## Perinatal Hepatitis C Webinar

Catherine Chappell, MD, MSc chappellca@upmc.edu

Anne-Marie Rick MD, MPH, PhD Annemarie.rick@chp.edu





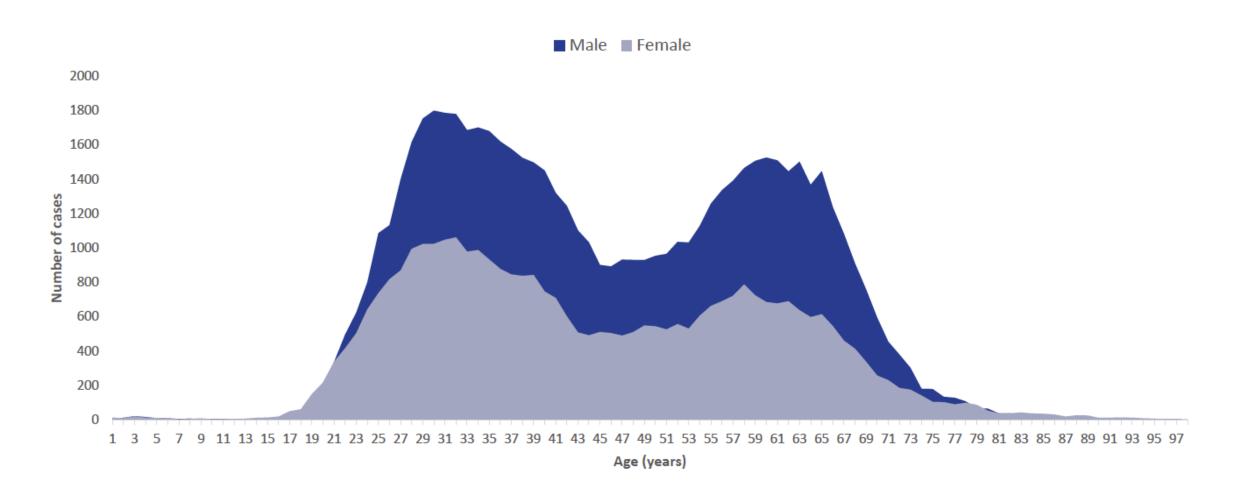




## Disclosures

- Dr. Rick
  - Consultant for Pfizer, Inc
  - Medical Director for the Human Milk
     Science Institute and Biobank
- Dr. Chappell
  - Consultant and research funding from Gilead Sciences
  - Research funding from Merck and Organon

## Newly reported Hepatitis C cases in 2020



#### CLINICAL SCENARIO

- TJ is a 33-year-old G2P1001 @ 14 weeks who presents for routine antenatal care. She has a history of opioid use disorder and has been in recovery for 2 years since the birth of her daughter. She was not screened in her previous pregnancy for HCV.
- Should she be screened for HCV?

## Timeline of HCV screening recommendations in the United States, 2018–2023

#### **March 2020**

U.S. Preventive Services
Task Force recommends
screening all adults aged
18–79, including
pregnant adults

#### **May 2021**

American College of Obstetricians and Gynecologists recommends screening all pregnant persons during each pregnancy

#### **November 2023**

CDC recommends HCV
PCR screening at age ≥26 months of age for atrisk children

#### 2018

American Association for the Study of Liver Diseases (AASLD) and Infectious Diseases Society of America (IDSA) recommend universal screening during pregnancy

#### **April 2020**

CDC recommends screening all adults ≥18 and all pregnant persons during each pregnancy\*

#### **June 2021**

Society for Maternal-Fetal Medicine recommends screening all pregnant persons during each pregnancy

<sup>\*</sup>except in settings where the prevalence of HCV infection is <0.1%

## HCV Screening in Pregnancy: Two for the price of one

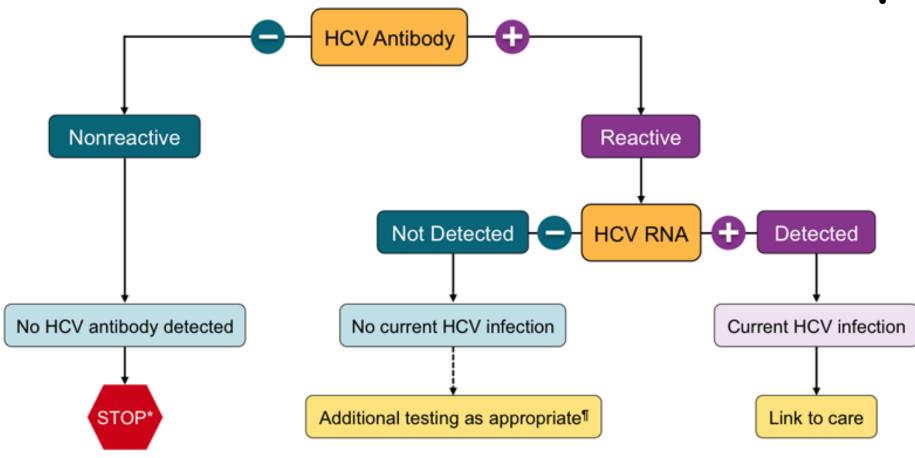


- 1. High engagement in healthcare
- 2. Unique motivation
- 3. Linkage to HCV care/treatment
- 4. Prevention of cirrhosis



- 1. Identification of all infants exposed
- 2. Early detection of perinatal HCV
- 3. Linkage to HCV care/treatment
- 4. Prevention of cirrhosis

#### Recommended Testing Sequence for Identifying Current HCV Infection



- Hepatitis C Ab with Reflex HCV RNA
  - If the HCV antibody test is positive, then an HCV RNA test will be automatically performed by the laboratory on the same blood sample.

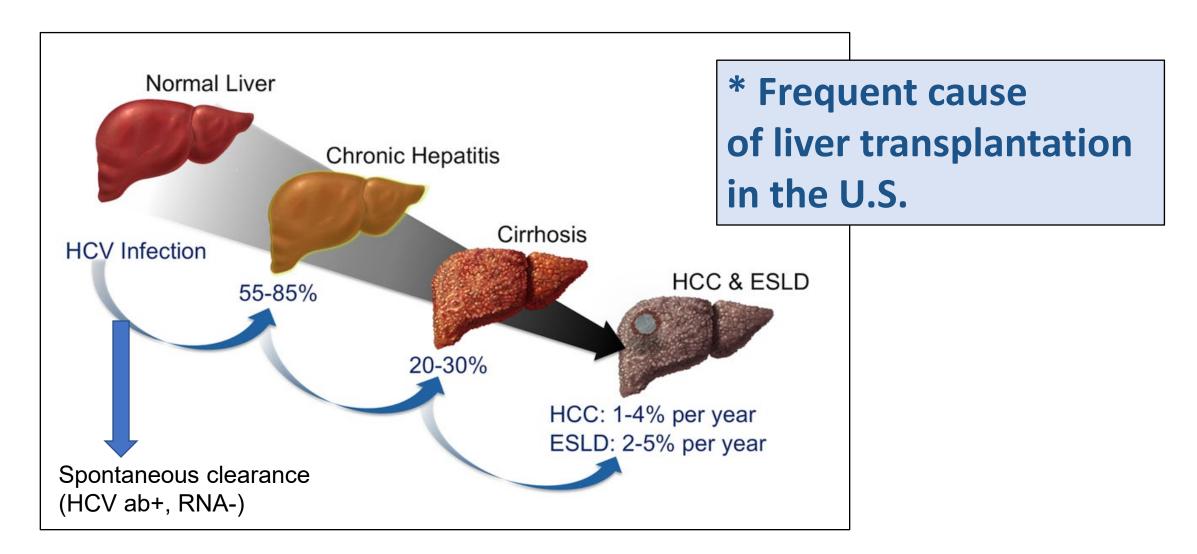
<sup>\*</sup> For persons who might have been exposed to HCV within the past 6 months, testing for HCV RNA or follow-up testing for HCV antibody is recommended. For persons who are immunocompromised, testing for HCV RNA can be considered.

<sup>¶</sup>To differentiate past, resolved HCV infection from biologic false positivity for HCV antibody, testing with another HCV antibody assay can be considered. Repeat HCV RNA testing if the person tested is suspected to have had HCV exposure within the past 6 months or has clinical evidence of HCV disease, or if there is concern regarding the handling or storage of the test specimen.

#### CLINICAL SCENARIO

- TJ is a 33-year-old G2P1001 @ 14 weeks who presents for routine antenatal care. She has a history of opioid use disorder and has been in recovery for 2 years since the birth of her daughter. She was not screened in her previous pregnancy for hepatitis C, and her current testing shows is as follows:
  - HCV antibody positive
  - HCV RNA 560,000 IU/mL
- What are the implications of HCV in pregnancy?

## **Natural History of HCV\***



## Impact of HCV on Pregnancy: Maternal Health

Study	HCV+ Cases	Controls	Gestational Diabetes
Pergam 2008	506	SUD, but HCV negative	OR 2.5 (1.04-6.03) in women with excessive weight gain
Reddick 2011	555	HCV negative	OR 1.6 (1.0-2.6)
Connell 2011	999	HCV negative	40% increase
Kushner 2022	1636	HCV ab+/RNA-	40% decrease

- Intrahepatic cholestasis of pregnancy
  - Meta-analysis of 3 studies showed a 20-fold increased risk (Wijampreecha, et al. *Clin Res Gasrto Hepatol*. 2017)
  - 4% vs. <2% prevalence of ICP (Kushner, 2022)</li>
  - Associated with 2.5x increase incidence of stillbirth (Ovadia C., et al. *Lancet*. 2019)
- Post-partum hemorrhage 9% vs. 5% (Kushner, 2022)

## Impact of HCV on Neonatal Outcomes

- Neonatal Outcomes
  - Preterm birth\*
  - Fetal growth restriction\*\*
  - Low birth weight \*\*
  - Admission to NICU
  - Mechanical ventilation
  - Congenital anomalies

\*\*\*Caveat: It is difficult to know with certainty whether the increased risk of such adverse fetal outcomes is due to the viral effect of HCV or to potential confounders in the population being studied

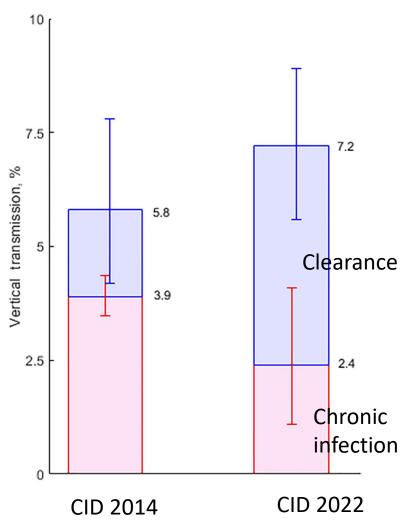
<sup>\*</sup>HCV ab+ RNA- vs. HCV ab+ RNA+

\*\*Supported by recent meta-analysis

### Perinatal Hepatitis C Transmission: Frequency?

- What is the rate of perinatal Hepatitis C transmission?
  - **5.8%** (95% CI 4.2-7.80) (HIV negative)<sup>1</sup>
  - 10.8% (95% CI 7.6-15.2) (HIV co-infected)<sup>1</sup>
  - **7.2%** (95% CI 5.6-8.9) ( HIV negative)<sup>2</sup>
  - 12.1% (95% CI 8.6-16.8) (HIV co-infected)<sup>2</sup>

## Overall, HCV perinatal transmission ~6-7%, but chronic infection 3-4%.



## Perinatal Hepatitis C Transmission: What do we know?



#### Risk factors for perinatal Hepatitis C transmission

- Prolonged rupture of membranes
- Obstetric procedures and intrapartum events that lead to infant exposure to Hepatitis C-infected maternal blood; eg, internal fetal monitoring, vaginal/perineal lacerations, operative delivery
- Maternal injection-drug use

#### When does transmission occur?

	Elective Cesarean Section	Non-elective cesarean section
Early in utero	27.5% (13.3–45.8)	24.8% (12.1–40.8)
Late in utero	72.5% (54.2–86.7)	66.0% (42.5–83.3
At delivery	N/A	9.3% (.5–30.6)

#### CLINICAL SCENARIO

- TJ is a 33-year-old G2P1001 @ 14 weeks who presents for routine antenatal care. She has a history of opioid use disorder and has been in recovery for 2 years since the birth of her daughter. She was not screened in her previous pregnancy for hepatitis C, and her current testing shows is as follows:
  - HCV antibody positive
  - HCV RNA 560,000 IU/mL
- What are the implications of HCV in pregnancy?
- How do we manage HCV?

### Management of HCV During Pregnancy

- Recommended lab tests only once:
  - LFTs, albumin, platelet count, HCV genotype\*
  - STI screening
  - Hepatitis B surface IgG, Hepatitis A total Ig
- Vaccinate if Hepatitis A or B nonimmune
- Avoid hepatotoxic substances (alcohol, Tylenol >2 grams per day)
- Transmission risk counseling (IVDU, sexual contacts, razors, etc.)
- Third trimester growth ultrasound due to increased risk of FGR

## Interventions to Decrease Perinatal Transmission: Lessons from HIV?

- Elective cesarean delivery?
  - No randomized controlled trials
  - Meta-analysis of 8 studies including 641 mother-infant pairs show no change in transmission rate (Gharmar ME, et al. Arch Gynecol Obstet. 2011)
- Avoidance of breast feeding?
  - No Hepatitis C RNA found in breastmilk (Polyweka S, et al. Clin Infect Dis. 1999)
  - No increased transmission with breast vs. bottle feeding (Kumar RM, et al. J Hepatol. 1998)
- Avoidance of procedures that might increase maternal to infant blood exchange
  - Avoid fetal scalp monitoring, amniocentesis, operative delivery, delayed cord clamping

#### The Revolution in HCV Treatment

- 2014: <u>Harvoni</u> (ledipasvir/sofosbuvir) licensed for treatment for genotype 1, 4, 5/6
- 2016: Epclusa (velpatavir/sofosbuvir) pan-genotypic coverage including genotype 2 & 3
- 2017: Mavyret (pibrentasvir/glecaprevir) pan-genotypic coverage, cheaper
- All >95% CURE with 8-12 weeks of treatment

## If I were to choose any chronic viral infection it would be HCV.



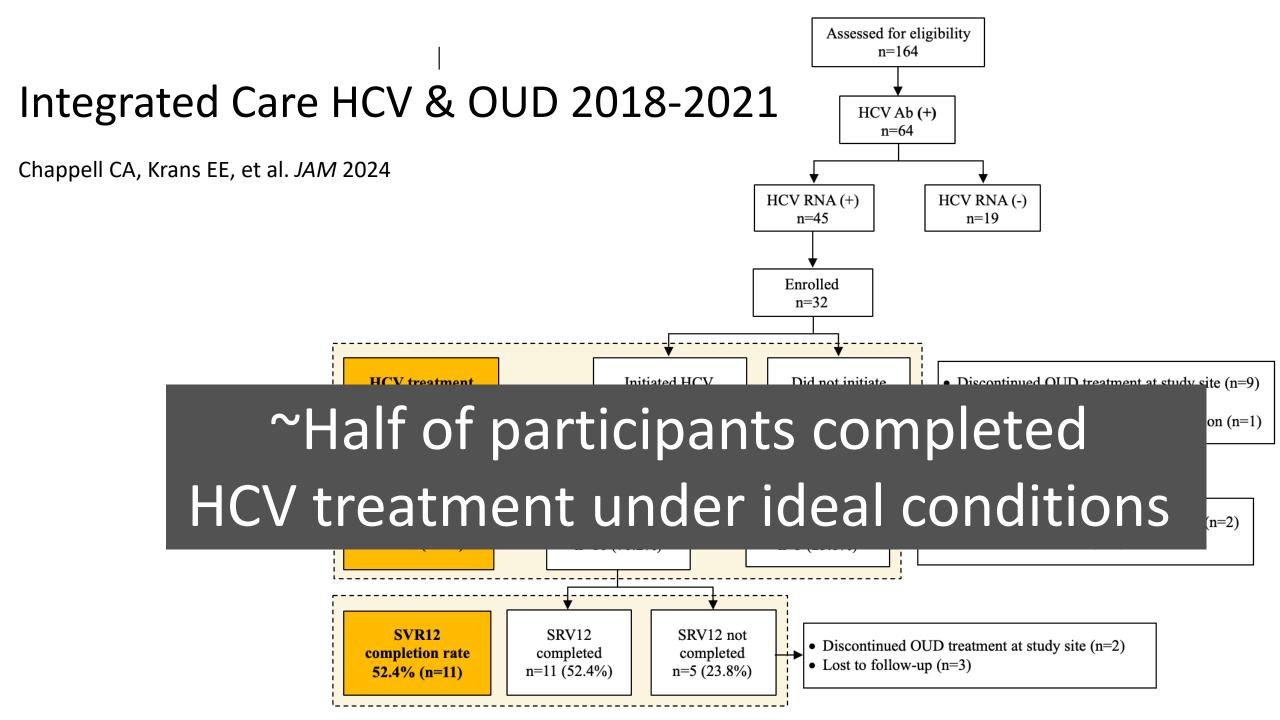




## Postpartum HCV Treatment Cascade for Women with Opioid Use Disorder 2016-2019: After DAAs

	Outcome	Probability	95% CI
60 days	HCV testing	70.3	61.5-79.1
	HCV diagnosis	30.9	16.2-45.7
	Linkage to treatment	3.2	2.1-4.3
6 months	HCV testing	70.0	60.4-79.5
	HCV diagnosis	30.9	23.6-38.2
	Linkage to treatment	<mark>5.9</mark>	4.9-6.9

<sup>\*</sup>Pooled Medicaid Data from Delaware, Kentucky, Maine, North Carolina, Pennsylvania and West Virginia

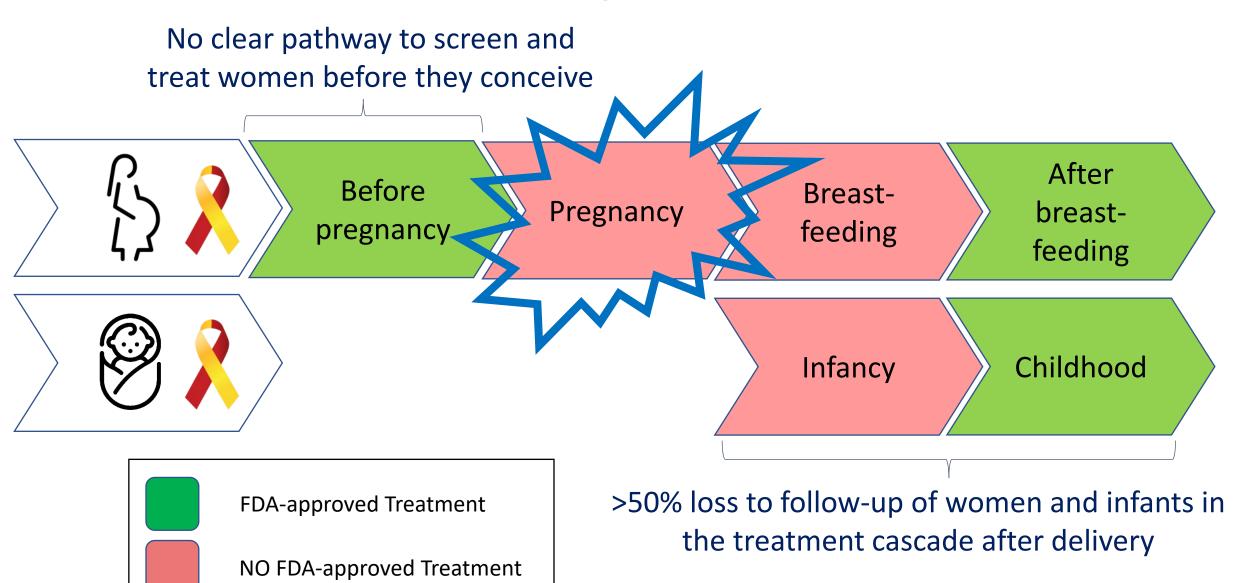


### TIPS FOR POSTPARTUM LINKAGE

- Antenatal consult with HCV treatment provider
- Co-locate with care
  - Postpartum care
  - Pediatric care
  - Opioid use disorder care
- Provide HCV treatment via tele-medicine
- Postpartum period is a window of opportunity for treatment because of increased insurance coverage associated with pregnancy



## **HCV Treatment Availability for Women and Children**



### Harms of Evidence Gaps

- Historically, pregnant women were considered "vulnerable" because of the presence of a third party (the fetus) was unable to give consent.
- Pregnant women are often excluded from research participation, leading to harms:
  - Unknown adverse consequences
  - Limited access to studies with direct benefit
  - Incorrect dosing



## HOW DO WE GET TO ROUTINE HCV TREATMENT IN PREGNANCY?

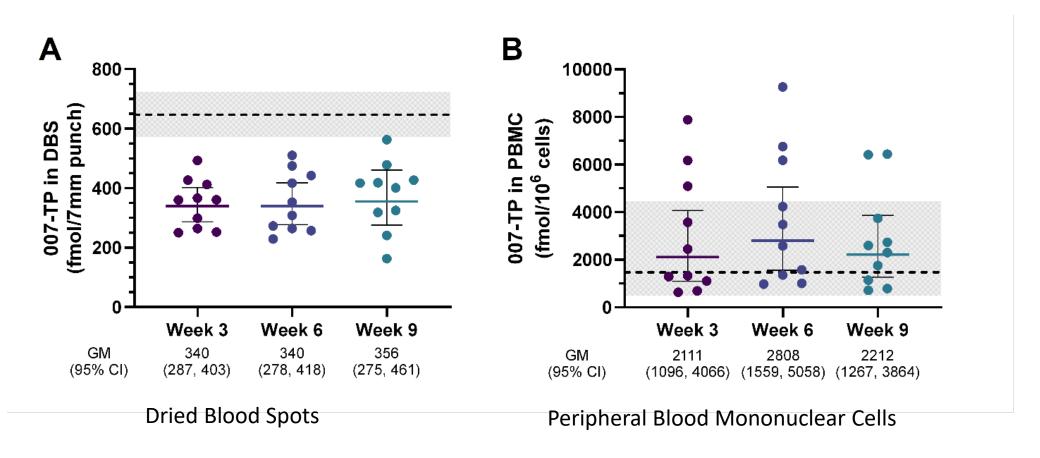
- We first need to make sure the dose for adults in appropriate for pregnancy.
- Small studies where we evaluate the concentrations of the drugs in pregnant people vs. those in non-pregnant people.
- Bear with me, while I present to pharmacology data.

## Pharmacokinetic Data for LDV/SOF and SOF/VEL in Pregnancy

Study	AUC* Mean (%CV)	Pregnant Women with HCV	Non-Pregnant Women with HCV	%GMR (90%CI)
HIP-1	SOF	1840 (15.2)	2210 (49.9)	92 (79, 107) -
	GS-331007**	8930 (12.0)	14800 (29.6)	62 (56, 69)↓
	LDV	10500 (34.4)	12100 (46.0)	90 (70, 117) -
HIP-2	SOF	2039.62 (29.75)	1483.83 (66.43)	<b>138 (106, 178)</b> ↑
	GS-331007**	9588.94 (18.75)	15361.31 (22.35)	<mark>62 (55, 71) ↓</mark>
	VEL	3244.45 (39.89)	3570.65 (72.04)	91 (67, 123) -

<sup>\*</sup>AUC = Area under the curve; \*\*GS-33007 = inactive, renally excreted SOF metabolite

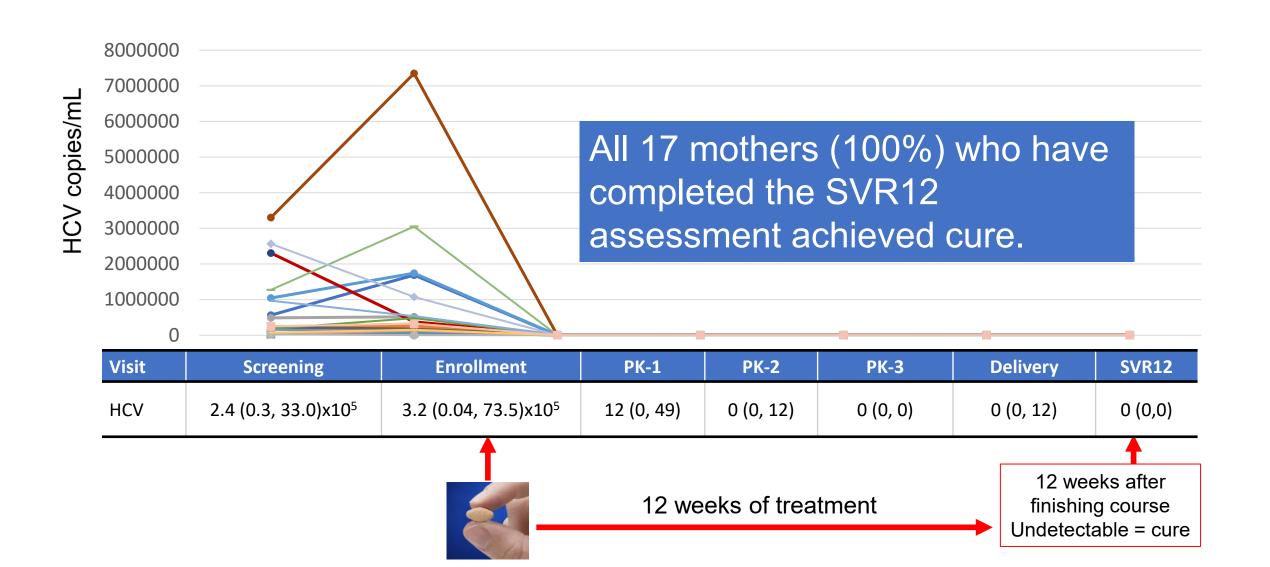
#### Intracellular Sofosbuvir Concentrations



Dried Blood Spots impacted by hemodilution of pregnancy.

Active Sofosbuvir Metabolite concentrations in PBMCs is reassuring.

## HCV Viral Response during Pregnancy to LDV/SOF and SOF/VEL



## Delivery and Neonatal Outomes (N=20)

Outcome	N (%) or Median (High, Low)	
Maternal Related Adverse Events	11 (55%)	
Maternal Related Adverse Events > Grade 2	1 (5%)	
Vaginal Delivery	12 (60%)	
Gestational age at delivery (weeks + days)	39+0 (35+4, 41+0)	
Preterm birth	3 (15%)	
Birth weight (g)	3,290 (2,580, 4,160)	
Infant Length of Hospital Stay (days)	3 (2, 12)	
Infant Related Adverse Events	0 (0%)	
Infant HCV RNA at Any Visit (copies/mL) (n=17)	0 (0, 0)	

## Hepatitis C treatment in pregnancy: increased self-esteem and sense of well-being, which was sometimes protective against relapse

I'm down to like barely detectable... I think it's definitely gonna help me not wanna keep relapsing or using because this has been such a process trying to cure it... that's not the life I wanna live anymore, I don't wanna use

"...Lifesaving..."

I think I'm.. a bright thing and it's a clean start...

I mean ecstatic, grateful. I don't know, kind of proud that I went through with something and accomplished it.

## CONCLUSIONS FROM EARLY PK STUDIES OF HCV TREATMENT DURING PREGNANCY

- No clinically significant PK changes in SOF, VEL, or LDV in identified attributable to pregnancy.
  - GS-331007 (inactive SOF metabolite) was reduced, likely due to increased GFR during pregnancy and is unlikely to be clinically significant.
- Reassuring preliminary safety and efficacy outcomes for LDV/SOF and SOF/VEL
- Larger study must be conducted to support safety and efficacy of antenatal HCV treatment

# <u>Safety, Tolerability, and Outcomes of Velpatasvir/SofosbuviR</u> in Treatment of Chronic Hepatitis <u>C</u> Virus during Pregnancy (STORC)

#### Primary Objectives:

- To evaluate the sustained virologic response 12 weeks after completion of SOF/VEL treatment (SVR12) in women treated during pregnancy.
- To evaluate impact of antenatal treatment with SOF/VEL on the gestational age at delivery for women who received SOF/VEL for HCV treatment during pregnancy.
- Secondary Objectives:
  - To evaluate the maternal and neonatal safety of HCV treatment during pregnancy with SOF/VEL
  - To determine the rate of HCV perinatal transmission among women treated with SOF/VEL during pregnancy according to HIV co-infection status

### STORC Study Design



#### 12-week treatment course

Enrollment 20-30 weeks' gestation V3: 4 weeks; safety labs V4: 8 weeks, safety labs

V5: End of treatment

Delivery: in person or chart review

Sustained viral response (SVR)12 visit (post-partum)

HCV viral load and adverse events



Delivery

Visit 1 (8w)

Visit 2 (6m)

Visit 3 (12m)

HCV viral load, adverse events, physical exam, growth and neurodevelopmental assessment



### **STORC Study Sites**

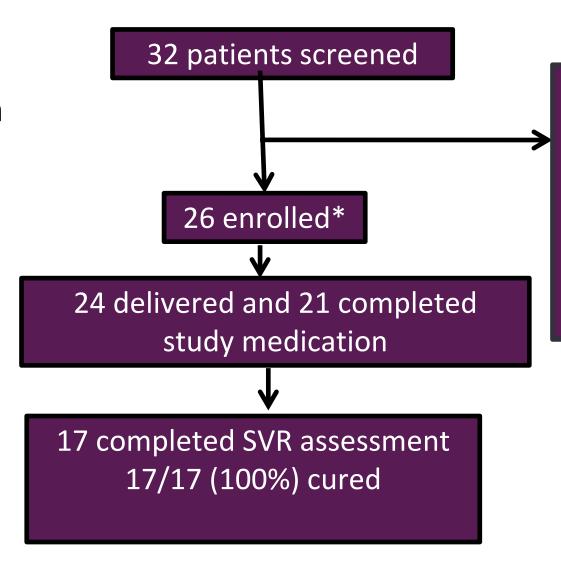
- Pitt/MWRI
- Ohio State
- The Christ Hospital
- University of Utah
- University Health Network
  - Saint Michael's Toronto
  - London HSC
- Marshall University\*
- Vanderbilt\*

N = 100 participants

-SVR <92%

-PTB rate > 13% difference

## STORC Interim Results



#### Screen Fails (n=5)

1 declined to participate
1 clinically significant drug use
2 incarceration
1 intrauterine transfusion due to

alloimmunization of pregnancy

100% of infants tested are
HCV RNA undetectable
(N=16)

1 infant did not get blood sampling, 1 had an insufficient sample

Chappell CA, et al. AASLD. 2023

#### CLINICAL SCENARIO REVISITED WITH KEY TAKE-AWAYS

- TJ is a 33-year-old G2P1001 @ 14 weeks with active HCV.
  - Labs only once (LFTs, hepatitis A/B serologies, HCV genotype maybe, platelet count and albumin)
  - Third trimester growth ultrasound
  - Watch out for gestational diabetes and cholestasis of pregnancy
  - Vaginal delivery and breastfeeding are OK! Try to avoid FSE, early amniotomy
  - Direct-acting antivirals could eliminate HCV
  - Facilitate linkage to care for HCV treatment
  - Someday soon, testing and treatment of HCV during pregnancy will be a reality which would cure maternal HCV and could prevent perinatal transmission

#### CLINICAL SCENARIO

TJ is worried about her child's risk of contracting Hepatitis C from her.
 She wants to do know what she should do and whether or not she can breastfeed.

- What is the risk that TJ's child will get HCV from their mother?
- What do you recommend to TJ in terms of HCV screening for her child and other precautions?
- Are there any other recommendations?

## **Increasing Prevalence of Pediatric HCV**

- 3.5 to 5 million children worldwide with chronic HCV
- 0.2%-0.4% of 6- to 19-year-olds in U.S. are HCV Ab+
- Perinatal mother-to-child transmission most common cause
  - 5% of infants exposed *in utero* become infected
  - Higher if mother HIV-infected or high viral load

Increased infections in pregnant women = increased infections in infants



Source: (Indolphi, 2019); (Gower, 2014) Alter, 1999).

# CDC PERINATAL HCV TESTING RECOMMENDATIONS

**HCV RNA at age ≥2–6 months** 

HCV RNA at age ≥2 months OR Anti-HCV at age ≥18 months

HCV RNA for infants and children aged 7–17 months who have not been tested

Anti-HCV with reflex NAT for RNA at age ≥18 months for children who have not been tested

Retest for HCV RNA before initiating treatment

**Test siblings** 



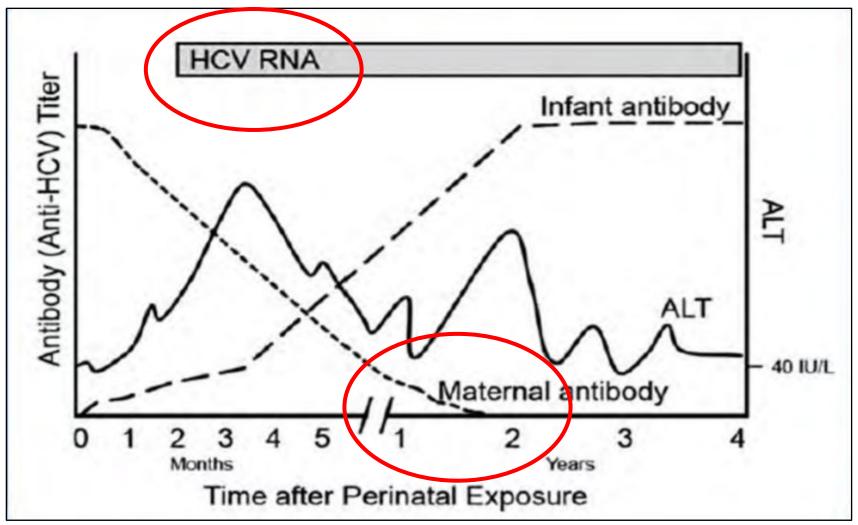
# PERINATAL HCV TESTING RECOMMENDATIONS

ORGANIZATION	HCV RNA at age ≥2–6 mths	Anti-HCV with reflex NAT for RNA at age ≥18 mths	Confirm Anti- HCV at age ≥18 mths	Test Siblings	Retest for HCV RNA before initiating treatment
CDC (Current)1	~	If not previously tested *	No	~	•
CDC (Prior to November 2023)	Consider (≥2 mths)	If not previously tested	NA	NA	NA
<b>AAP (2021)</b> 2	Consider	•	•	NA	NA
AASLD-IDSA (2020)3	Consider (≥2-12 mths)	•	•	•	•
1 Panagiotako poulos L. Sandul AL, et al. CDC	Recommendations for	'RNA for infants and		Slide cr	rodit: Pachaol Rioltz MPH

1 Panagiotako poulos L, Sandul AL, et al. CDC Recommendations for Hepatitis C Testing Among Perinatally Exposed Infants and Children — 'RNA for infants and children aged 7-17 months

Slide credit: Rachael Bieltz, MPH

# Why screen at 2-6 months rather than 18 months?



Source: Squires JE and Balistreri WF. Hepatology Commun. 2017; 1(2):87-98.



# Barriers to hepatitis C Screening for Infants/Toddlers

- Loss to follow-up
- In care of guardian / DHS
- Unaware of maternal hepatitis C status
- Inconsistent documentation in the EHR
- Infrequently see 'at-risk' infants
- Lack of awareness of screening guidelines
- Wrong test ordered
- In-office vs lab-based phlebotomy
- Child does not obtain test.

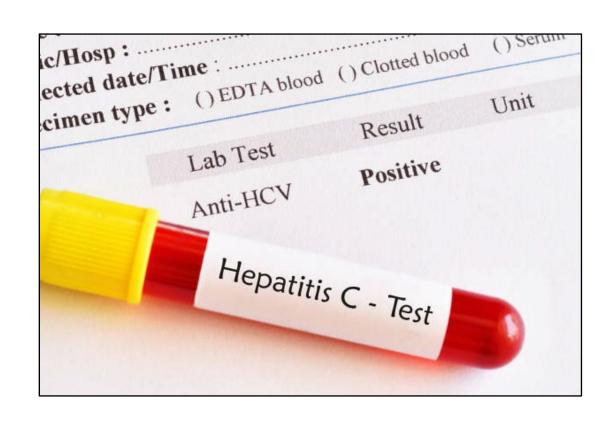
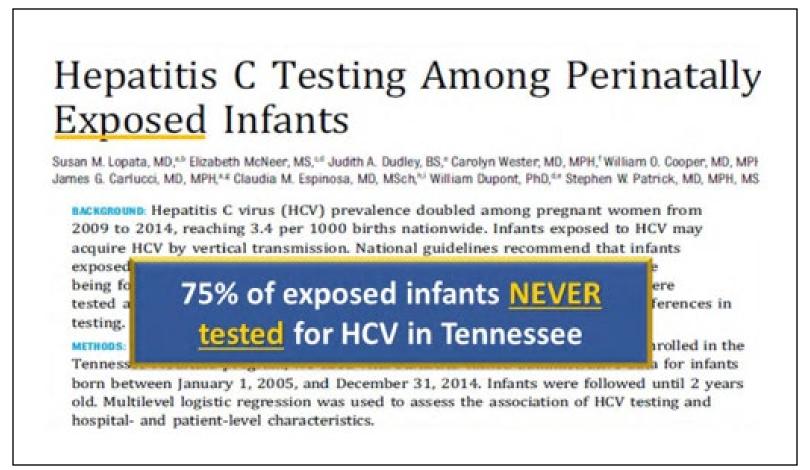


Image Source: iStock

# **Lopata Study**

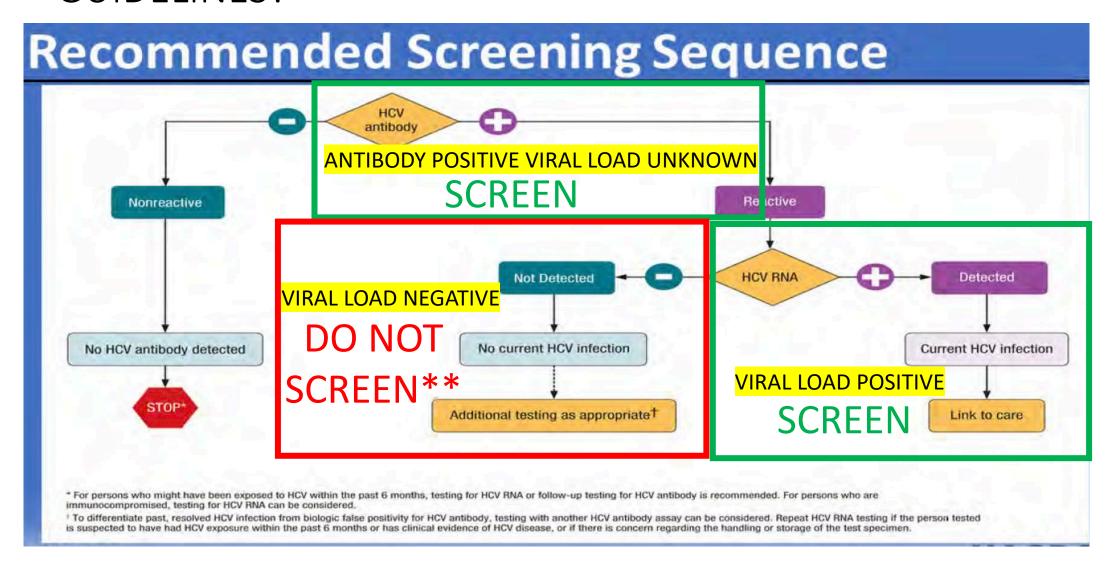
75% of exposed infants never tested for HCV in Tennessee



Source: Lopata SM, et al. Pediatrics. 2020; 145(3):e20192482.



# WHICH INFANTS NEED SCREENING UNDER 2023 CDC GUIDELINES?



# **Pediatric HCV Antiviral Therapy**

Indications: ≥ 3 years; HCV viremia

Advantages: Safe, single pill, minimal side effects >95% cure

Genotype	DAA	Age	
2 and 3	Sofosbuvir with ribavirin x 12 weeks	≥ 3 year; approved 2017/2019	
1, 4, 5, 6	DAA: Ledipasvir/Sofosbuvir x 12 weeks	≥ 3 years; approved 2017/2019	
All	Glecaprevir/Pibrentasivr x 8–12 weeks	≥ 12 years; approved 2019	
All	Sofosbuvir/velpatasvir x 12 weeks	≥ 6 years; approved 2020	

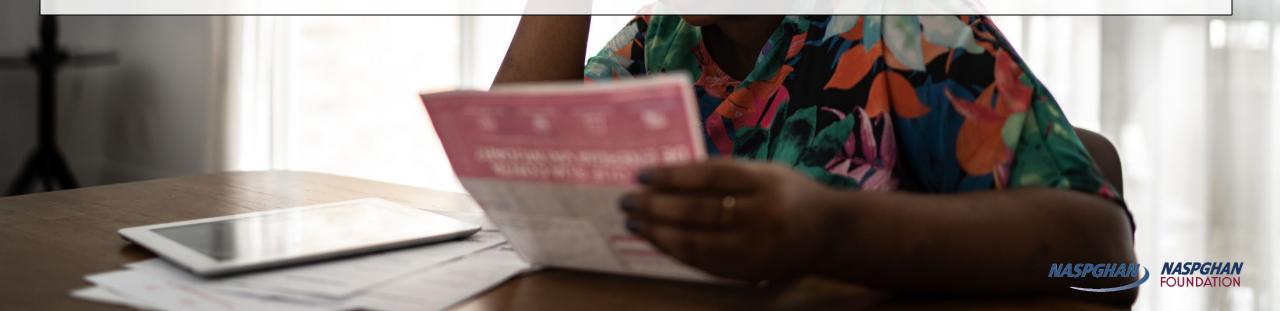
## Barriers to Cure with DAA's in Children with HCV

- Cost
- Palatability
- Medical Restrictions
- Paperwork/Appeals
- Adherence



## **The Initial Sticker Shock of Treatment**

- Can cost between \$26,000–75000 cash for a 12-week treatment
- In some cases, nearly \$1000 per pill
- Actual cost paid for the medications may be significantly lower. Patient assistance and support programs available can be as low as \$5 per co-pay with commercial insurance.



# Perinatal HCV Quality Improvement Collaborative

**Global Aim:** Improve HCV screening of at-risk children to enhance diagnosis, linkage to care and ultimately cure of chronic HCV in children.

- By 6 months: 90% identified, 90% test ordered, 80% tested, 100% of positives referred
- Refine algorithm for dissemination/scaling

#### Gen Peds:

- Anne-Marie Rick, MD, PhD
- Deborah Moss, MD
- Jennifer Zarit, MD
- Robert Cicco, MD
   GI/Hepatology
- James Squires, MD
- Mary Ayers, MD
   Peds ID
- Divna Djokic, MD Biostatistics
- Hui Liu, MS







Improve Pediatric HCV Screening



- Alison Kost, RN
- Suzanna Masartis, RN

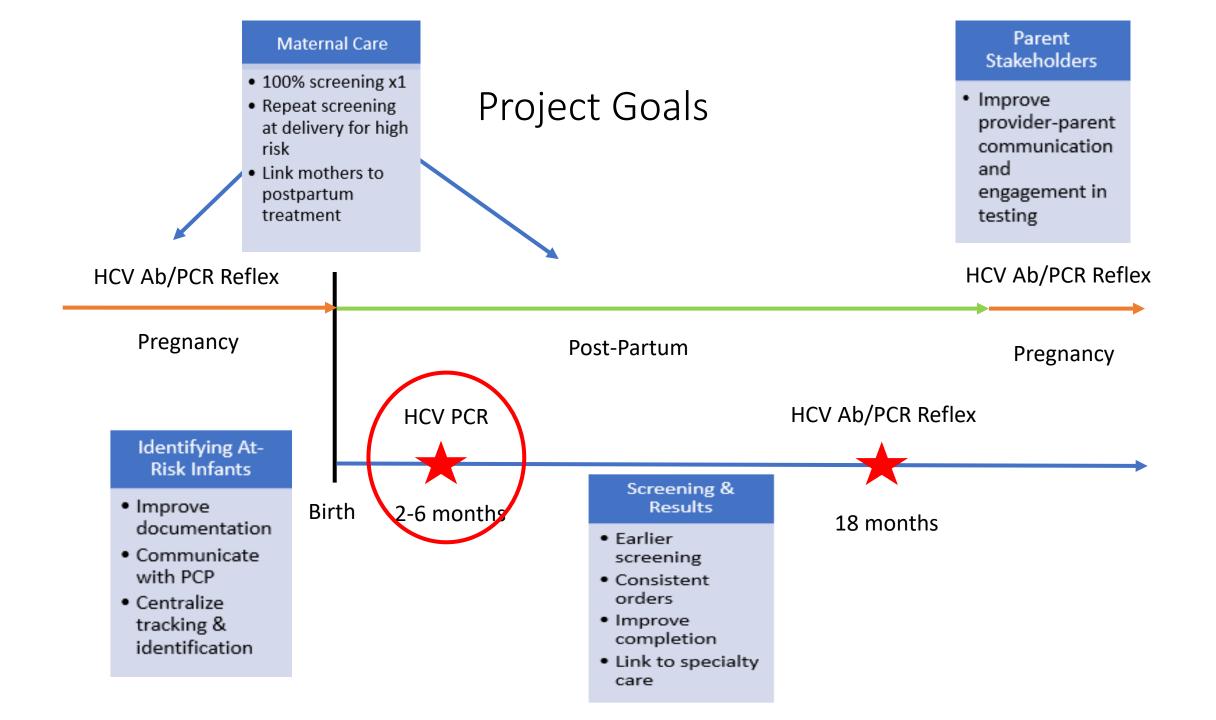
#### Pennsylvania Chapter

American Academy of Pediatrics
DEDICATED TO THE HEALTH OF ALL CHILDRENS



- OB
- Catherine Chappell, MD
- Yasaswi Kislovskiy, MD
   QI specialist
- Samantha Faulds, MS, RHIA Clinical Staff
- Desra Keller, RPT Residents
- Jennifer Deng, MD
- Zachariah Shalginewicz, MD

- Epidemiologists
  - Jennifer Fiddner, MPH, CIC
  - Rachel Bieltz, MPH, CHES
  - Bethany Reynolds



### Timeline of Perinatal HCV QI Collaborative

#### October 2022

PDSA#1: presented to newborn attendings; detailed VL status documentation MWH/GAP; HCV PCR screening for children ≥2-17 months of age if at-risk for HCV

#### June 2023

PDSA#3: tweaked lab work-flow/working with Quest; health department HCV handouts available

#### **June 2024**

PDSA#5: narrowed screening indications; rescreening of VL-mothers; expand to other practices

#### **July 2022**

SIDM DxQI Funding and QI approval obtained

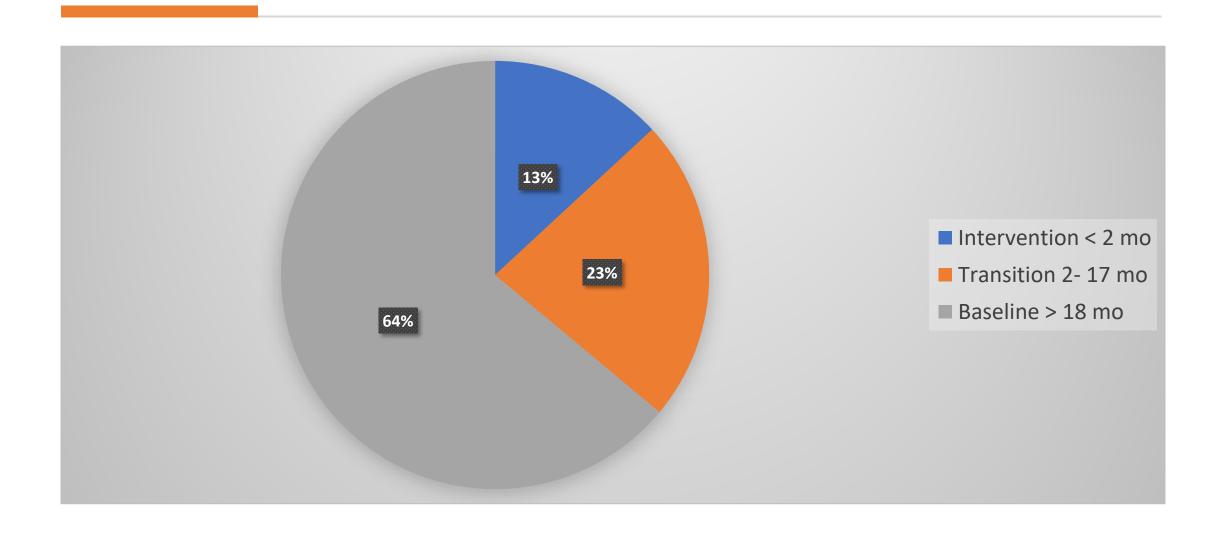
#### January 2023

PDSA#2: Presented at faculty and staff meeting; introduced smartphrase; collected baseline data

#### October 2023

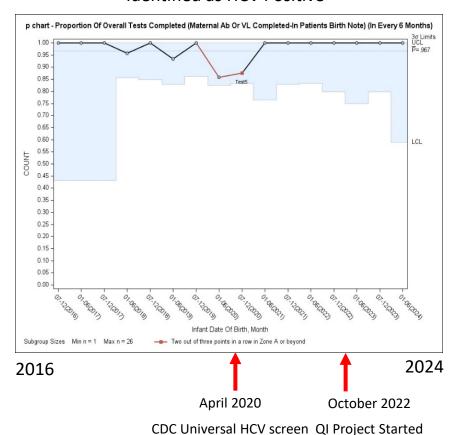
PDSA#4: Made repeat 18 month HCV Ab screen optional; engaging care coordinators

## 183 Perinatally HCV-Exposed Children

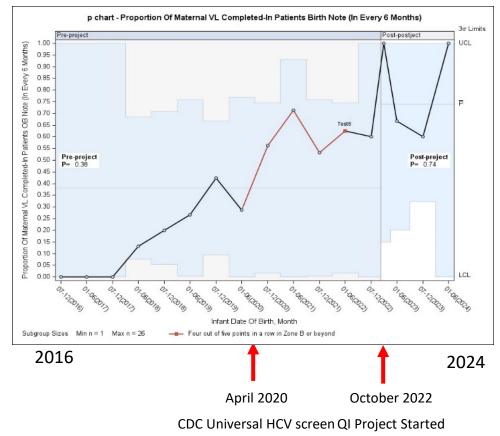


#### Pediatric Birth Note Documentation

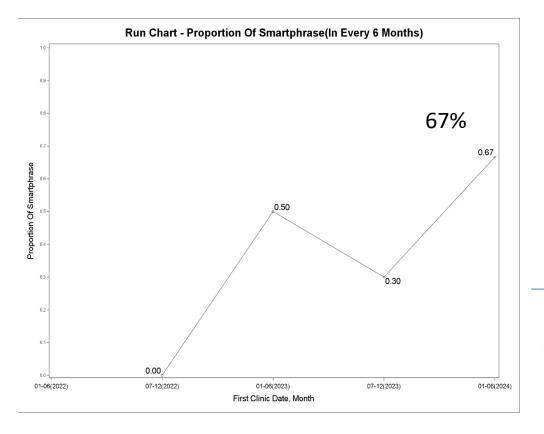
#### Identified as HCV Positive

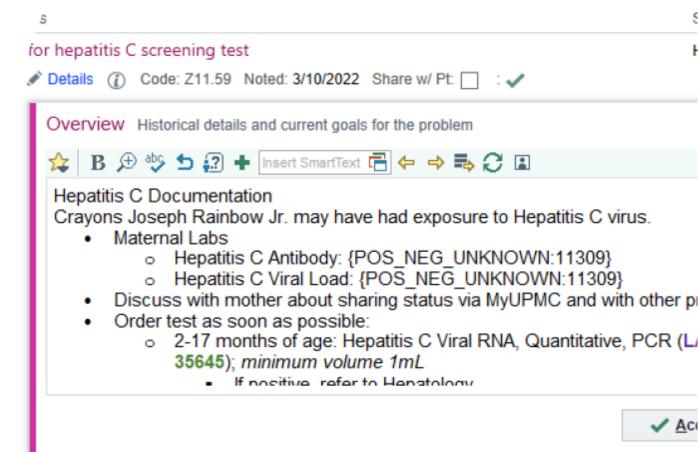


#### **HCV Viral Load Documented**



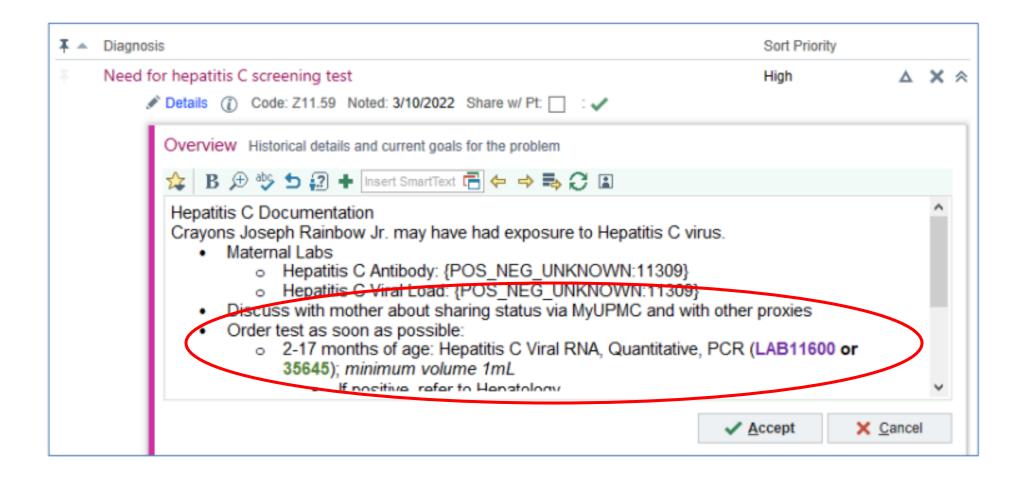
# Increasing use of SMARTPHRASE





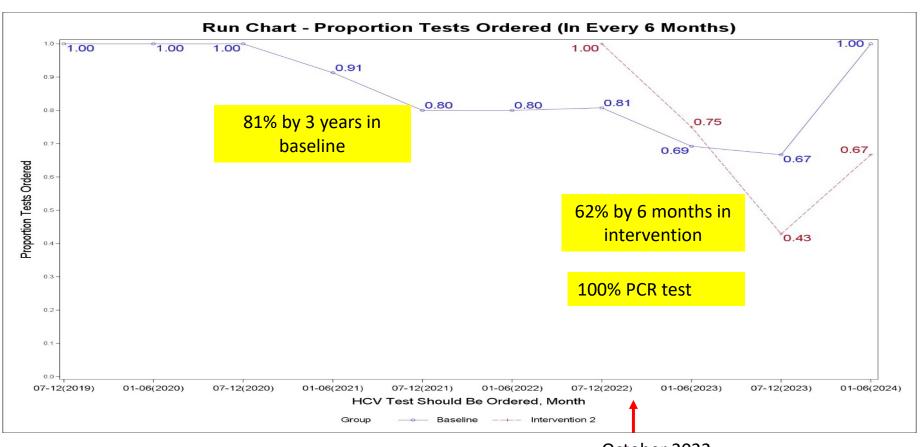
incuss screening plans with family and place future order if patient is < 2 months tompt collection via heel stick, in-clinic venipuncture (if > 20 lbs) or CHP lab references.

1 de family pediatric Hepatitis C and Children Fact Sheet



- Discuss screening plans with family and place future order if patient is < 2 months of age OR order and attempt collection via heel stick, in-clinic venipuncture (if > 20 lbs) or CHP lab referral.
- 3. Provide family pediatric Hepatitis C and Children Fact Sheet

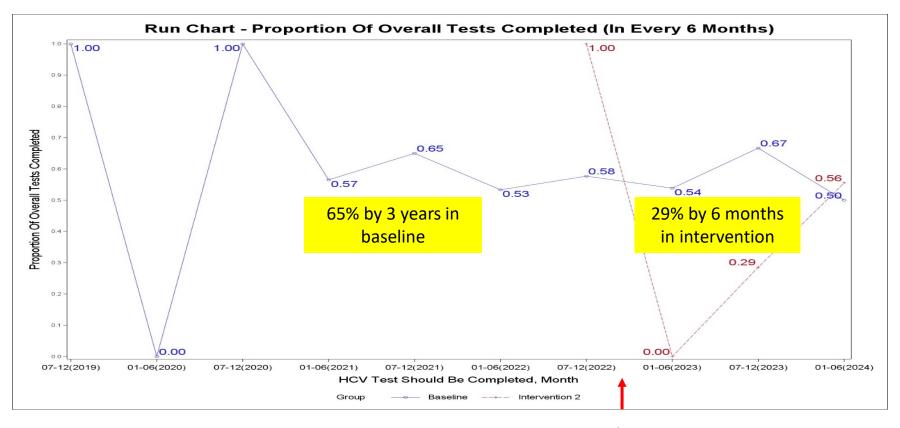
# **HCV Screening Tests Ordered**



October 2022

QI Project Started

## **HCV Screening Tests Completed**



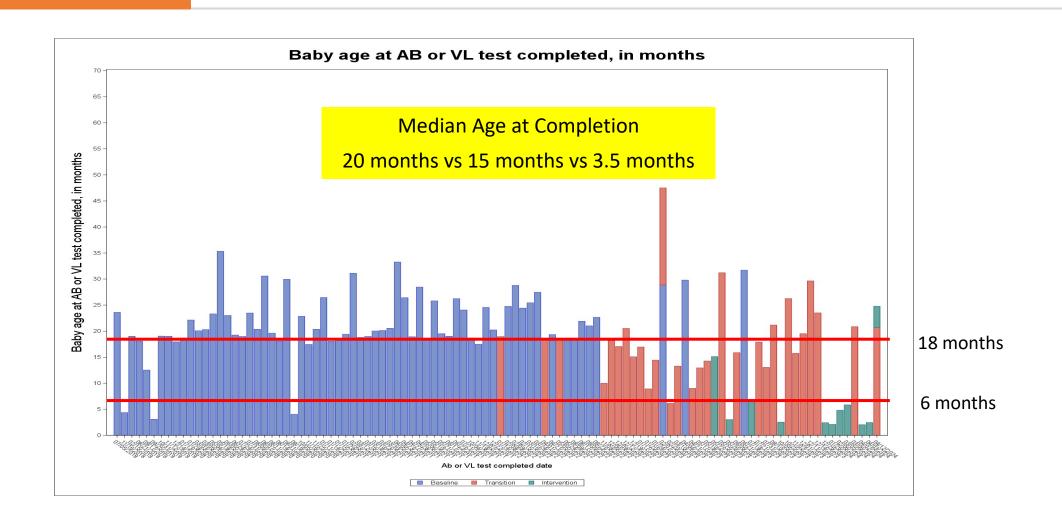
October 2022 QI Project Started



# Deep Dive on Screening

- No Order
  - 5 transferred clinics between 1-4 months
- No Result
  - 3 transferred clinic before 6 months
  - 2 had outside lab script sent, parent has not gone
  - 1 parent refusal mother viral load negative
- Results of those screened
  - 1 positive at limit of detection; subsequent neg
  - 3 negative

### Time to Test Completion



# **Future Directions**

Sibling screening

Improving maternal HCV screening

Obtain HCV viral load on all HCV Ab+ pregnant women

Repeat viral load at delivery if IVDU

Linking mothers to treatment/care

#### CLINICAL SCENARIO REVISITED WITH KEY TAKE-AWAYS

- TJ is a 33-year-old G2P1001 @ 14 weeks with active HCV. Her child is at risk of contracting HCV.
  - ~5% of children exposed to a HCV (i.e. positive viral load) in utero will contract HCV (1:20)
  - Breastfeeding is OK! Avoid temporarily if cracked/bleeding nipples.
  - Infants should be screened with PCR (viral testing) between 2-6 months of age
    - If negative, no other screening needed
    - If positive, refer to pediatric hepatology and rescreen at 3 years
  - Siblings should be screened if not previously screened
  - Avoid sharing of toothbrushes, razors, nail clippers ok to share cups, utensils; kisses OK!
  - No need to disclose on daycare forms



#### Resources

- Panagiotakopoulos L, Sandul AL; DHSc; Conners EE, Foster MA, Nelson NP, Wester C; Collaborators. CDC Recommendations for Hepatitis C Testing Among Perinatally Exposed Infants and Children - United States, 2023. MMWR Recomm Rep. 2023 Nov 3;72(4):1-21.
- Kimberlin DW, Barnett ED, Lynfield R, Sawyer MH, editors. Red Book 2021–2024: report of the Committee on Infectious Diseases, 32nd edition. Itasca, IL: American Academy of Pediatrics; 2021.
- Infectious Diseases Society of America. HCV in children. Arlington, VA: Infectious Diseases Society of America; 2022. https://www.hcvguidelines.org/uniquepopulations/children