




CLINICAL CARE OPTIONS®  
HEPATITIS

# HCV in Women: Updated Guidance on Screening and Management

This program is supported by an educational grant from Gilead Sciences, Inc. 



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# Faculty

## **Tatyana Kushner, MD, MSCE**

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Division of Liver Diseases

Icahn School of Medicine at Mount Sinai

New York, New York

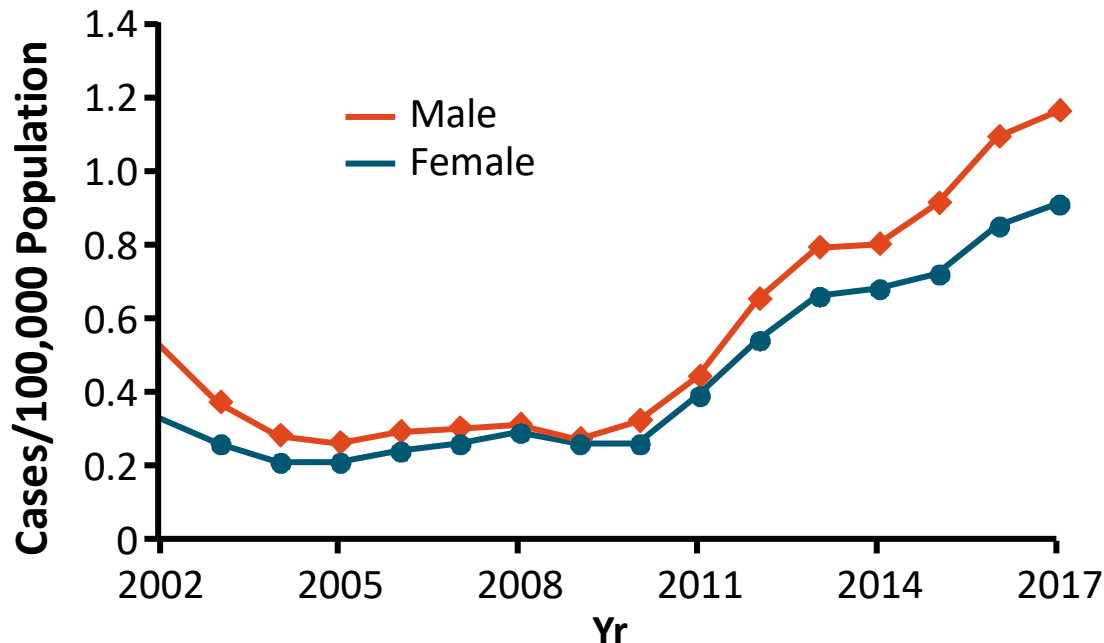
**Tatyana Kushner, MD, MSCE**, has disclosed that she has received consulting fees from Gilead Sciences.



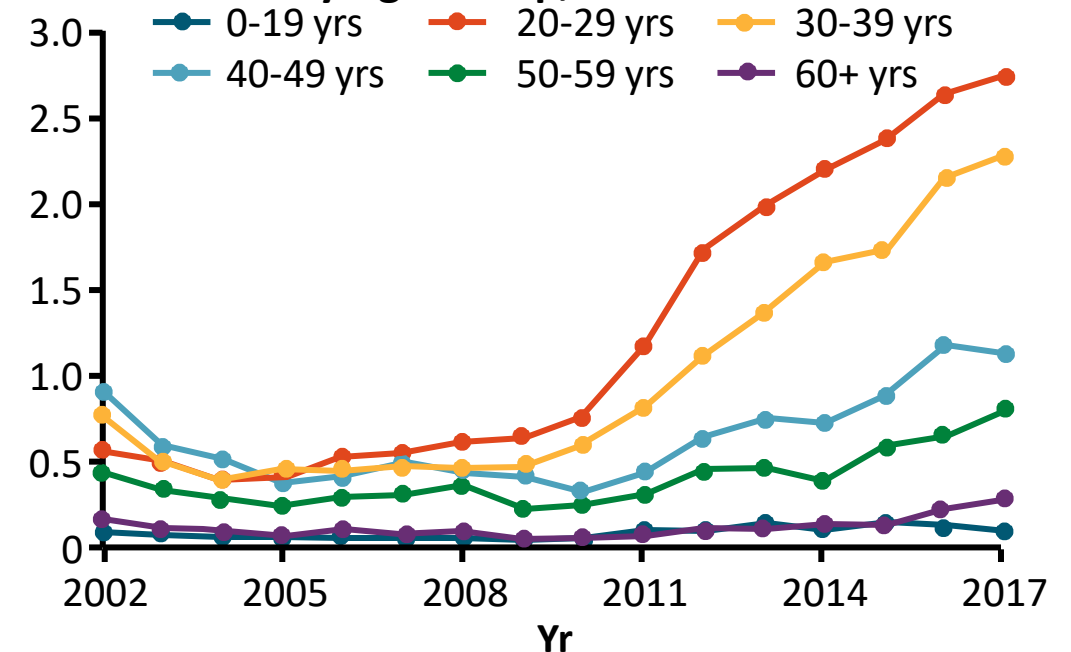
# Incidence of Acute HCV Is Increasing in the United States

- ~ 33,900 new HCV infections in 2015<sup>[1]</sup>
- Approximate 1:1 male:female ratio; predominantly White race<sup>[2]</sup>
- Highest incidence among persons 20-29 yrs of age,<sup>[1]</sup> nonmetropolitan areas<sup>[2,3]</sup>

**Reported Cases of Acute HCV by Sex,  
2002-2017<sup>[1]</sup>**



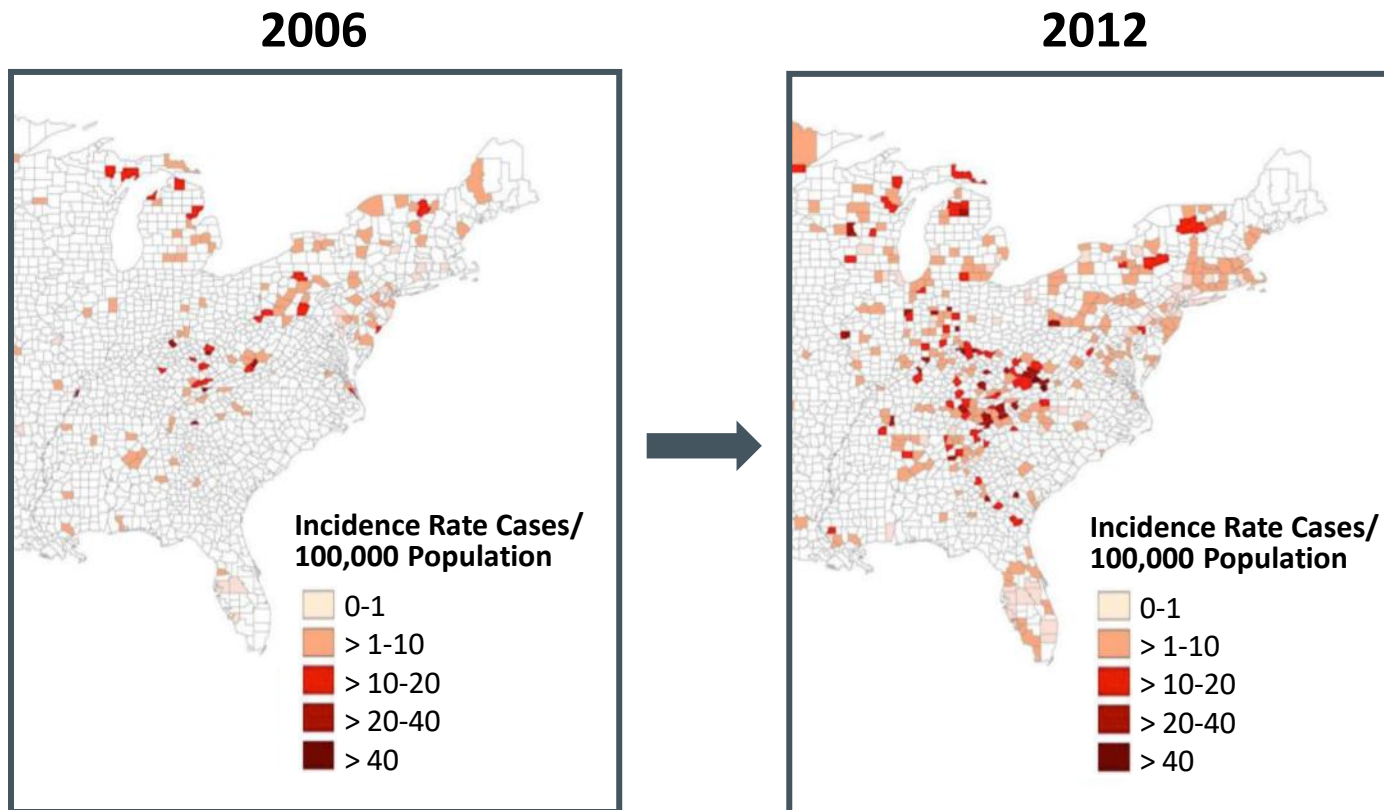
**Reported Cases of Acute HCV,  
by Age Group, 2002-2017<sup>[1]</sup>**



1. CDC. Viral Hepatitis Surveillance United States, 2018. 2. Suryaprasad. Clin Infect Dis. 2014;59:1411.

3. Zibbell. MMWR Morb Mortal Wkly Rep. 2015;64:453.

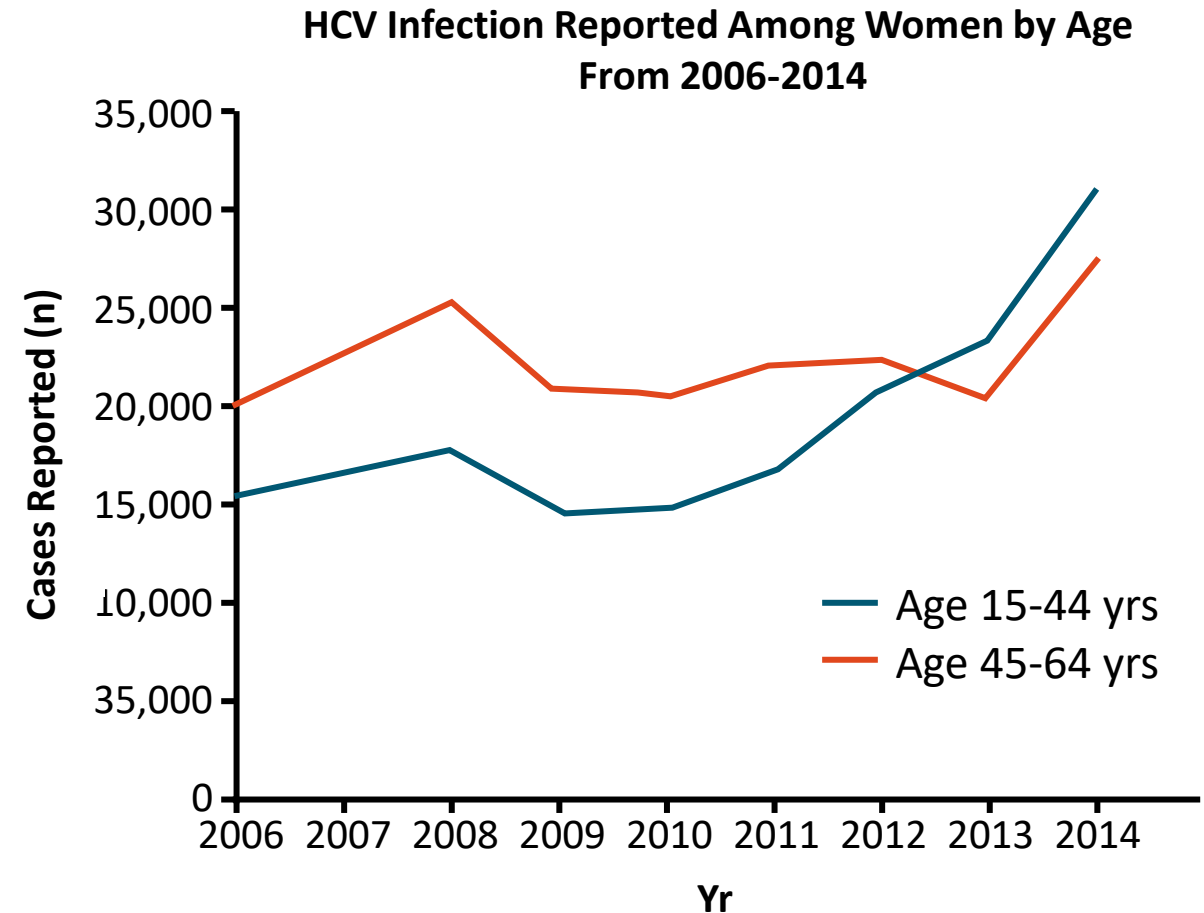
# New HCV Infections in the United States: Emerging Epidemic Among Young People Who Use Heroin



- HCV incidence: 13% annual increase rural; 5% annual increase urban<sup>[1]</sup>
- Regional doubling of first-time heroin use<sup>[2]</sup>
- 3 of 4 had history of prescription opioid use disorder<sup>[2]</sup>
- 97% initiated drug use before 20 yrs of age<sup>[1]</sup>
- **In separate meta-analysis, HCV incidence 17% higher in women than men who inject drugs<sup>[3]</sup>**

# HCV in Women of Childbearing Age

- In pooled data from the National Notifiable Diseases Surveillance System and the Quest laboratory database
  - Among women of childbearing age:
    - Number of **acute** cases of HCV **increased 3.4-fold**
    - Number of **past or present cases** **doubled**
    - Case number **higher** in **younger** vs older **women** since 2013



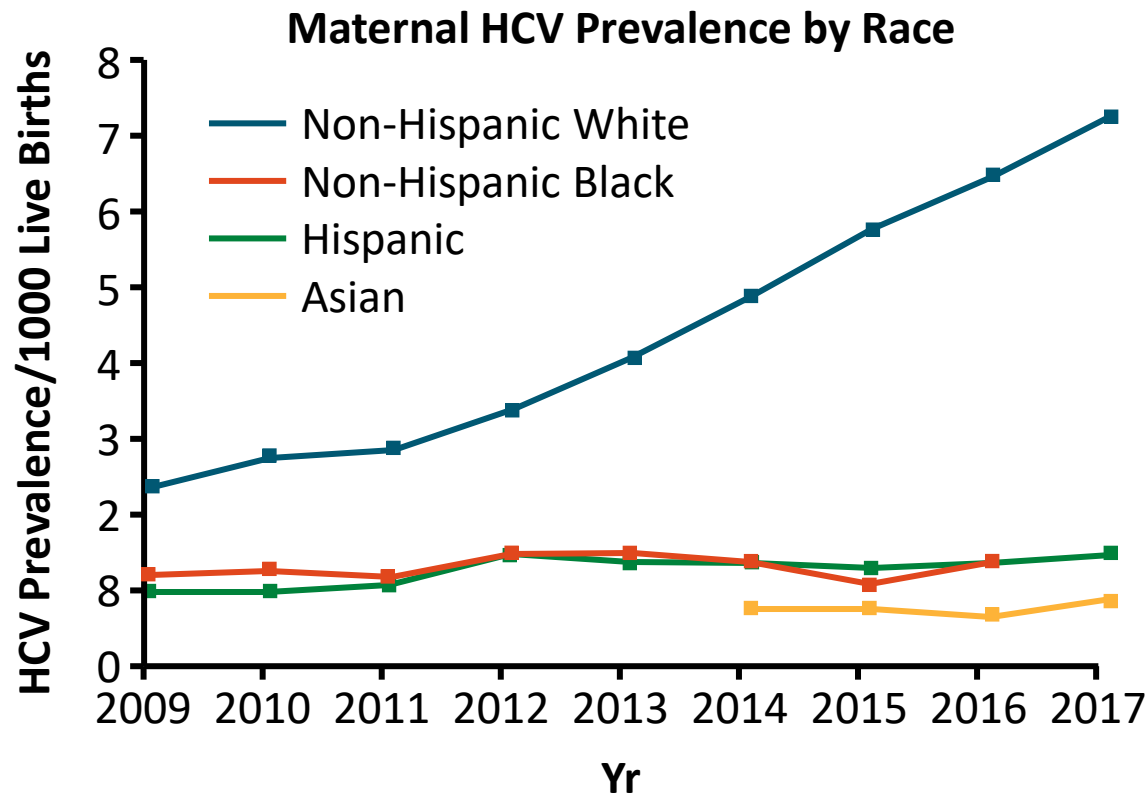
# Why Might Women Be at Higher HCV Risk?

- Women who inject drugs have been shown to have higher incidence of HIV and higher rate of injection-related risk behaviors than men who inject drugs<sup>[1]</sup>
  - Higher rates of equipment and syringe sharing in women than men<sup>[1]</sup>
  - More women using injection equipment after their male partners<sup>[1]</sup>
  - More women injected by others<sup>[1]</sup>
- More likely than men to have IDU sex partners<sup>[2]</sup>
  - Overlapping sexual and injection partnerships → increased injection risk<sup>[2]</sup>
- Female PWID face stigma; less likely to participate in harm reduction services<sup>[1]</sup>

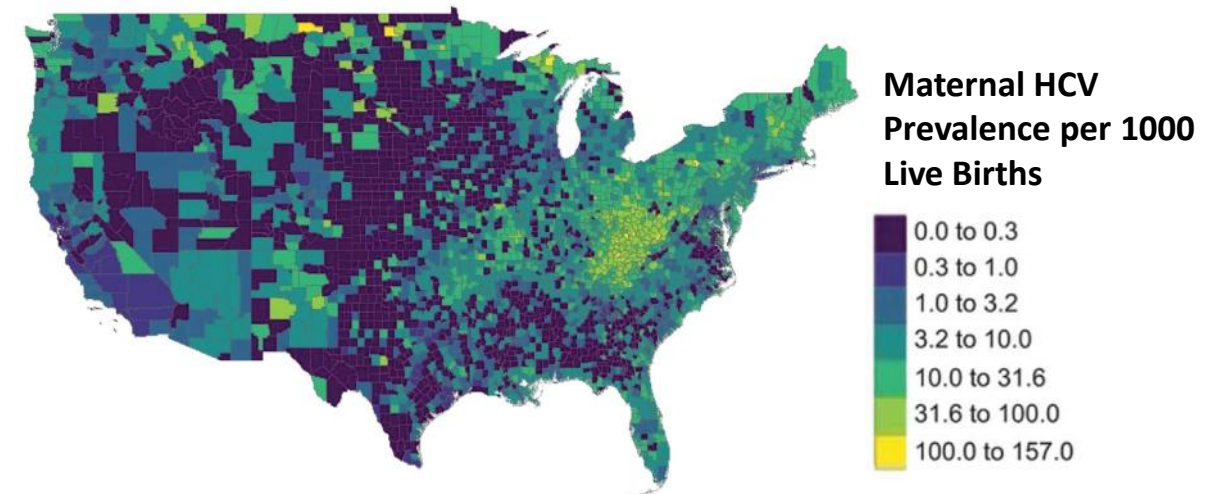
**It is critical to counsel women on harm reduction services and safe injection practices!**

# HCV in Pregnant Women, 2009-2017

- Retrospective, population-based, cohort study of live births in the United States from 2009-2017 using National Center for Health Statistics birth records



Overall, reported prevalence of **maternal HCV infection increased by 161% from 2009 to 2017**





# AASLD/IDSA Guidance: Testing for HCV During Pregnancy

- Previous HCV screening recommendation was based on risk (eg, prior blood transfusion, PWID and shared needles, persons with HIV, persons born to mother with HCV)
- In May 2018, guidance revised to recommend universal testing of pregnant women

## Universal HCV Screening in Pregnancy

### Recommended

### Rating

As part of prenatal care, all pregnant women should be tested for HCV infection with each pregnancy, ideally at the initial visit

IIb, C

# New HCV Screening Recommendations From the USPSTF

- **USPSTF recommends HCV screening in adults 18-79 yrs of age (grade B)**
- **To whom does this apply?** All adults, 18-79 yrs of age without known liver disease
- **What's new?** This recommendation expands the population who should be screened
  - Previously, task force recommended screening adults born between 1945 and 1965 and others at high risk

**“Pregnant adults should be screened.** HCV prevalence has doubled in women aged 15 to 44 years from 2006 to 2014. From 2011 to 2014, 0.73% of pregnant women tested had an HCV infection, with a 68% increase in the proportion of infants born to HCV-infected mothers. Approximately 1700 infected infants are born annually to 29,000 HCV-infected mothers. Because of the increasing prevalence of HCV in women aged 15 to 44 years and in infants born to HCV-infected mothers, clinicians may want to consider screening pregnant persons younger than 18 years.”



# Further HCV Screening Recommendation Updates: CDC and ACOG

- April 10, 2020: newly released CDC recommendations include<sup>[1]</sup>:

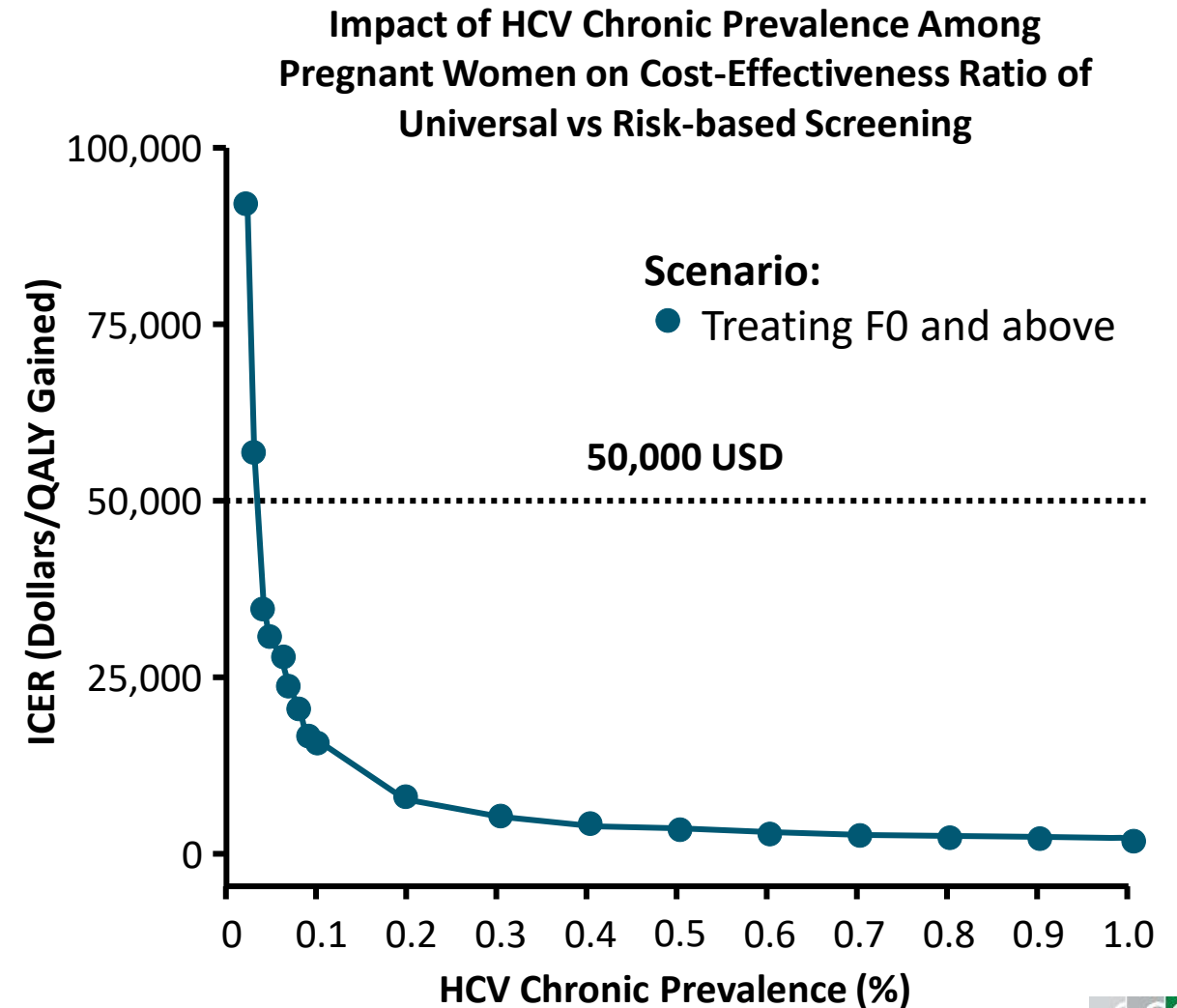
**“Hepatitis C screening is recommended for **all pregnant women** during each pregnancy except in settings where the prevalence of HCV infection is < 0.1%.”**

- April 2020 ACOG Practice Advisory<sup>[2]</sup>:

**“The American College of Obstetricians and Gynecologists (ACOG) is actively reviewing the new guidance from the CDC and USPSTF. Updated guidance from ACOG will be posted on ACOG’s website and published in *Obstetrics & Gynecology* when available. ACOG is also reviewing its current guidance on the screening and management of hepatitis for pregnant individuals in ACOG Practice Bulletin No. 86, ***Viral Hepatitis in Pregnancy*** (2007).”**

# Is Universal HCV Screening During Pregnancy Cost-Effective?

- Incremental cost-effectiveness ratio analysis comparing universal and risk-based screening
- Universal screening of ~ 5 million pregnant women in 2018 could **result in detection and treatment of an additional 33,000 women and 300 children born with HCV**
- HCV screening cost-effective even in low prevalence areas and across all fibrosis stages



# AASLD: Monitoring of Women With HCV During Pregnancy

Recommendation	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 MTCT and severity 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 ICP with subsequent assessment of ALT, 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

# What Is the Effect of HCV Infection on Pregnancy?

- HCV may have negative effects but difficult to tease apart from effects of associated factors (eg, injection drug use)

**Meta-analysis of > 4,000,000 women with  
> 5000 HCV infection cases<sup>[1,2\*]</sup>**

Birth Outcome	OR With vs Without HCV (95% CI)
Preterm birth <sup>[1]</sup>	1.62 (1.48-1.76)
Intrauterine fetal growth restriction <sup>[2]</sup>	1.53 (1.40-1.68)
Low birth weight <sup>[2]</sup>	1.97 (1.43-2.71)

**Swedish Birth Registry: > 1 million women,  
> 2000 births to HCV+ women, 2001-2011<sup>[3]</sup>**

Birth Outcome	aRR With (n = 1,091,913) vs Without (n = 2056) HCV (95% CI)
Preterm birth	1.32 (1.08-1.60)
Late neonatal death	3.79 (1.07-13.79)

\*1. 4,186,698 participants with 5218 HCV infection cases; 2. 4,185,414 participants with 5094 HCV infection cases.

- Multicenter observational US study to assess outcomes in pregnant women with HCV (N = 772) and their infants launched in 2012<sup>[4,5]</sup>

# HCV and ICP

- Population-based cohort study in Sweden included 11,000 women with ICP and 11,000 healthy women<sup>[1]</sup>
  - ICP HR with vs without HCV: 4.16 (95% CI: 3.14-5.15)
- Meta-analysis of 3 studies of ICP in pregnancy (N = 95429) in women with (n = 308) vs without HCV<sup>[2]</sup>
  - ICP pooled OR with vs without HCV: 20.40 (95% CI: 9.39-44.33)

**Counsel women with HCV on the increased risk of ICP!**



# AASLD: Treatment of Women of Childbearing Age

Recommendation Regarding HCV Treatment and Pregnancy	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

- Counsel about benefit of antiviral treatment before pregnancy
- If a woman becomes pregnant while receiving HCV DAA therapy, providers should discuss the risks vs benefits of continuing treatment
- Ribavirin is contraindicated in pregnancy due to teratogenicity (wait at least 6 mos after completion of ribavirin therapy to get pregnant)



# AASLD Statement: HCV Treatment During Pregnancy

**“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.”<sup>[1]</sup>**

**“For women on therapy who become pregnant, the decision to continue therapy requires careful consideration of (1) risk for virologic relapse; (2) risk of MTCT; (3) access and financial concerns; (4) patient and clinician preferences; and (5) limited safety data on DAAs in pregnancy.”<sup>[2]</sup>**

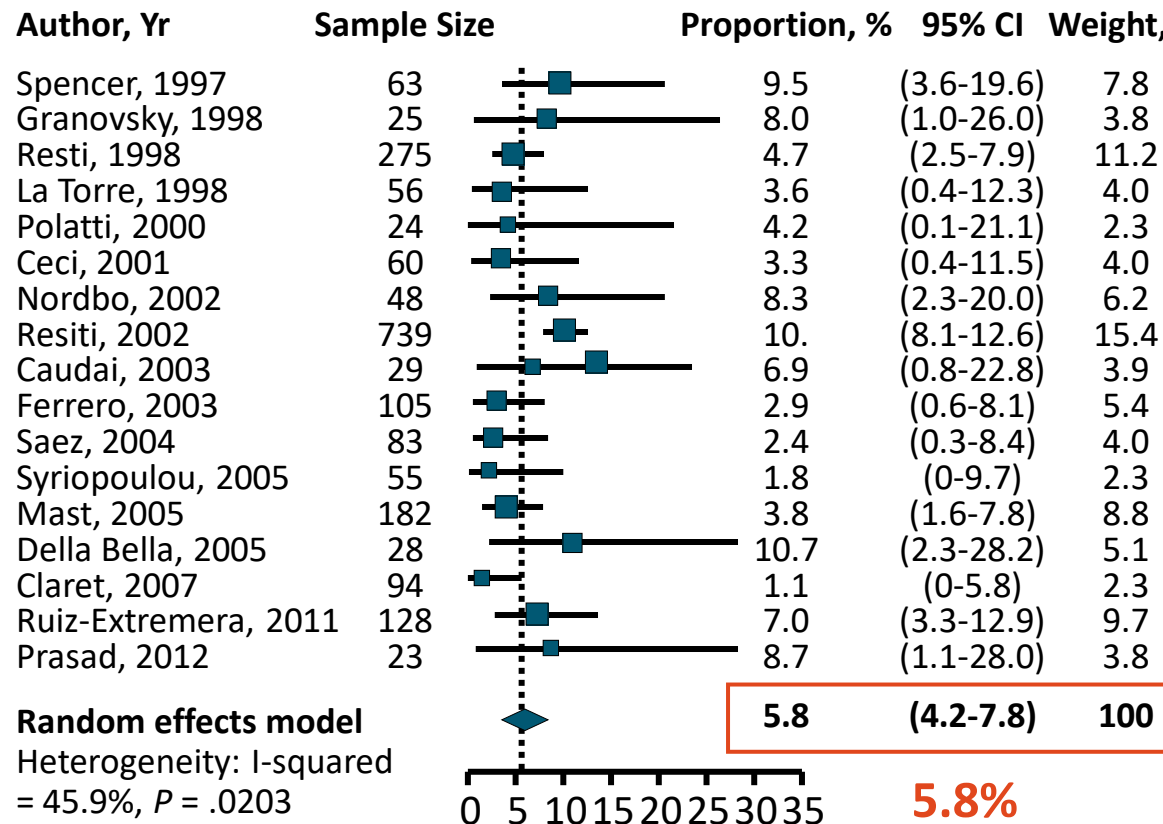
# Why Consider Antiviral Therapy During Pregnancy?

- Potential to reduce risk of MTCT; similar to HBV
- Pregnancy is often a time when women have health insurance; opportune time to treat HCV concurrent with pregnancy care
- Provides opportunity to cure HCV in women with high-risk behaviors to prevent transmission to others, including injecting partners

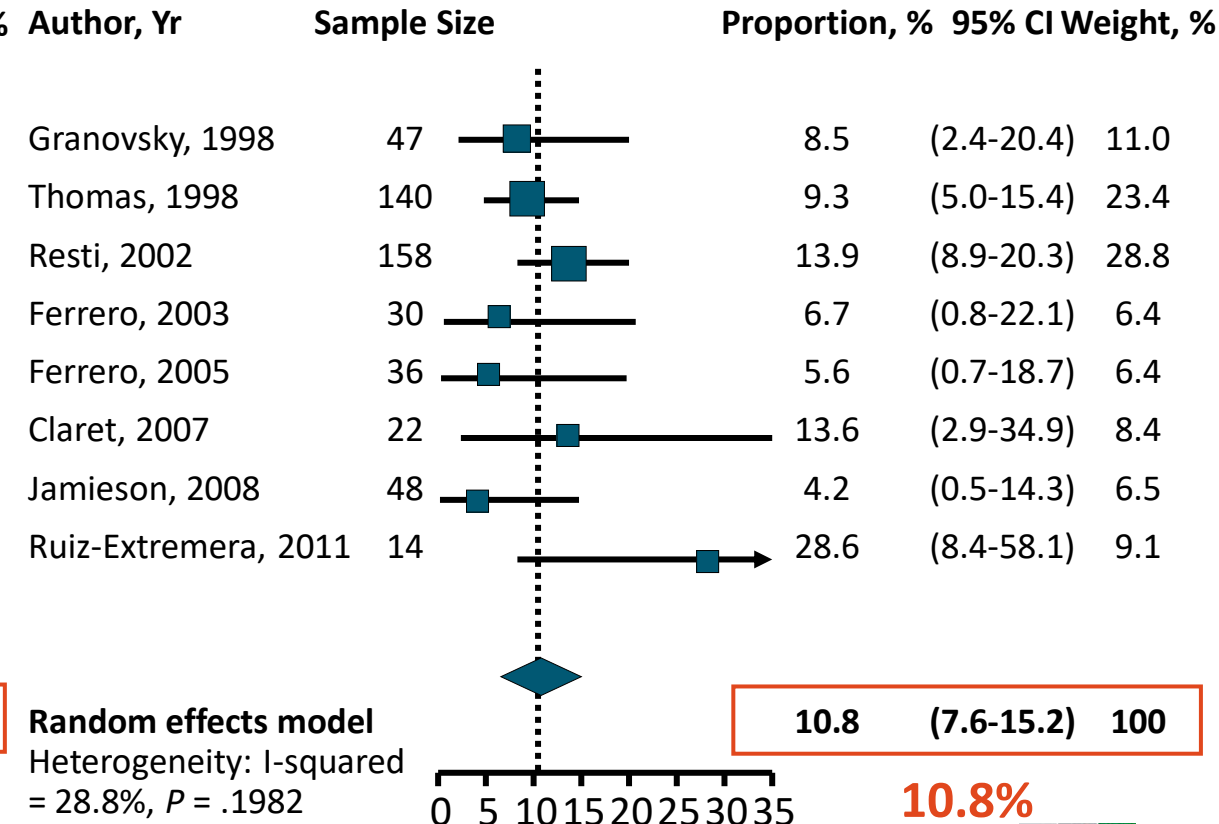
# Risk of MTCT of HCV by Maternal HIV Serostatus

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

## HIV-negative women



## HIV-positive women



# Can MTCT Be Prevented During and After Pregnancy?

Variable	Studies (N)	Precision of Evidence	Summary of Findings
Elective C/S vs vaginal delivery	4 cohort studies (N = 2080)	Low	<b>Inconsistent results</b> with trends in opposite directions in highest quality studies
All C/S vs vaginal delivery	11 cohort studies (N = 2308)	Low	<b>No association</b> between mode of delivery and risk of HCV transmission
Invasive fetal monitoring vs none	3 cohort studies (N = 928)	Low	<b>Inconsistent results:</b> 1 good quality study (N = 181) showed increased risk of HCV transmission (aOR: 6.7, 95% CI: 1.1-36); another (N = 724) showed no association (RR: 1.2, CI: 0.7-2.2)
Prolonged rupture of membranes vs no	2 cohort studies (N = 245)	Low	Membrane rupture > 6 hrs before delivery <b>increased risk of transmission</b> (OR: 9.3, 95% CI: 1.5-18)
Breastfeeding	14 cohort studies (N = 2971)	High	<b>No association</b> between breastfeeding women with HCV and transmission to infants



# Recommendations of Society of Maternal and Fetal Medicine Regarding Prevention of MTCT of HCV

Recommendation	Grade of Recommendation
Amniocentesis is recommended over chorionic villus sampling given the lack of data on the latter	2C
We recommend against cesarean delivery solely for the indication of HCV infection.	1B
We recommend that obstetric care providers avoid internal fetal monitoring, prolonged rupture of membranes, and episiotomy in managing labor in HCV-positive women	1B
We recommend that providers not discourage breastfeeding based on a positive HCV infection status	1A

# MTCT Most Common Cause of HCV in Children

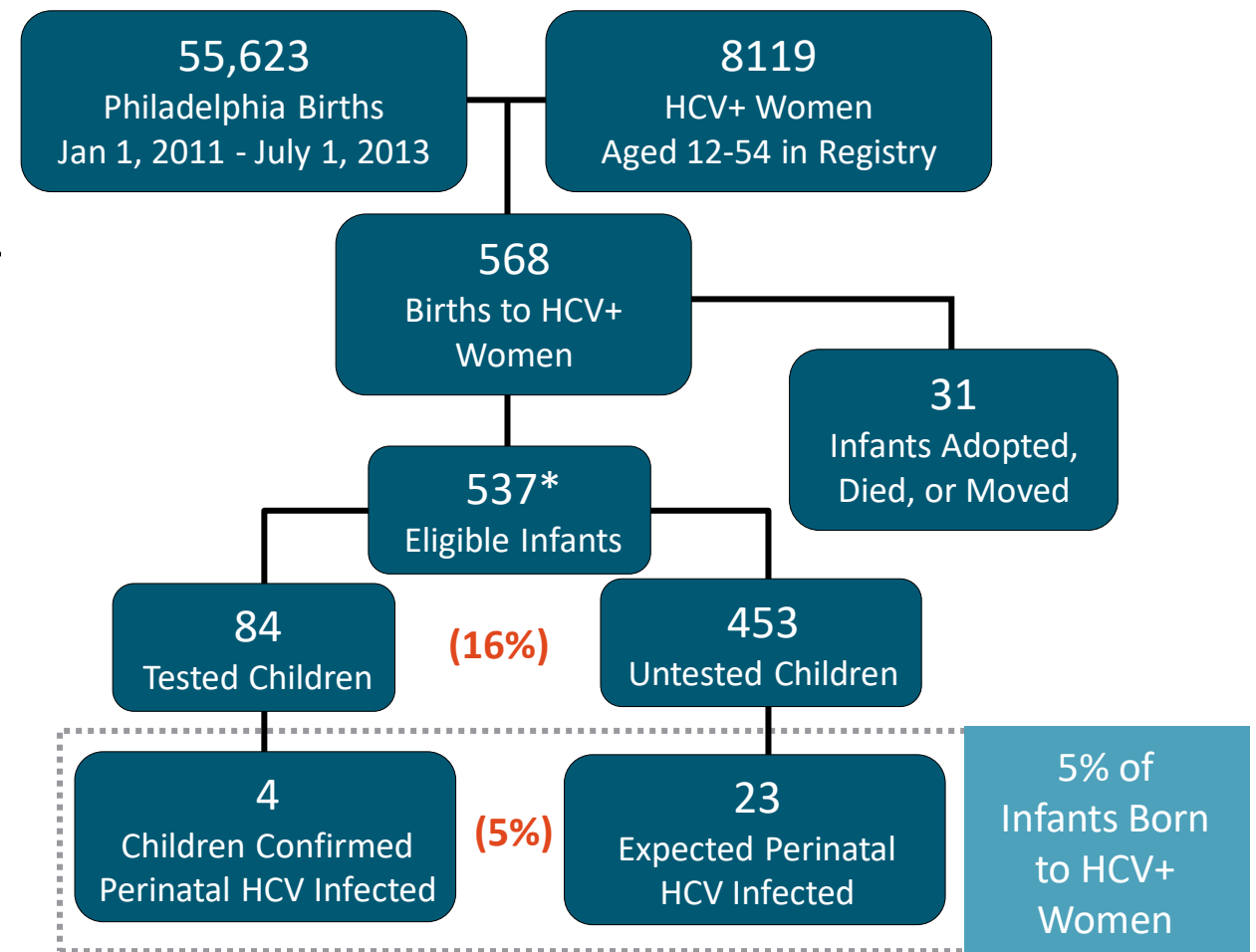
- 25% to 40% of infants clear HCV by 2-3 yrs of age<sup>[1]</sup>
- Impact of HCV infection in children on quality of life<sup>[1,2]</sup>
  - Reduced physical functioning<sup>[1,2]</sup>
  - Executive function impairment in 20% of children with HCV<sup>[1]</sup>
  - Worse cognitive functioning vs children without HCV<sup>[1]</sup>
    - Parental emotional impact and decrement in parental quality of life<sup>[1]</sup>
- Higher rates of cirrhosis in children who acquire HCV through MTCT<sup>[1]</sup>
- Hepatocellular carcinoma is second most common hepatic malignancy in children<sup>[1,3]</sup>

# AASLD/IDSA: Screening of Children Born to Mothers With HCV Infection

Recommendation	Rating
All children born to HCV-infected women should be tested for HCV infection; testing is recommended using an antibody-based test at or after 18 mos of age	I, A
Testing with an HCV-RNA assay can be considered in the first year of life, but the optimal timing of such testing is unknown	IIa, C
Testing with an HCV-RNA assay can be considered as early as 2 mos of age	IIa, B
Repetitive HCV RNA testing prior to 18 mos of age is not recommended	III, A
Children who are anti-HCV positive after 18 mos of age should be tested with an HCV-RNA assay after age 3 to confirm chronic hepatitis C infection	I, A
The siblings of children with vertically acquired chronic HCV should be tested for HCV infection, if born from the same mother	I, C

# Are We Actually Testing Children?

- Testing rates evaluated in children born to mothers with HCV, using HCV surveillance data from Philadelphia Department of Public Health, Hepatitis Registry
- Follow-up testing not conducted in majority of infants born to mothers with HCV infection



\*Followed for up to 20 mos after birth.



# AASLD/IDSA: Treatment in Children and Adolescents With HCV Infection

Recommendation	Rating
Direct-acting antiviral treatment with an approved regimen is recommended for all children and adolescents with HCV infection aged $\geq 3$ yrs 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

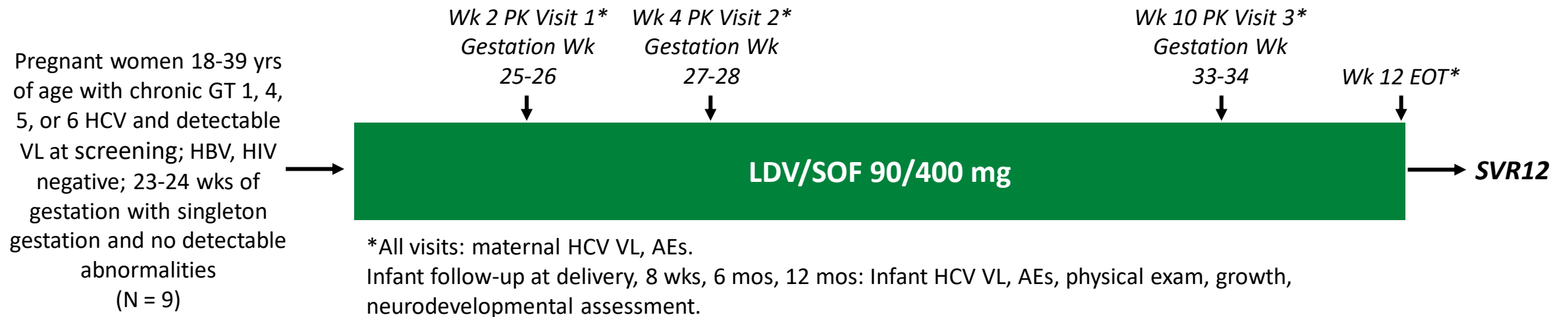
# Safety of DAAs in Pregnancy

DAA	Pregnancy	Lactation	Fertility	Historical FDA Classification
Glecaprevir/ pibrentasvir	No birth defects reported in animal data	Detected in rat milk; no human data	No effect on fertility in rats; no human data	None assigned
Ledipasvir/ sofosbuvir	No birth defects reported in animal data	Detected in rat milk; no human data	No effect on fertility in rats; no human data	B*
Sofosbuvir/ velpatasvir	Increase in visceral malformations with velpatasvir alone in rabbits	Detected in rat milk; no human data	No effect on fertility in rats; no human data	None assigned

\*Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women.

# HCV Treatment With LDV/SOF During Pregnancy

- Open-label, phase I study of ledipasvir/sofosbuvir (LDV/SOF) for 12 wks in pregnant women with HCV

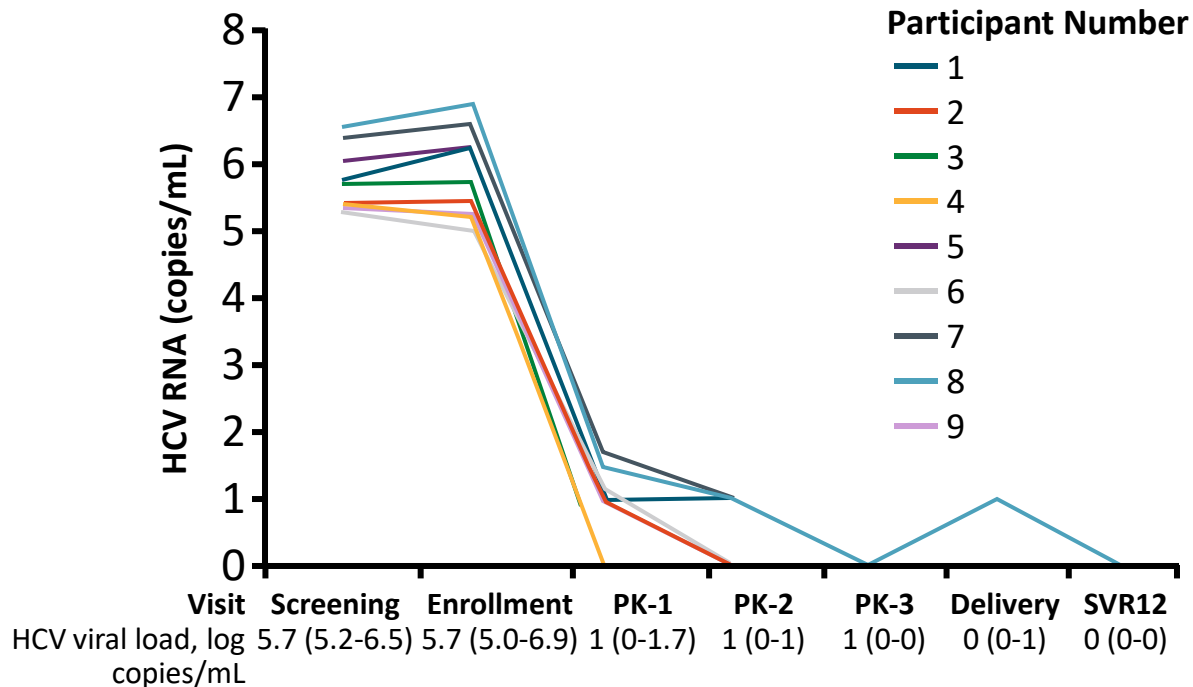


- Primary endpoint: PK of LDV/SOF 90/400 mg therapy in pregnancy
- Secondary endpoints: SVR12, maternal and neonatal safety, neonatal growth, MTCT rate

# HCV Treatment With LDV/SOF During Pregnancy: Results

- 9 women (100%) who completed SVR12 assessment achieved cure

**HCV Viral Response to LDV/SOF**



\*Grade 1 nausea/vomiting, n = 3; grade 1 diarrhea, n = 1; grade 2 fatigue, n = 1.

†Due to umbilical cord prolapse. \*Shoulder dystocia, n = 1; neonatal opioid withdrawal syndrome, n = 2.

Maternal AEs and Pregnancy Outcomes	Patients
Maternal AEs related to LDV/SOF,* n (%)	5 (56)
Maternal AEs related to LDV/SOF grade > 2, n (%)	0
D/c of LDV/SOF due to AEs, n (%)	0
Median gestational age at delivery, wks + days (range)	39 + 2 (36 + 6 to 41 + 0)
Delivery, n (%)	
▪ Vaginal	5 (56)
▪ Scheduled cesarean section	3 (33)
▪ Emergent cesarean section†	1 (11)
Median Apgar scores (range)	
▪ 1 min	8 (6-9)
▪ 5 min	9 (8-9)
Median infant birth weight, kg (range)	3.29 (2.60- 4.16)
Median infant hospital stay duration, days (range)	3 (2-12)
Detectable HCV RNA in cord blood, n (%)	0
Admission to neonatal intensive care unit‡, n (%)	3 (33)

# Conclusions

- HCV among women of childbearing age and during pregnancy is increasing due to opioid epidemic
- Guidelines have been updated to **recommend HCV screening for all pregnant women**
- HCV treatment recommended before pregnancy for women of childbearing age
- HCV treatment during pregnancy is not currently recommended by guidelines, but can be considered on an individual basis

# Conclusions

- Mother-to-child HCV transmission rates range from ~ 6% to ~ 11%
  - Coinfection with HIV significantly increases risk of HCV MTCT
- **All children of mothers with HCV infection should be tested for HCV antibodies at 18 mos of age and referred to specialty care as needed**
- HCV treatment is currently recommended in children  $\geq 3$  yrs of age
- Based on limited animal data, some HCV DAA agents generally safe in pregnancy
  - Studies underway to determine safety and efficacy of DAA agents on pregnancy

# Go Online for More Information From CCO on Screening and Management of HCV in Women!

**Interactive Text Module** featuring expert insights on key strategies for improving HCV detection and care in women

**ClinicalThought Commentary** in which expert faculty provide helpful insights from their own clinical practice experience



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