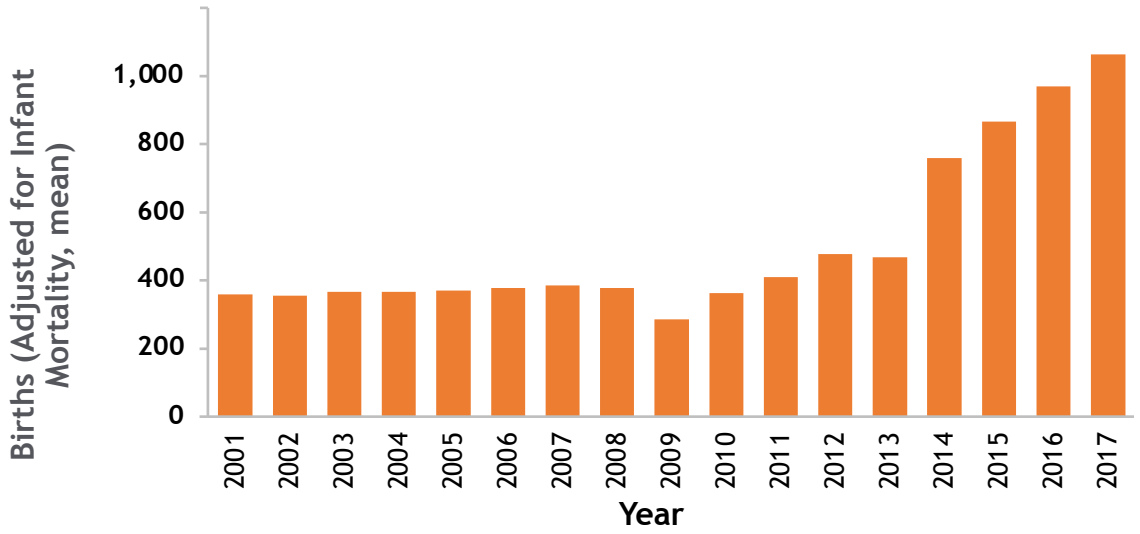
% of Total Live Births

0.01%

Number of Children with HCV Over Time



Births Affected by HCV (Contributed by Vertical Transmission)



The number of HCV-infected women of childbearing age is increasing, resulting in an increase in the number of infants born with HCV infection

Rahal H, et al. J Viral Hepat 2020 Dec;27(12):1455-1461. doi: 10.1111/jvh.13377

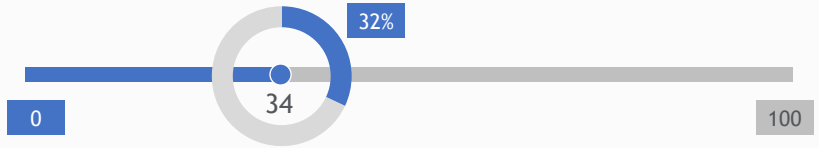
Cirrhosis Following Perinatal Acquisition of HCV

UK registry of 1049 individuals who had acquired HCV in childhood

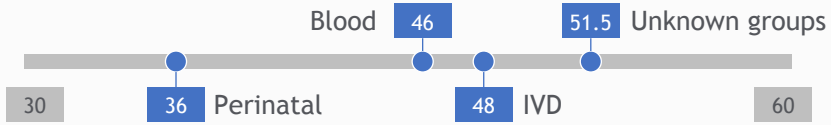
111 perinatal infections

=10 perinatal infections

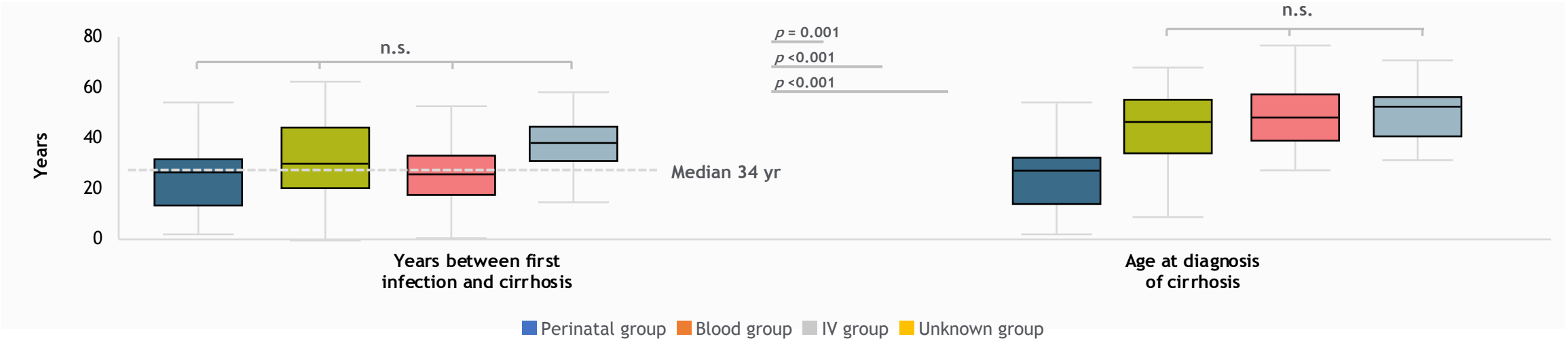
Cirrhosis in **32%** of patients after median **34** years, with no significant difference between modes of infection, suggesting a similar pattern of development of cirrhosis irrespective of infection route



Patients with perinatal infection developed cirrhosis earlier at a median age of **36** years compared to **48** years, **46** years, and **51.5** years in the IVD, blood, and unknown groups, respectively ($p < 0.001$).



Time between first infection and diagnosis of cirrhosis and real age in patients infected with HCV in childhood.



Modin L, et al. *J Hepatol*. 2019;70(3):371–378. https://doi.org/10.1016/j.jhep.2018.11.013.

Management of HCV in Pregnant Individuals

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

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

AASLD/ IDSA Guidance for HCV treatment

- "Treatment recommendations during pregnancy are largely unchanged from the previous update [5]. Although there have been no published large-scale clinical trials to evaluate the safety of DAA therapy during pregnancy, smaller studies and case series have not demonstrated any safety concerns [67–71]. The Guidance Panel suggests that DAA treatment may be considered during pregnancy on a case-by-case basis after a discussion of potential risks and benefits."

Bhattacharya D, et al. CID May 2023.

Antiviral Therapy During Pregnancy

Treatment with DAAs during pregnancy

Pro

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?

Con

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. *J Hepatol*. 2021;74(3):734-741. https://doi.org/10.1016/j.jhep.2020.11.027.

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]

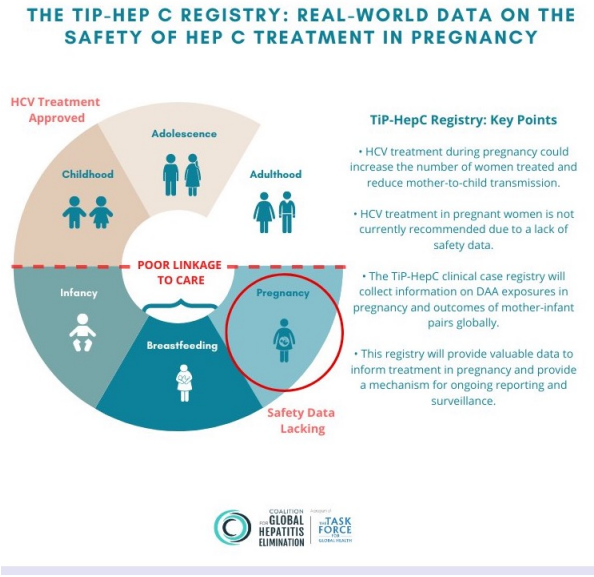
- Recent guidelines recommend that research with pregnant individuals be “promoted”
  - US Federal regulations governing research removed pregnant individuals from list of “vulnerable populations”
- Exclusion without justification denies pregnant individuals and fetuses access to potential health benefits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

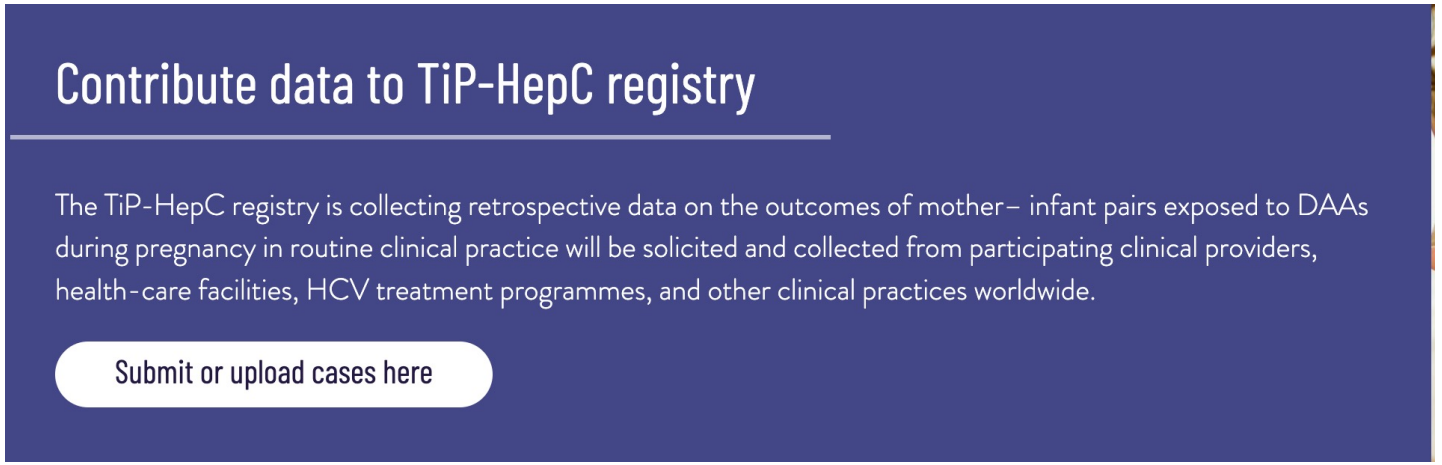
Is there data supporting DAA use in pregnancy?

Trial Number/ Trial Phase	Study Design	# of Participants (or Estimation)	Status
NCT04382404 Phase 1	SOF/VEL	10	Completed
NCT02683005 Phase 1	LDV/SOF	9	Completed (Chappell CA et al. *Lancet Microbe*. 2020;1:e200-e208.)
IMPAACT 2041	GIE/ PIB	TBD	Site selection completed 7/2023
NCT05140941 (STORC) Phase 4	SOF/VEL	100	Recruiting, 26/100 enrolled

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





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

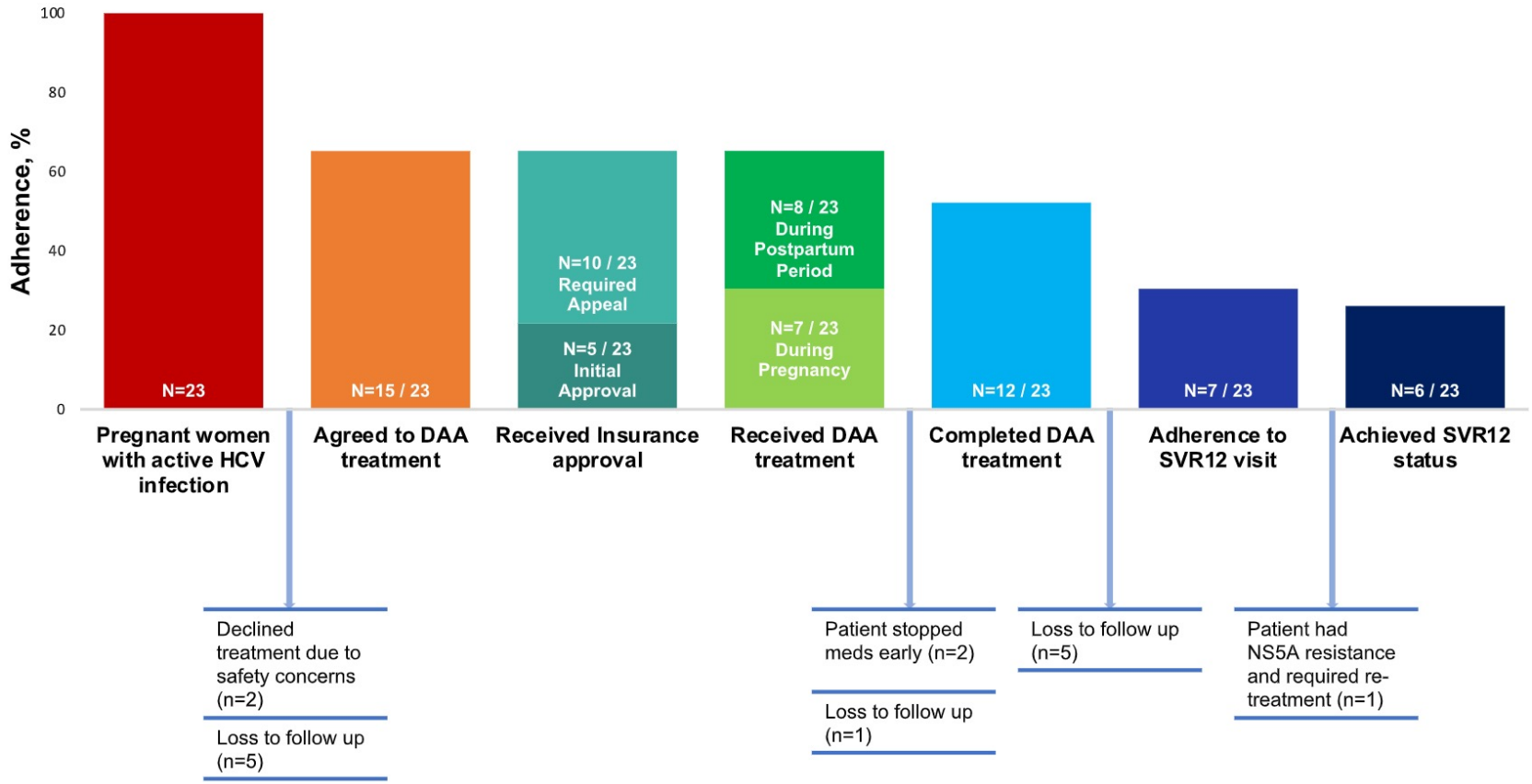


Figure 1. Compliance with steps in the HCV pregnancy cascade of care.

Kushner T, et al. *Gastroenterology 2022*.

HCV Management after Pregnancy

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 Treatment is Difficult to Achieve

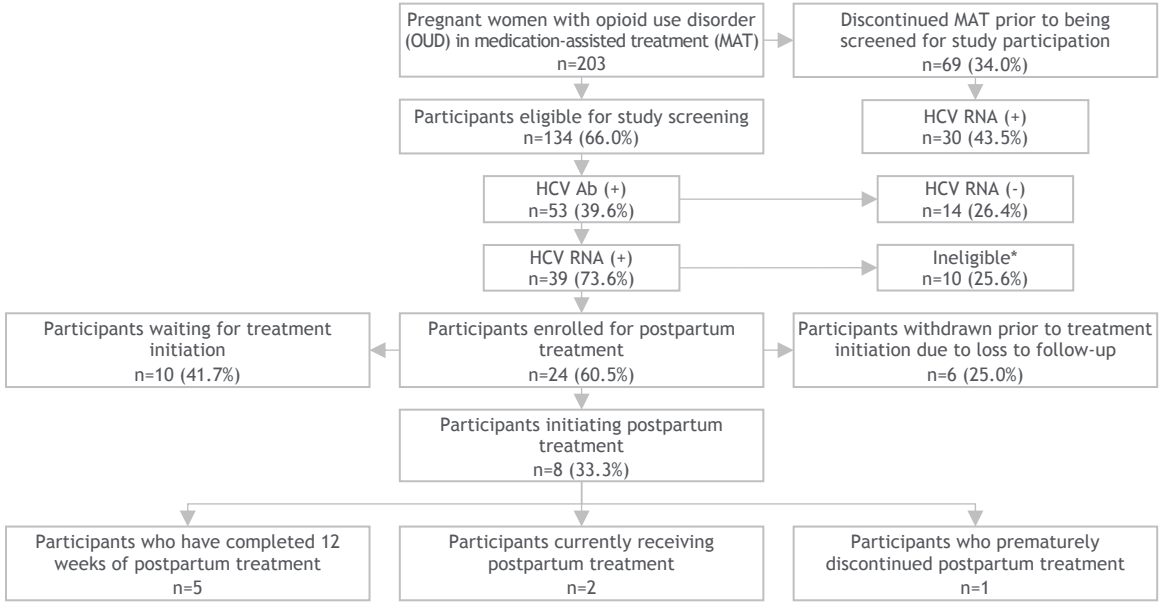
Retrospective Cohort study using administrative data from 6 states in Medicaid Outcomes Distributed Research Network; 23,780 people from 2016-2019 with OUD during pregnancy*[1]

Table 1. Results from Random-Effects Meta-analysis of Average Predicted Probabilities of Hepatitis C Virus Infection Testing and Diagnosis in Pregnancy and Follow-up in the Postpartum Period Among Women With Opioid Use Disorder in Pregnancy, by Follow-up Period

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	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

Less than 10% of women at risk for HCV get linked to care in the 6 months after delivery

Interim analysis of a study evaluating HCV treatment initiation and SVR among postpartum women at a single center in Pittsburgh, PA January 2018-July 2019[2]
All Women with OUD and receiving Medication Assisted Treatment



100% (3/3) achieved SVR12

In an integrated OUD and HCV Treatment Model, only 33.3% of patients started treatment[2]

OUD, opioid use disorder

*23,780 who had at least 60 days of follow up after delivery; 19,697 (87%) who had 6 months of follow up postpartum

1. Jarlenski et al, Obstet & Gynecol 2022 May;5(139): 916-918; 2. Laird H, et al. *Am J Obstet Gynecol*. 2019;221(6):693-694, https://doi.org/10.1016/j.ajog.2019.10.058.

Successful Postpartum Treatment Takes a Village

Improved postpartum linkage to care and treatment can be achieved by linking mother and infant care in a multidisciplinary setting[1]

HCV treatment rates estimated before and after implementation of a maternal-infant HCV linkage program. 343 women with HCV AB positivity reviewed in single center retrospective cohort study

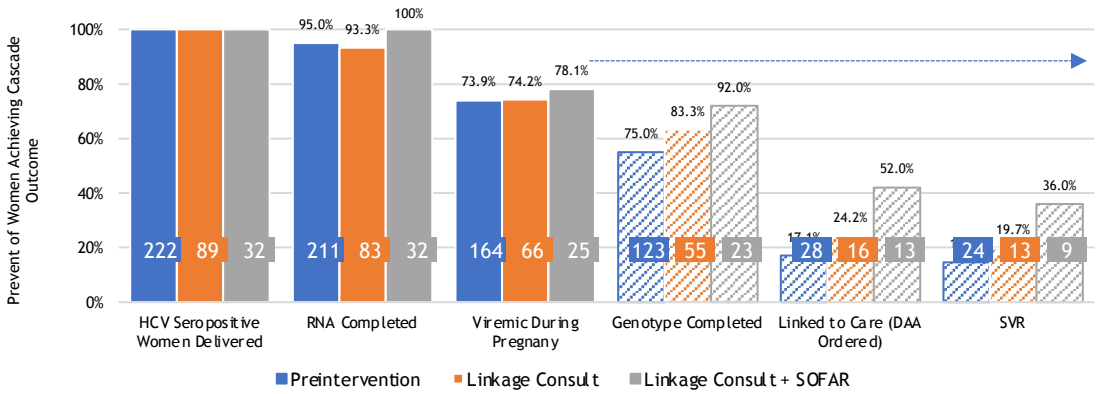
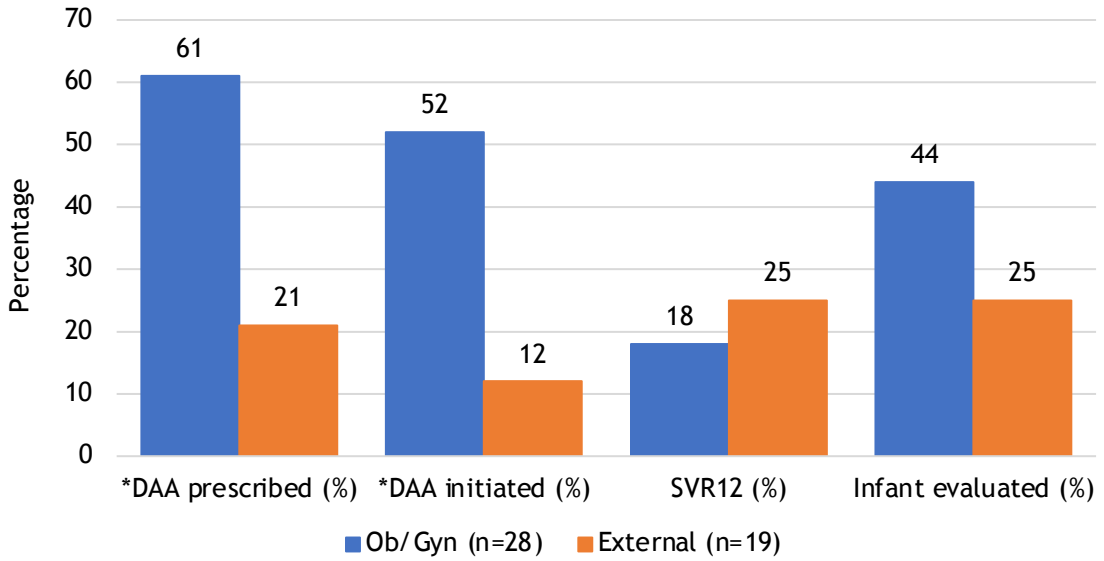


FIG. 1. HCV cascade to cure, preintervention period (January 2014-September 2016) and during the intervention period (October 2016-March 2018), by intervention received. Number of women achieving each HCV care cascade outcome, by intervention period and intervention type. Numbers at base of bars indicate total number (n). Percentages for the first three columns (solid bars) are per total women delivered who were HCV seropositive; percentages for the last three columns (dashed bars) are per those with evidence of HCV viremia during pregnancy, as indicated by the arrow. Linkage indicates linkage intervention exposure only; Linkage + SOFAR indicates women exposed to both the linkage and collocated care interventions

Treatment by trained OB/GYN can increase treatment; less than half of infants evaluated[2]

Interdisciplinary team created an antenatal navigation plan for pregnant women with HCV (OB, ID, psychiatrist, pharmacist); 28 women enrolled in this plan, 19 women referred for external evaluation and treatment



1. Epstein et al, Hepatol Commun 2021;5(9):1543-1554; 2. Behnke et al, J Amer Pharm Assoc 2022;62:864-869

HCV implications on children

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.

Perinatal HCV Testing Recommendations

AASLD Recommendations

- All children born to HCV-infected women should be tested with antibody at or after 18 months
- Can consider HCV RNA as early as 2 months of age
- Children who are HCV antibody positive at 18 months should get HCV RNA after age 3
- Other children of same mother should be tested if child is HCV+

CDC Proposed Recommendations

- All children should be tested with HCV RNA at age 2-6 months

American Association for the Study of Liver Diseases. (2020, January 23). HCV in Children. Retrieved from HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C: https://www.hcvguidelines.org/unique-populations/children
https://www.federalregister.gov/documents/2022/11/22/2022-25421/cdc-recommendations-for-hepatitis-c-testing-among-perinatally-exposed-infants-and-children-united

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

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

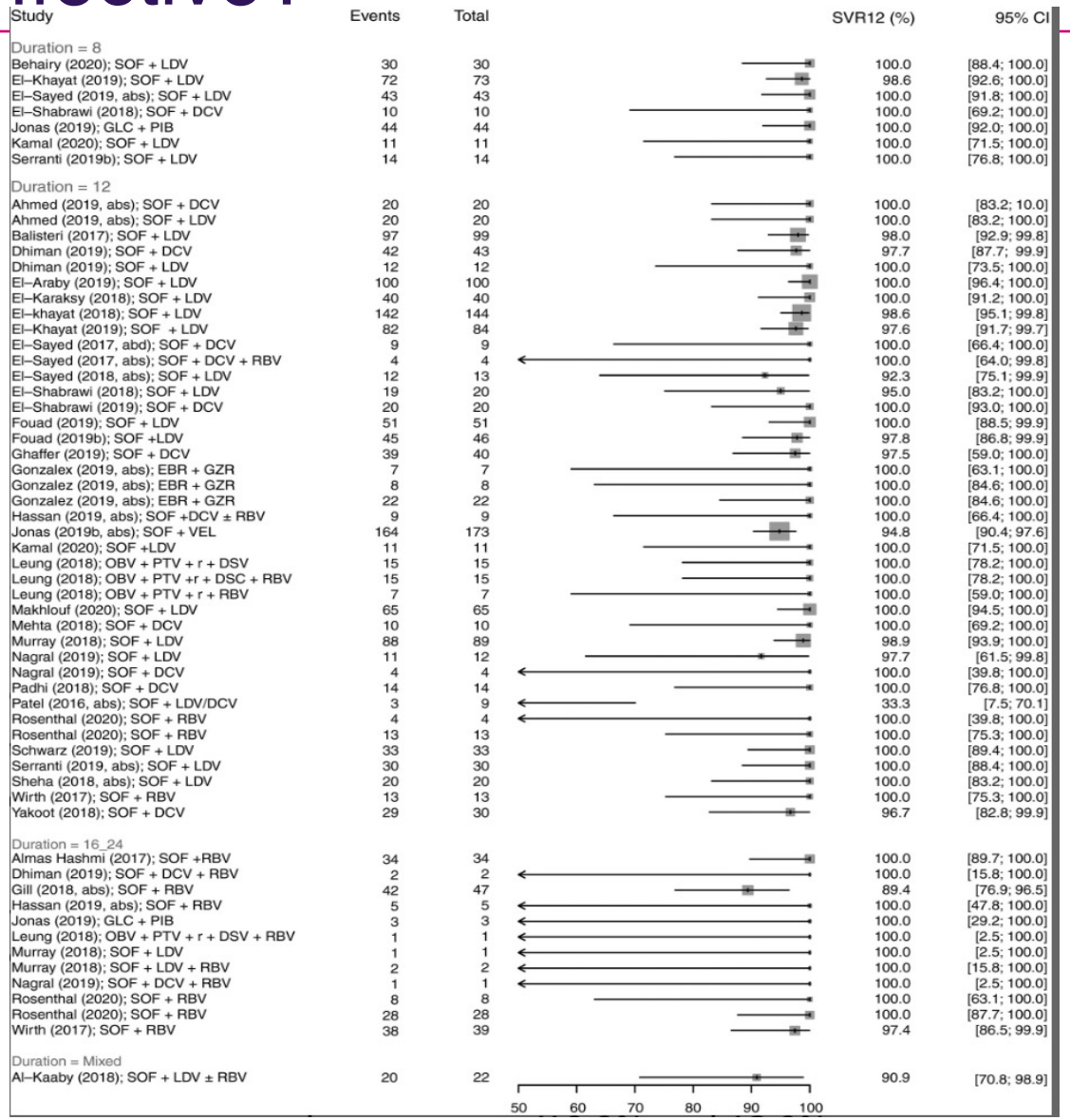
Recommendations for Whom and When to Treat Among Children and Adolescents With HCV Infection	
RECOMMENDED	RATING
Direct-acting antiviral (DAA) treatment with an approved regimen is recommended for all children and adolescents with HCV infection aged ≥3 years as they will benefit from antiviral therapy, 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.*

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



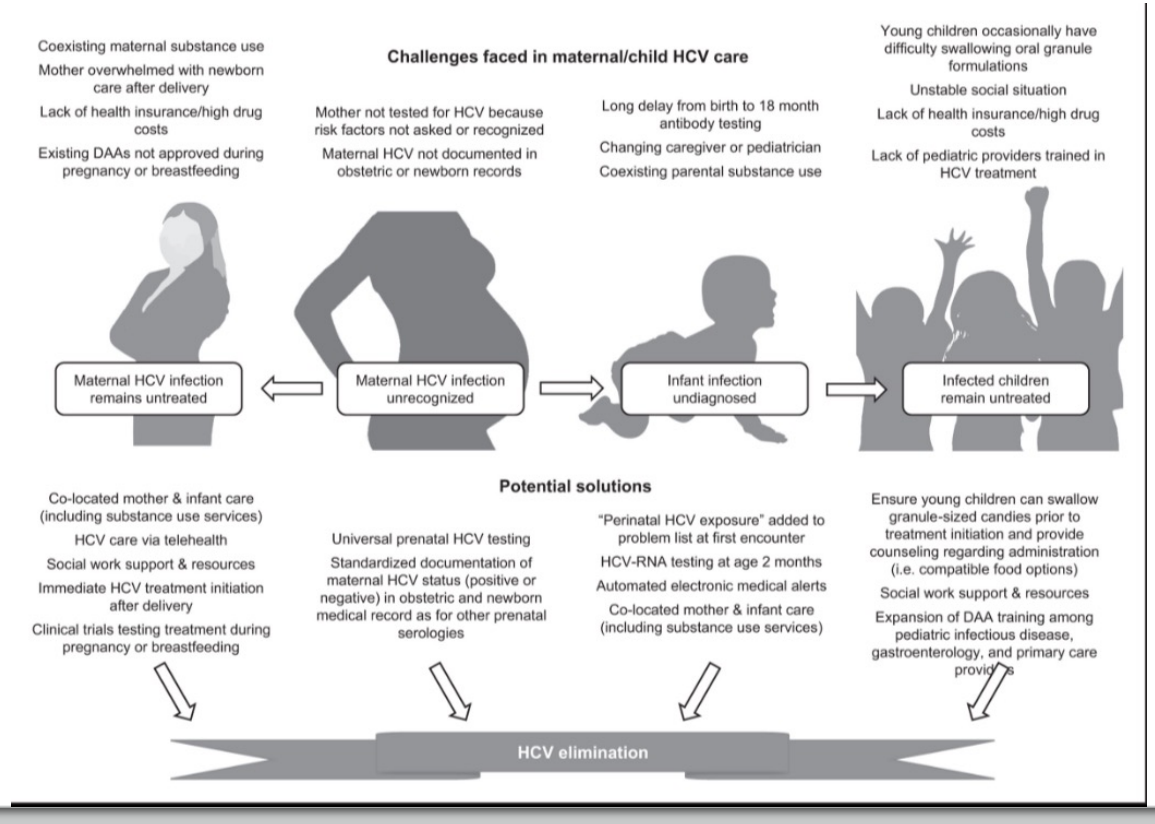
Study	Events	Total	SVR12 (%)	95% CI
Duration = 8				
Behairy (2020); SOF + LDV	30	30	100.0	[88.4; 100.0]
El–Khayat (2019); SOF + LDV	72	73	98.6	[92.6; 100.0]
El–Sayed (2019, abs); SOF + LDV	43	43	100.0	[91.8; 100.0]
El–Shabrawi (2018); SOF + DCV	10	10	100.0	[69.2; 100.0]
Jonas (2019); GLC + PIB	44	44	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*.

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 is recommended in all women, during every pregnancy, and annually in those at risk
- 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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