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USF HEALTH

Pregnancy Screening and Follow Up of Perinatally Exposed Infants
9th Viral Hepatitis Conference
Ending the Epidemic
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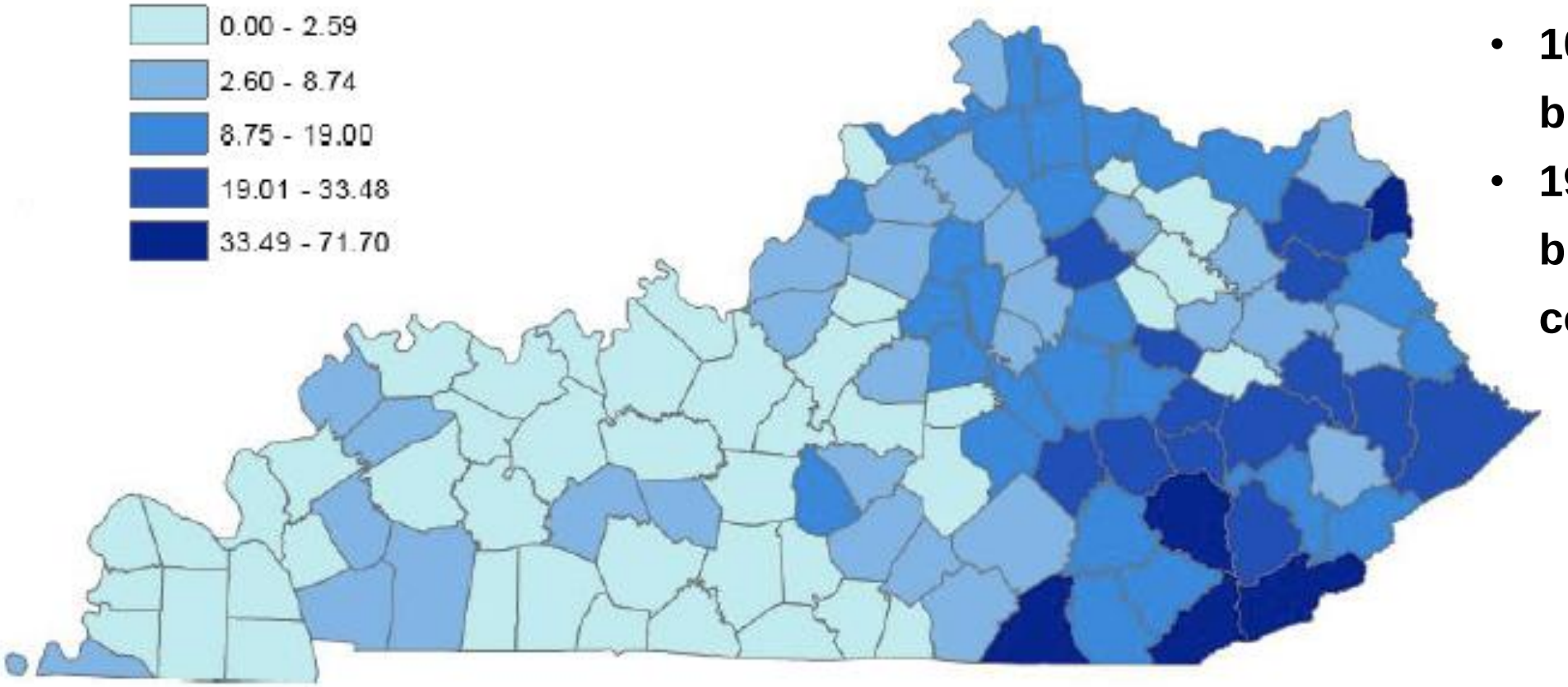
Disclosures

- I have participated in advisory board meetings as a consultant for Gilead and Sanofi
- I have participated as principal investigator or sub-investigator in multiple sponsored clinical trials with multiple companies including Gilead, AstraZeneca, Novavax, and Jansen and Jansen

KY Viral Hepatitis Prevention Program

- 2013, voluntary reporting of HCV positive pregnant women, their infants, and children <5 yr
- 2015 (Feb), mandatory reporting
- 2017 (May), expansion of harm reduction efforts
- 2018 (Jul), universal screening of pregnant women mandated

Rate of HCV infection among pregnant/post-partum women per 1000 (live births, by county – KY 2014-2016)



- **10.6 per 1,000 live births per KVHPP**
- **19.3 per 1,000 live births per birth certificate data**

Wilburn et al. CSTE poster presentation

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Testing pregnant women for hepatitis C

Hepatitis C virus testing in pregnant women

In May 2021, ACOG updated their recommendations: universal testing of all pregnant women is now recommended

Table 1
HCV testing recommendations during pregnancy

Guiding Body	Recommendation	Year Updated	Source
US Centers for Disease Control and Prevention (CDC)	Test in each pregnancy, except if community prevalence <0.1%	2020	Schillie,[16] 2020
US Preventative Services Task Force (USPSTF)	Test all adults 18–79 years old once in their lifetime, consider in pregnant women <18 y, unclear benefit in low-risk pregnant women who have previously been tested	2020	Owens et al,[17] 2020
American Association for the Study of Liver Disease (AASLD)/ Infectious Diseases Society of America (IDSA)	Test in each pregnancy, ideally at the initial prenatal visit	2018	AASLD-IDSA HCV Guidance Panel,[18] 2018, AASLD-IDSA,[60] 2020
Society for Maternal-Fetal Medicine	Test only if risk factors present, at first prenatal visit, and retest later in pregnancy if ongoing or new risk present	2017	Hughes et al,[20] 2017
American College of Obstetricians and Gynecologists (ACOG)	Test only if risk factors present	2007[a]	ACOG,[19] 2007

[a] The ACOG website states that the organization is currently reviewing the CDC and USPSTF 2020 guidance, after which ACOG will issue updated guidance.[21].

Epstein & Espinosa. Clin Perinatol, 2021

Changes in clinical practice

- Retrospective study evaluating trends of prenatal HCV testing before and after a universal HCV screening requirement
- Women with an ICD-9/ICD-10 code indicating delivery at UK Healthcare (UKHC) in 2016 through 2018 were identified
- Those with laboratory results for HBsAg in the 10 months prior to delivery were considered to have had prenatal care within UKHC and included in the study cohort
- EMR was reviewed to identify maternal characteristics and anti-HCV test results

Winter K. Obstetrics & Gynecology, 2020

Changes in clinical practice

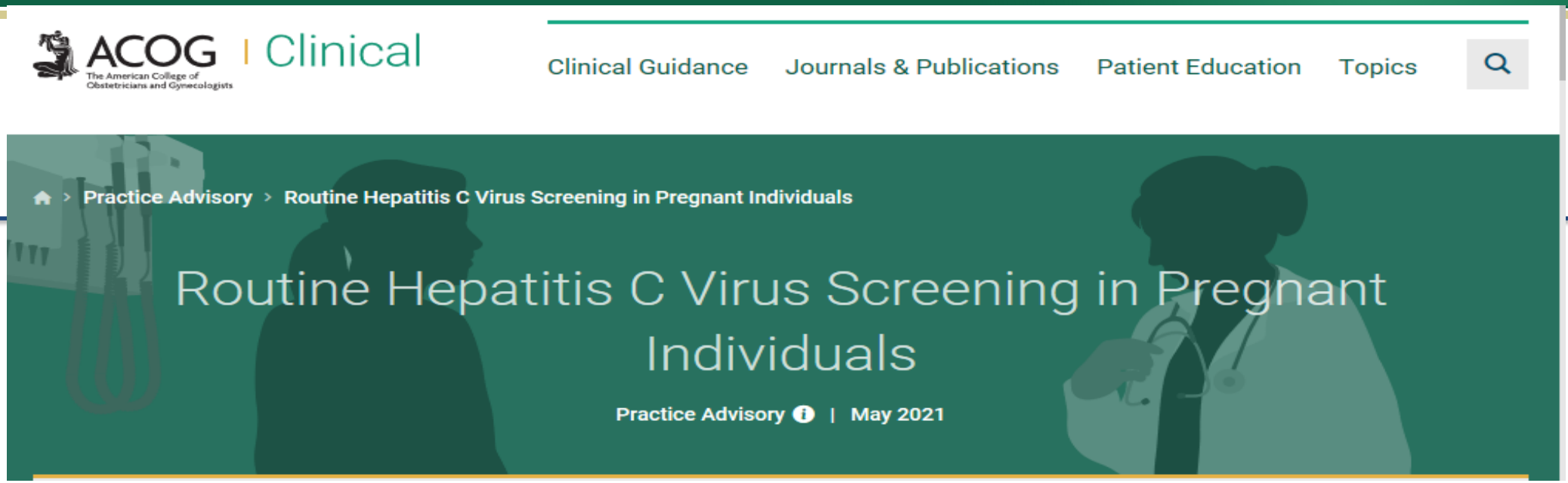
- **5,616 women delivered and 3,869 (69%) had documentation of HBsAg and included in the study**
- **48 (1.2%) of included women had a diagnosis of HCV infection**
- **716 (19%) had prenatal anti-HCV testing**
- **Among women screened for HCV, 179 (25%) were anti-HCV positive**

Winter K. Obstetrics & Gynecology, 2020

Changes in clinical practice

- A total of 363/3869 (9%) women had a diagnosis indicating illicit drug use
- 15% were neither tested for HCV nor had an existing HCV diagnosis
- Prevalence of prenatal HCV screening in UK increased significantly from 18% at baseline to 31% (P<.0001) among women delivering after the universal screening legislation became effective

Winter K. Obstetrics & Gynecology, 2020



- **Updated recommendation HCV**
  - **Screening for all pregnant individuals during each pregnancy**
  - **Screening during the first prenatal blood assessment to identify pregnant individuals with HCV infection and infants who should follow up**
  - **Hepatitis C screening should be an opportunity to promote a dialogue between pregnant individuals and their clinician about transmission and risk factors**

https://www.acog.org/clinical/clinical-guidance/practice-advisory/articles/2021/05/routine-hepatitis-c-virus-screening-in-pregnant-individuals

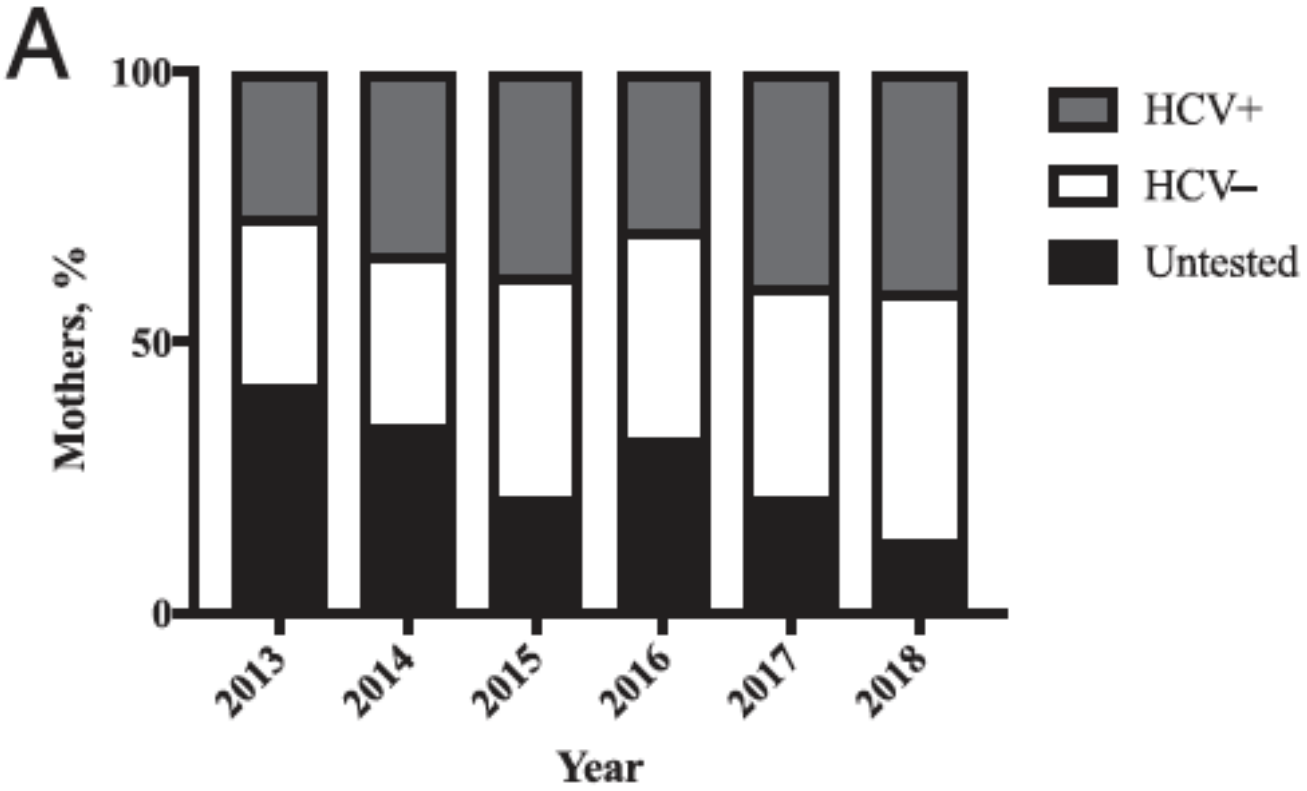
Successful universal screening implementation

- **Increased number of pregnant women with HCV risk factors in 2016 led to implementation of universal screening**
- **Implementation achieved by EMR (standing order)**
  - ***HCV Antibody at initial OB visit***
  - ***HCV antibody may be repeated in the third (3rd) trimester at the discretion of the provider***
- **HCV reflex RNA PCR for all antibody positive test**

Rose M, et al. AASLD: Best of the LIver #87, 2018

Maternal linkage to care

- Maternal HCV status
- Untested mothers
  - Inadequate screening
  - Poor prenatal care
  - Fragmentation of care
  - Parental addiction
  - Parental mental health problems



Bell R, et al. Hosp Pediatr, 2019

Illicit drug use during pregnancy

- Several studies comment on the relationship between illicit drug use and HCV
- Few studies focus specifically on illicit drug use during pregnancy in HCV positive mothers
- We sought to describe rates of illicit drug use during pregnancy in a convenience cohort of infants perinatally exposed to HCV
- Retrospective analysis of perinatally exposed infants born in Louisville metro area and surrounding hospitals between February 2012 and July 2018 and followed at UofL pediatric infectious disease clinic

Niestrath, Green, and Espinosa. Open Forum Inf Dis, 2020

Cohort

Maternal Characteristics	
Maternal Age, median (IQR)	28 (IQR 25-31)
Gravidity, median (IQR)	3 (IQR 2-4)
Parity, median (IQR)	2 (IQR 1-3)
Race	
White, % *(n)*	91.0 (101)
Black, % *(n)*	5.4 (6)
Other, % *(n)*	3.6 (4)
Prenatal Care	
Completed, % *(n)*	61.0 (153)
Insufficient, % *(n)*	15.9(40)
None, % *(n)*	23.1 (58)
Birth Hospital	
Urban, % *(n)*	63.8 (277)
Suburban, % *(n)*	24.2 (105)
Rural, % *(n)*	12.0 (52)

- **Most women are young, white, and have 2 children or more**
- **40% of women had inadequate or no prenatal care**

Niestrath, Green, and Espinosa. Open Forum Inf Dis, 2020

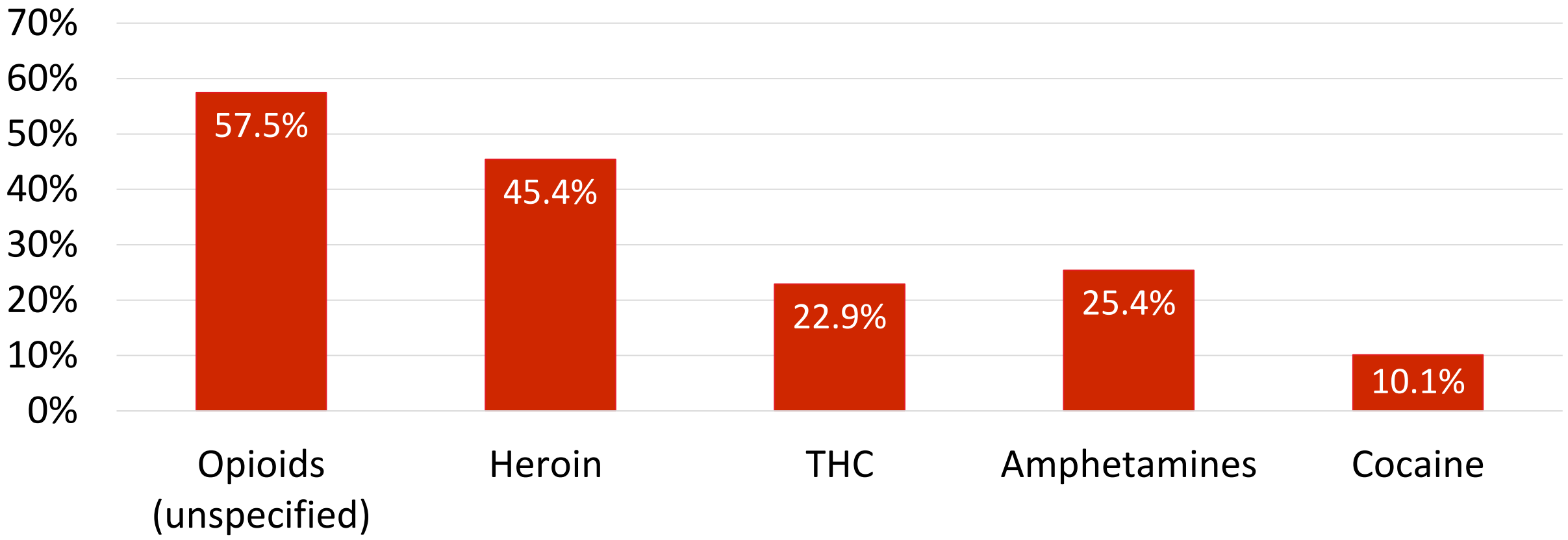
Reported maternal active and history of substance use

Categories of Reported Substance Use	Percent (*n*)
History of Tobacco Use	83.9 (256)
Tobacco Use During Pregnancy	74.8 (190)
History of Illicit Drug Use	89.0 (380)
Illicit Drug Use During Pregnancy	63.1 (277)
History of IVDU[1]	81.0 (355)
IVDU[1] During Pregnancy	32.0(140)

[1]Intravenous drug use

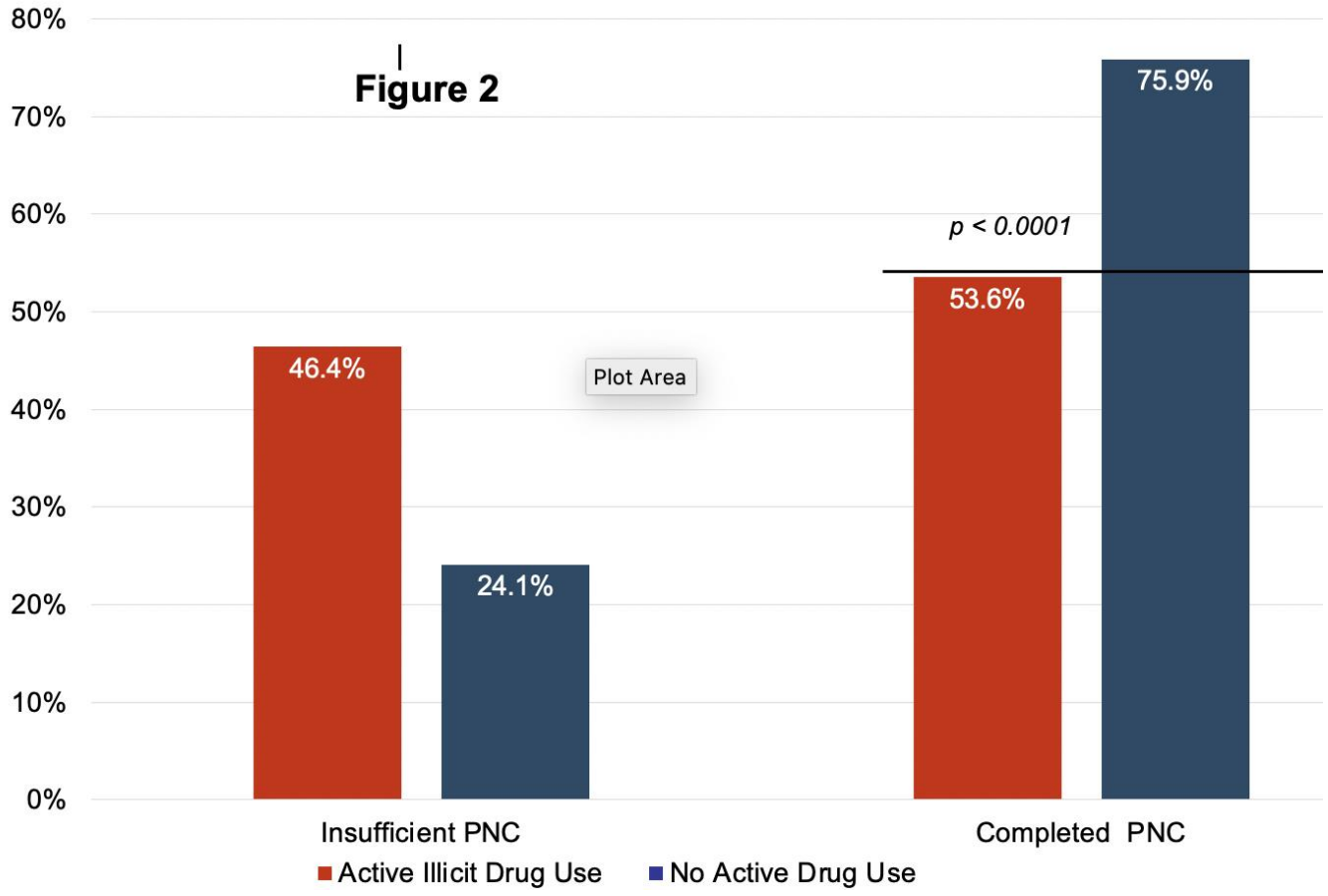
Niestrath, Green, and Espinosa. Open Forum Inf Dis, 2020

Rates of various illicit drug use during pregnancy



Niestrath, Green, and Espinosa. Open Forum Inf Dis, 2020

Rates of active illicit drug use in those who has insufficient vs. completed prenatal care



Niestrath, Green, and Espinosa. Open Forum Inf Dis, 2020

Conclusions

- **HCV positive pregnant women have high rates of past and continued illicit and intravenous drug use during pregnancy**
- **Most common illicit and recreational drugs reported used in this cohort were opioids, including heroin**
  - **67.3% had a history of heroin use**
  - **45.4% reported active heroin use during pregnancy**
- ***Prenatal care was associated with decreased use of illicit drugs and IVDU in pregnant patients (aOR, 0.33; $p < 0.003$)***

Niestrath, Green, and Espinosa. Open Forum Inf Dis, 2020

Conclusions

- Pregnancy represents a unique opportunity to link HCV infected women to care
- Public health initiatives should be instituted in areas with high prevalence of illicit drug use and HCV to increase prenatal care participation
- Interdisciplinary health care teams that include obstetrics, pediatrics, social work, and medical assisted treatment should be developed to provide adequate attention to mothers suffering from drug addiction and their infants

Niestrath, Green, and Espinosa. Open Forum Inf Dis, 2020

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Testing infants exposed to hepatitis C

Testing infants

- Hepatitis C antibodies cross the placenta
- Antibodies circulate in newborns until 18-30 months of age
- Early testing with HCV PCR is controversial

Who to test?

- **Guidelines recommend testing all infants born to HCV seropositive women**
  - **Low rates of RNA testing are possible**
  - **Difficulty ascertaining infection status**
- **Universal maternal testing during each pregnancy, and the increasing use of reflex RNA testing following a positive maternal antibody test translates into a recommendation to test infants born to *HCV-infected* women only (detectable RNA suggestive of a current infection)**

Who to test?

- HCV testing should be ordered for infants born to
  - HCV seropositive women with an unknown HCV RNA status
  - HCV antibody status unknown, particularly in the setting of known or suspected injection drug use, intrauterine opioid exposure, incarceration, or foster care
- Detection of maternal antibody at age 3 months or younger suggests exposure

Testing guidance for HCV exposed infants

Guiding Body	Recommendation		Year Updated
	Who to Test	How to Test	
US Centers for Disease Control and Prevention (CDC)	Infants born to women with HCV infection	More information needed to balance benefits and costs of earlier RNA test(s)	2020
United States Preventative Services Task Force (USPSTF)		No specific mention (Ab recommended in general)	2020
American Association for the Study of Liver Disease / Infectious Diseases Society of America		Test with Ab at 18 months; can consider RNA testing as early as 2 months of age but recommends against repeated RNA testing	2018
Redbook / American Academy of Pediatrics		Test with Ab at 18 months; can consider RNA testing as early as 1-2 months of age if significant maternal anxiety	2018
North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN)			2012

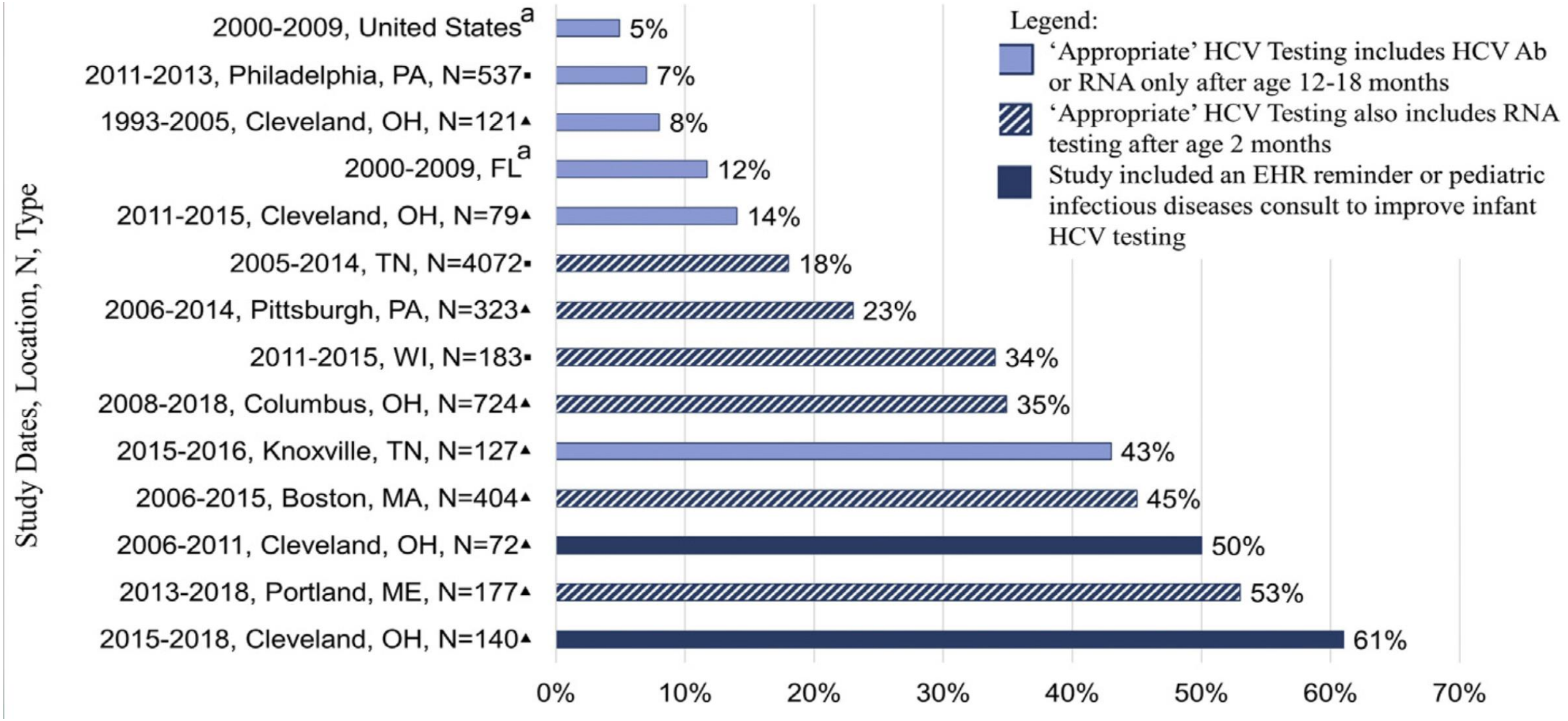
Epstein & Espinosa. Clin Perinatol, 2021

When to test?

- AAP defines the diagnosis of HCV infection:
  - Presence of HCV-specific antibodies after age 18 months
  - Two positive HCV RNA tests on separate dates after age 2 months
- Guidelines recommend to wait until 18 months or later to test children
- Documentation of clearance of maternal antibodies is impacted by:
  - Type of antibody test used
  - Delayed in infants born to viremic mothers
- Some infants also lose maternal antibody just before seroconverting in response to infection
- Other markers of infection such as HCV IgM have been considered unreliable, and they are not commercially available

Epstein & Espinosa. Clin Perinatol, 2021

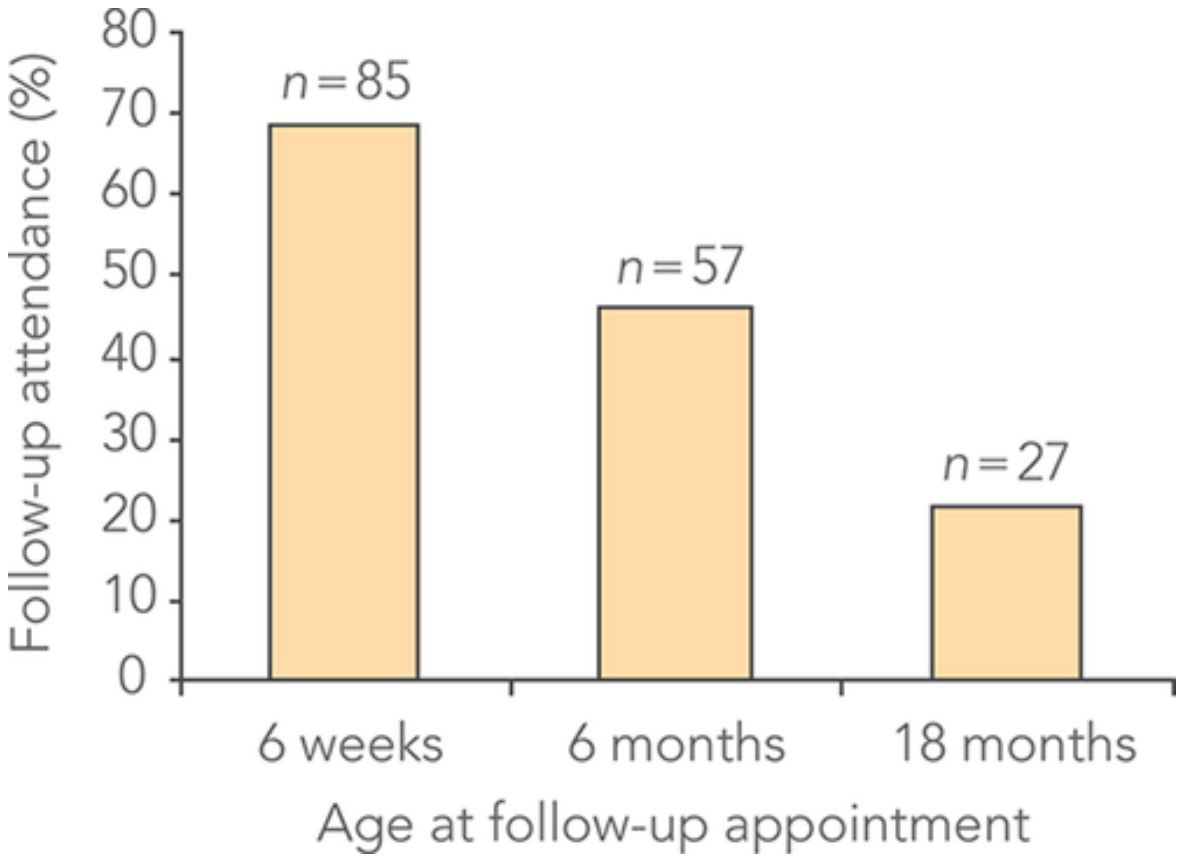
Summary of studies analyzing testing of HCV-exposed infants in the United States



Epstein & Espinosa. Clin Perinatol, 2021

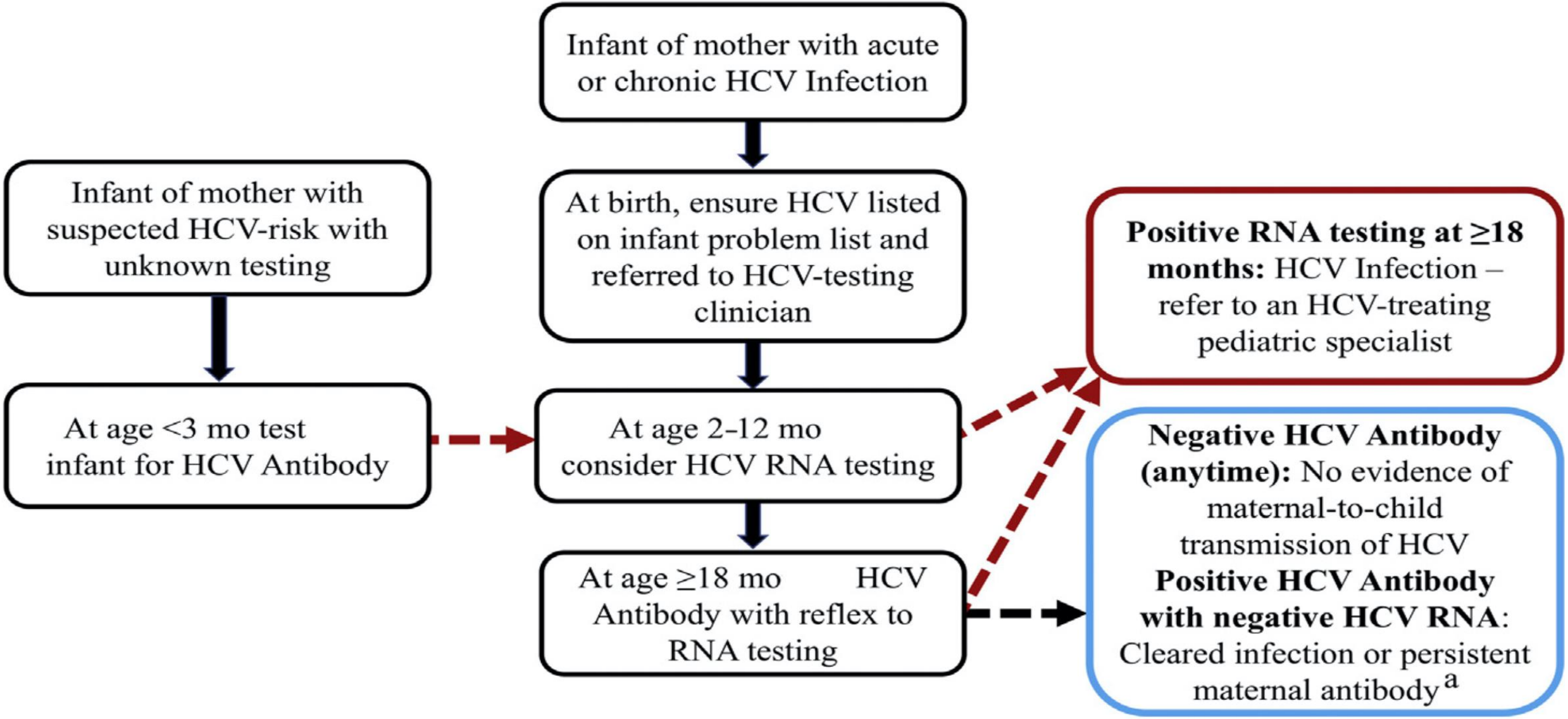
Children follow up

Screening for HCV infection in methadone-maintained mothers and their infants



Liu AJW, et al. Med J Austrl, 2009

Proposed algorithm to test HCV-exposed infants by an HCV testing clinician



Epstein & Espinosa. Clin Perinatol, 2021

Early testing

Disadvantages

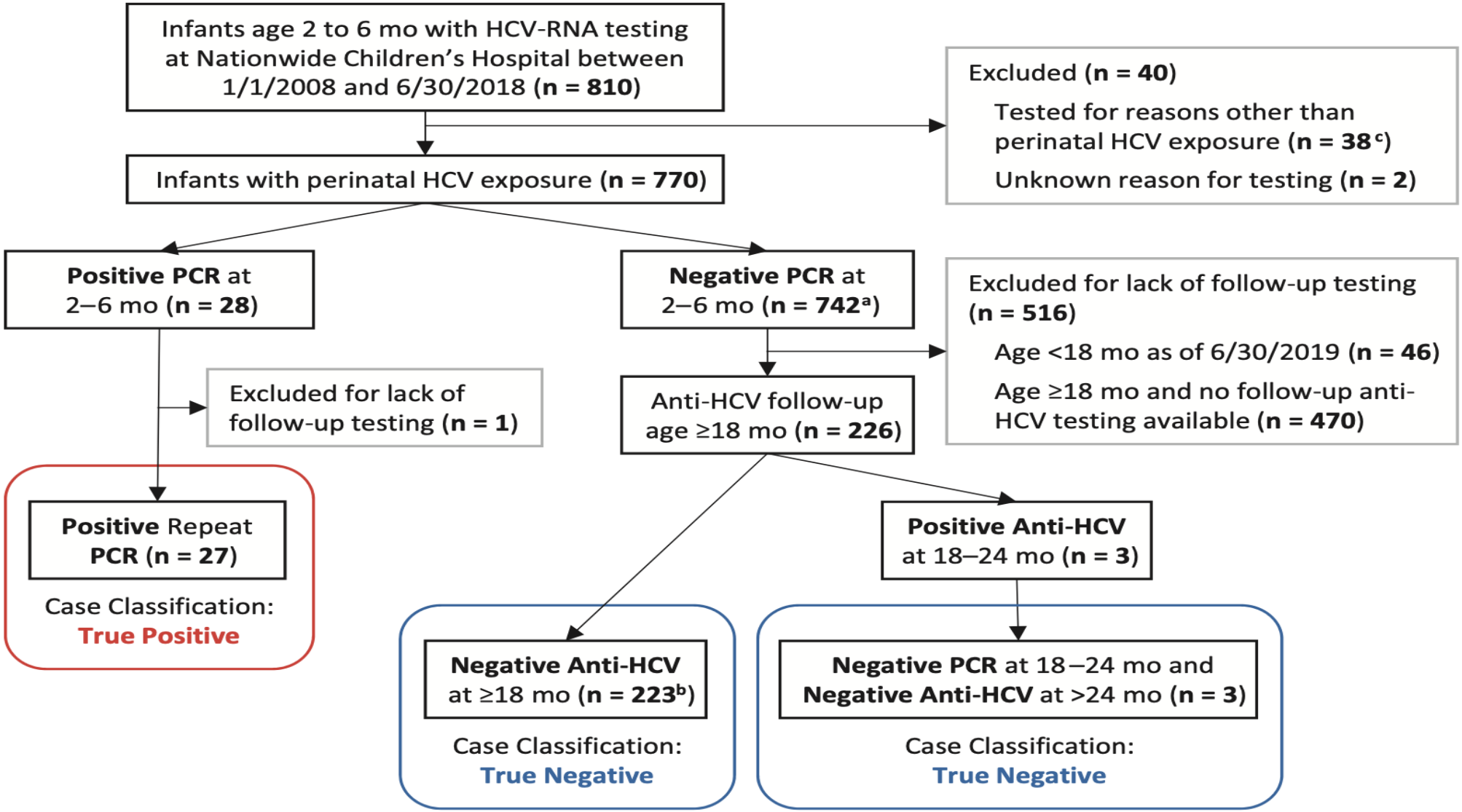
- Cost
- Additional blood draws
- Phlebotomy logistics (volume requirements, not all pediatric or specialty clinics have phlebotomy on site)
- Parental acceptance or understanding of the need for additional testing

Benefits

- Decreased parental anxiety
- Completion of testing before an infant may be lost to follow-up
- If done at 9 to 12 months of age in conjunction with a well-child visit could minimize extra visits and, when applicable, ordering it simultaneously with anemia or lead scre

Epstein & Espinosa. Clin Perinatol, 2021

Follow-up and case classification of infants tested for HCV-RNA at age 2–6 months



Gowda et al. CID, 2020

Diagnostic performance of HCV-RNA PCR in perinatally exposed infants aged 2-6 months

	Point Estimate	95% CI
Sensitivity, (%)[a]	100	87.5–100
Specificity, (%)[a]	100	98.3–100
Positive likelihood ratio[b]	∞	78.0–∞
Negative likelihood ratio[b]	0	0–.103
Assume 5.8% prevalence[c]		
Positive-predictive value, (%)[d]	100	82.8–100
Negative-predictive value, (%)[d]	100	99.4–100
Assume 3.6% prevalence[e]		
Positive-predictive value, (%)[d]	100	74.5–100
Negative-predictive value, (%)[d]	100	99.6–100

Gowda et al. CID, 2020

Increasing rates of follow up

- Universal screening in pregnant women calls for new strategies to identify the increasing number of HCV-exposed infants
- Multiple institutions have implemented routine screening of infants earlier than 18 months of age
- Settings using both antibody and RNA testing before age 18 months have overall higher HCV testing completion rates compared with settings only evaluating infant HCV antibody after 18 months of age

Increasing rates of follow up

- Multiple programs have implemented successful interventions to expand testing in primary care by pediatricians through education, linkage or ensuring HCV exposure is clearly documented in the electronic health record
- Other practitioners have created programs to actively link infants to pediatric infectious disease specialists for testing
- Many primary or subspecialty clinics may not have adequate resources to sustain demands in areas of high HCV prevalence

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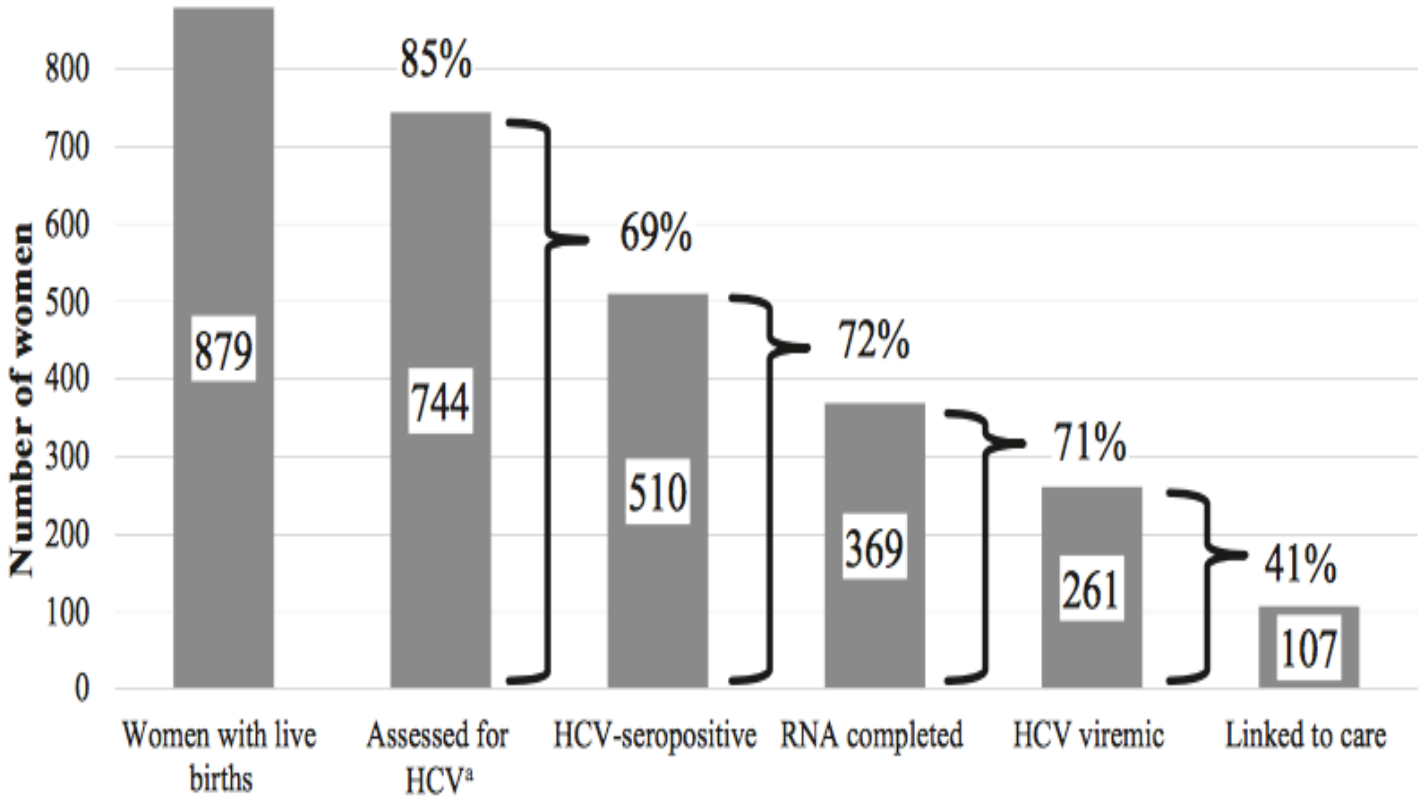
Therapy

Maternal cascade of care

- Percentage values at the top of each bar are conditional
- Assessed for HCV refers to history of HCV or completed HCV testing



Epstein RL et al. J Pediatrics, 2018

Treatment with DAAs after positive screening

Testing practice	Risk-based 5/14-12/15 N=10420 (%)	Universal 5/16-12/17 N= 9033 (%)	OR [95%CI]
HCV antibody screening	1867 (17.9)	9033 (100)	
HCV antibody positive	81 (4.3)	483 (4.9)	1.1 [0.9-1.1]
HCV RNA	44 (54.3)	483 (100)	1.8 [1.5-2.3]
HCV RNA positive	31 (1.7)	306 (3.4)	2.1 [1.4-3.0]
DAAs	16 (0.8)	92 (1.0)	1.2 [0.7-2.0]

Rose M, et al. IDWeek, 2019

Therapy

- DAAs have revolutionized HCV treatment in adults, but currently there are not approved therapies for pregnant women
- A phase I clinical trial using ledipasvir/sofosbuvir in HCV infected pregnant women showed rapid achievement of undetectable HCV viral load and sustained virologic response without significant adverse events
- A phase I study with a pangenotypic DAA combination (sofosbuvir/velpatasvir) begun in October 2020 is expected to be completed by June 2023

Why it is important to link women to care?

THE LANCET
Microbe

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ARTICLES | VOLUME 1, ISSUE 5, E200-E208, SEPTEMBER 01, 2020

Ledipasvir plus sofosbuvir in pregnant women with hepatitis C virus infection: a phase 1 pharmacokinetic study

Catherine A Chappell, MD • Kimberly K Scarsi, PharmD • Brian J Kirby, PhD • Vithika Suri, MSc • Anuj Gaggar, MD • Prof Debra L Bogen, MD • et al. Show all authors

Open Access • Published: July 27, 2020 • DOI: https://doi.org/10.1016/S2666-5247(20)30062-8

Check for updates

PlumX Metrics

Therapy

- We hope the results of clinical trials will support the possibility of treatment during pregnancy, because this is a time that many women are engaged in health care services
- Treatment during pregnancy could be a key strategy to both decrease vertical transmission and eliminate maternal infection
- Pregnancy is still an opportune time to identify and to link women to care with the possibility of treatment after delivery to improve their own health care and decrease subsequent vertical transmission. More research will be needed to understand how the recent recommendations for universal HCV screening impact care of the maternal–infant dyad.

Therapy

- DAAs are now approved for children as young as age 3 years for HCV genotypes 1, 4, 5, and 6, and pangenotypic regimens are approved in children ages 6 years older; additional studies are ongoing in younger children.
- As infants have minimal risk of hepatoxicity due to HCV infection before age 3 and high spontaneous clearance rates (~25-50%), DAAs are not expected to be tested or recommended for the treatment of children younger than 3 years of age
- Spontaneous viral clearance usually occurs by 3 years of age
- If there are insufficient CD4 and CD8 responses, chronic infection might develop

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