



Pregnancy: a window of opportunity to test and treat hepatitis c virus

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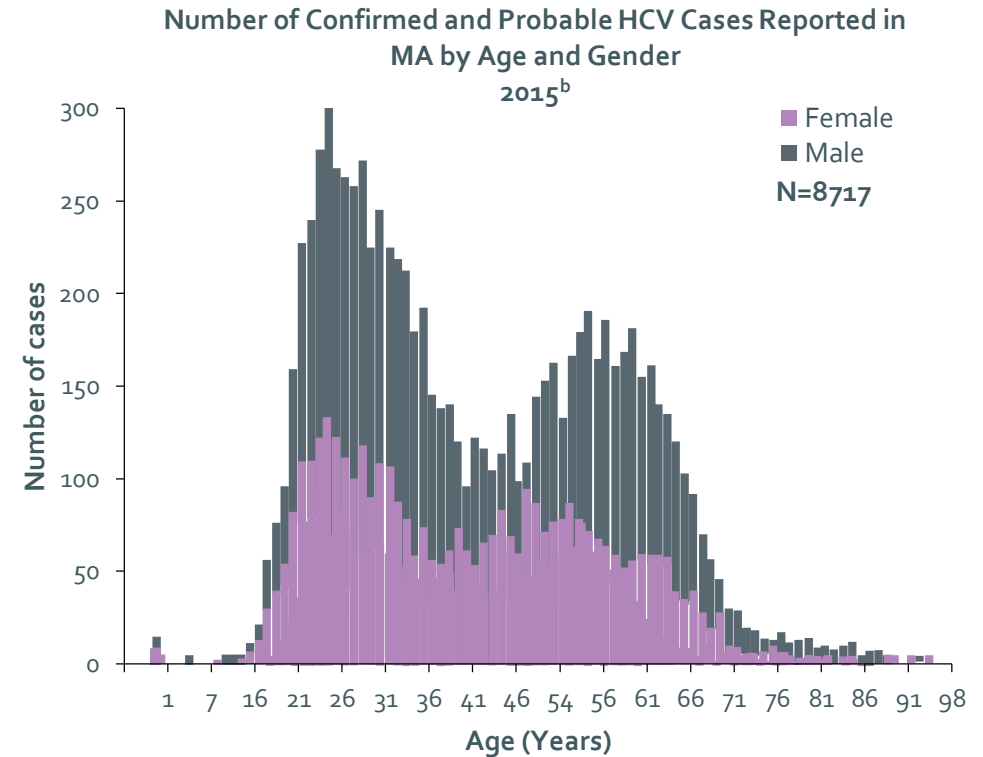
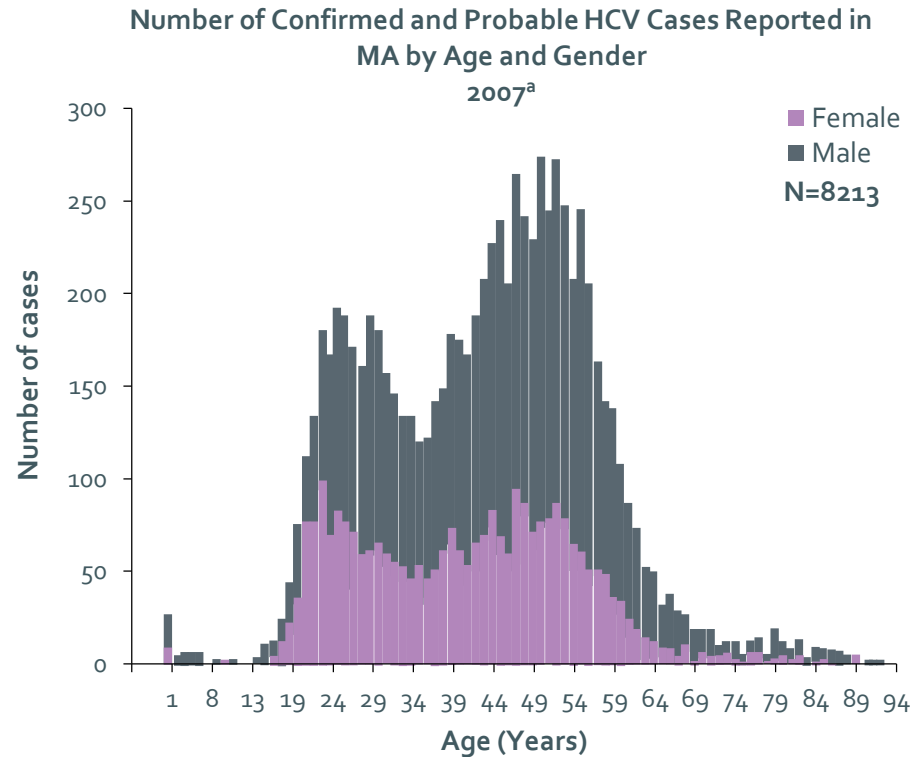
Outline

- Shifting Epidemiology
- Current Cascade of Care
- HCV and Pregnancy
- Risk and Risk Factors for Perinatal Transmission
- Ledipasvir/sofosbuvir treatment during pregnancy safety and pharmacokinetic study
- The path forward

HCV Shifting Epidemiology

- Worldwide there are an estimated 71 million people chronically infected with the hepatitis C virus
- Nationwide, there is a high prevalence of chronic HCV among “baby boomers” (adults born 1945-1965). However, more recently the incidence of HCV infection is increasing in younger persons, including women of childbearing age
- This shifting epidemiology has been linked to the burgeoning problem of illicit injection drug use
 - In 2015, CDC reported 364% increase in HCV infection related to injection drug use among persons age <30 in Appalachia

Distribution of HCV Demographics in the US



These data may be indicative of emerging trends in HCV transmission in other regions of the US.

^aExcludes 915 cases with missing age or sex information.

^bExcludes 362 cases with missing age or sex information.

Data are current as of Nov 15, 2016 and are subject to change.

Increasing HCV Burden in Young Adults in the US

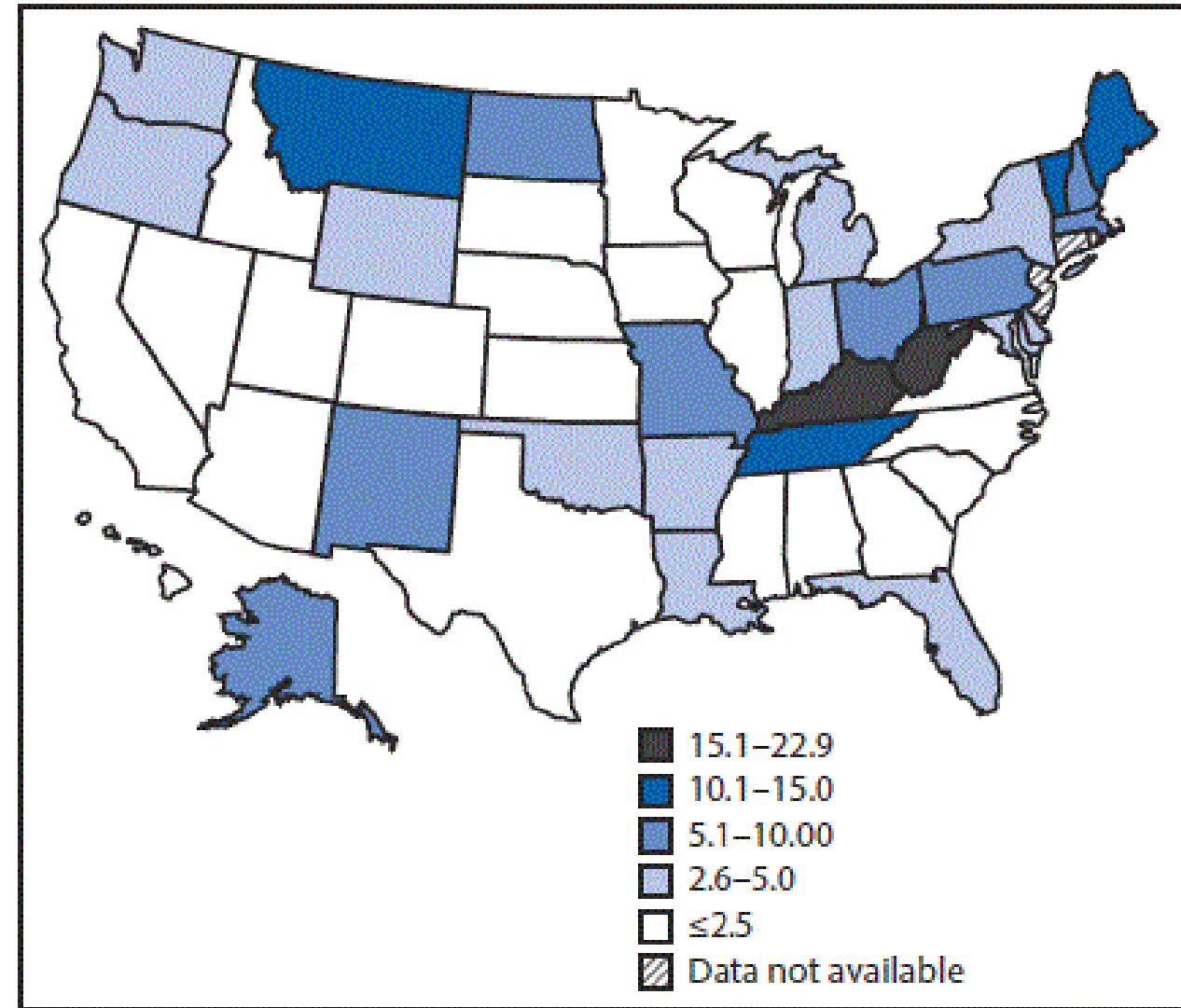
- Analysis of Public Health Department data for all 50 states to compare rates of HCV infection in young adults vs. Baby Boomers
- 11 States have rates of HCV infection in young adults surpassing that of Baby Boomers

| Young adults > Baby Boomers | Population Totals | Young Adult is on incline | Population Totals | Young Adults = Baby Boomers | Population Totals |
|-----------------------------|-------------------|---------------------------|--------------------|-----------------------------|-------------------|
| Pennsylvania | 12,784,227 | California | 39,250,017 | Michigan | 9,928,300 |
| Ohio | 11,614,373 | Florida | 20,612,439 | Wisconsin | 5,778,708 |
| Massachusetts | 6,811,779 | New York | 19,745,289 | Colorado | 5,540,545 |
| Indiana | 6,663,053 | Virginia | 8,411,808 | Connecticut | 3,576,452 |
| Kentucky | 4,436,974 | Washington | 7,228,000 | | |
| Arkansas | 2,998,248 | Arizona | 6,931,071 | | |
| New Mexico | 2,081,015 | Louisiana | 4,681,666 | | |
| West Virginia | 1,831,102 | Oregon | 4,093,465 | | |
| Maine | 1,331,479 | Iowa | 3,134,693 | | |
| North Dakota | 757,952 | Utah | 3,051,217 | | |
| Vermont | 624,594 | South Dakota | 865,454 | | |
| Total population | 51,894,796 | Total population | 118,065,119 | Total population | 24,824,005 |

Fraction of US population – 76%; Total population 20-39 = 66,249,672; Total females 20-39 = 32,733,899

Changing HCV Prevalence Among Pregnant Women

- During 2009–2014, HCV infection present at the time of delivery among pregnant women from states reporting HCV on the birth certificate increased 89%, from 1.8 to 3.4 per 1,000 live births
- The highest infection rate in 2014 (22.6 per 1,000 live births) was in West Virginia



Current Cascade of HCV Care in Pregnancy

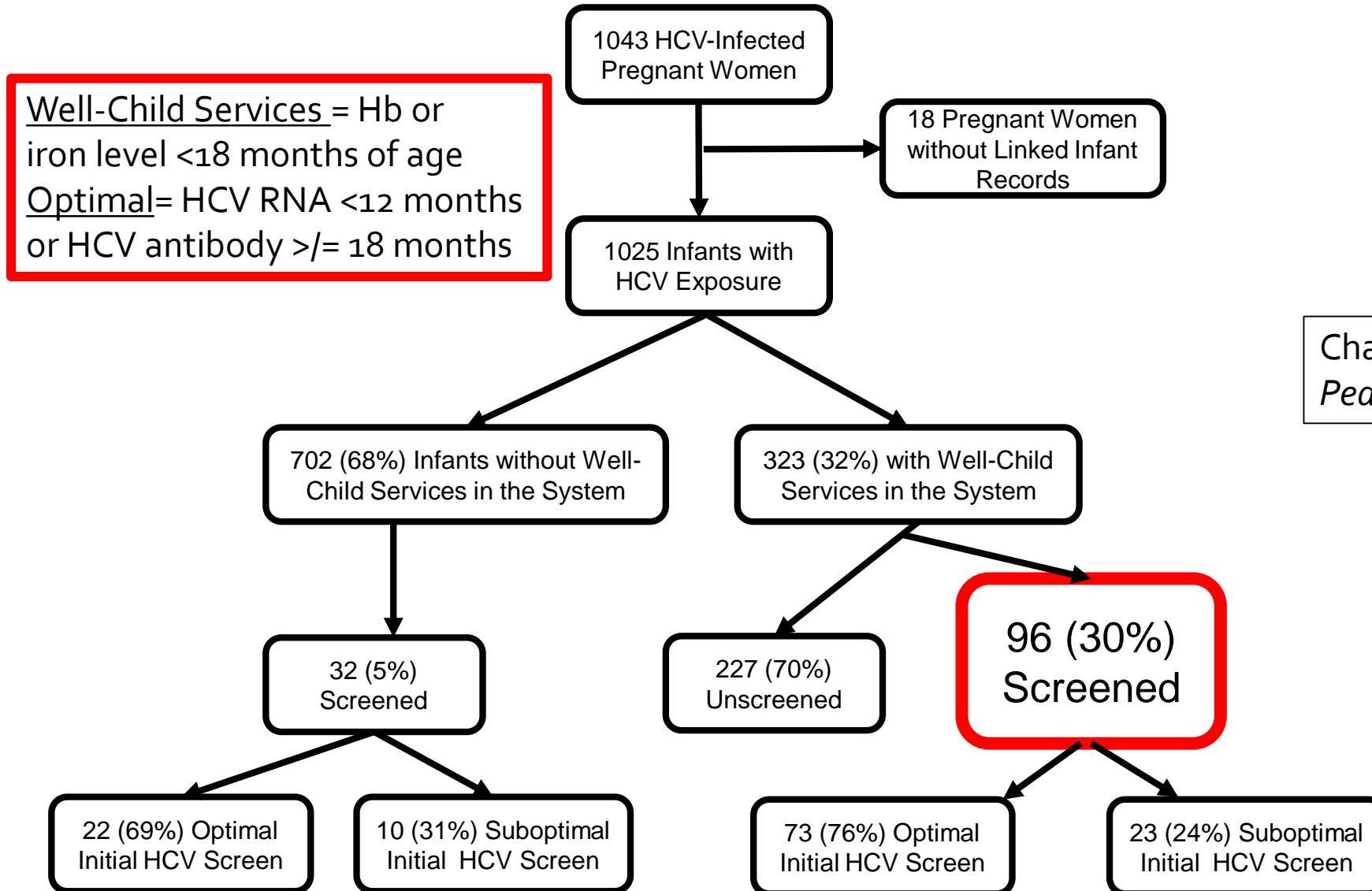
- 1) Risk-based Antenatal Screening for HCV (everywhere but Kentucky and a few other places)
- 2) Cases Identified are referred for treatment postpartum
- 3) Infants that were exposed are screened by primary pediatrician

Cascade of Care in Pittsburgh, Pennsylvania

- Retrospective cohort of 791 opioid dependent pregnant women who delivered at Magee-Womens Hospital between 2009-2012
 - Among 791 women, 611 (77.2%) were HCV screened
 - Among 611 women screened, 369 (60.4%) were HCV antibody positive

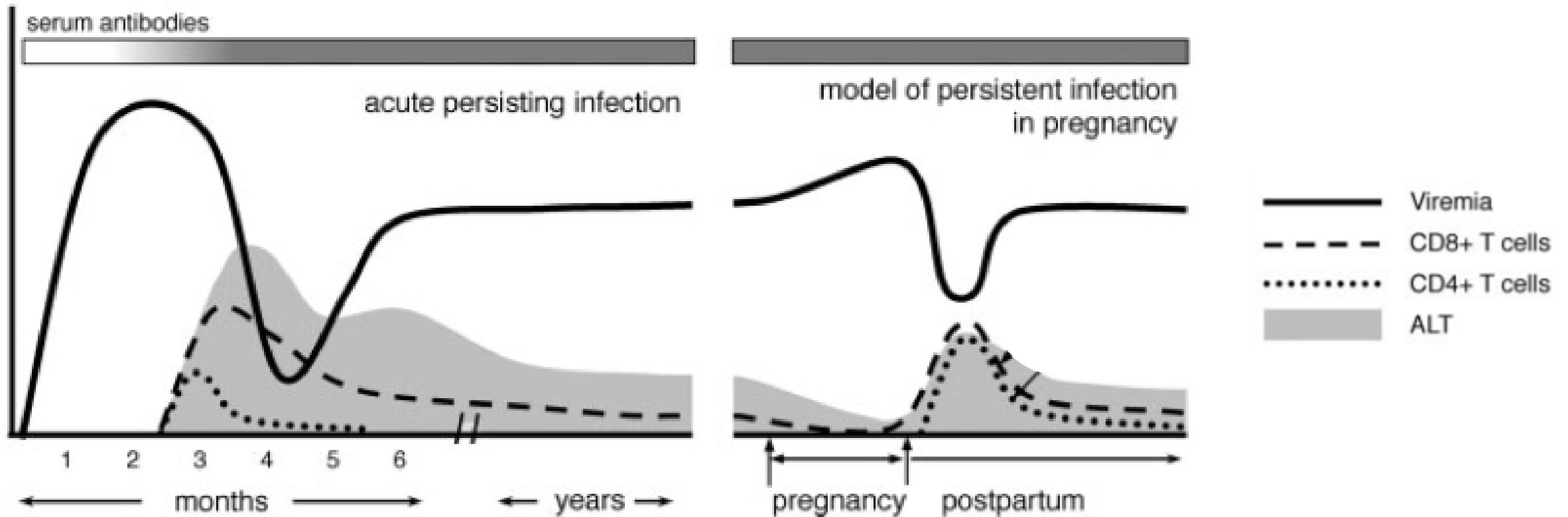
| n=369 | n (%) |
|---|-------------------|
| New HCV diagnosis during pregnancy | 108 (29.3) |
| Liver function tests | 336 (91.1) |
| HCV viral load | 94 (25.5) |
| HCV genotype | 61 (16.5) |
| Referral to Hepatology | 285 (77.2) |
| Attended Hepatology Consultation | 71 (24.9) |
| Were treated for Hepatitis C within 1 year | 6 (1.6) |

HCV Screening among Exposed Children in Pittsburgh



Chappell, et al
Pediatrics, 2018

Impact of Pregnancy on Chronic HCV Infection



In one study of 54 Egyptian women, 27% resolved chronic HCV infection in the postpartum period

Prasad MR, et al. *Am J Perinatol.* 2013

Hashem M, et al. *CID.* 2017

Impact of Pregnancy on Chronic HCV Infection: Liver Fibrosis

Two conflicting studies and very limited data:

- Retrospective cohort study:
 - 157 pregnant women with chronic HCV infection
 - history of pregnancy was independently associated with a lower likelihood of fibrosis progression
- Prospective case-controlled study:
 - 12 HCV+ (HIV-) women comparing liver biopsies before and after delivery to 12 women age, duration of infection matched controls without pregnancy.
 - 83% (pregnant) vs 25% (nonpregnant) showed deterioration in their necroinflammatory score
 - 42% (pregnant) vs. 8% (nonpregnant) showed deterioration in their fibrosis score

Impact of HCV on Pregnancy: Maternal Health

| Study | HCV+ Cases | Controls | Gestational Diabetes |
|--------------|------------|----------------------------|--|
| Pergam 2008 | 506 | Drug using 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 |

- Intrahepatic cholestasis of pregnancy
 - Meta-analysis of 3 studies showed a 20-fold increased risk (Wijampreecha, et al. *Clin Res Gasrto Hepatol.* 2017)

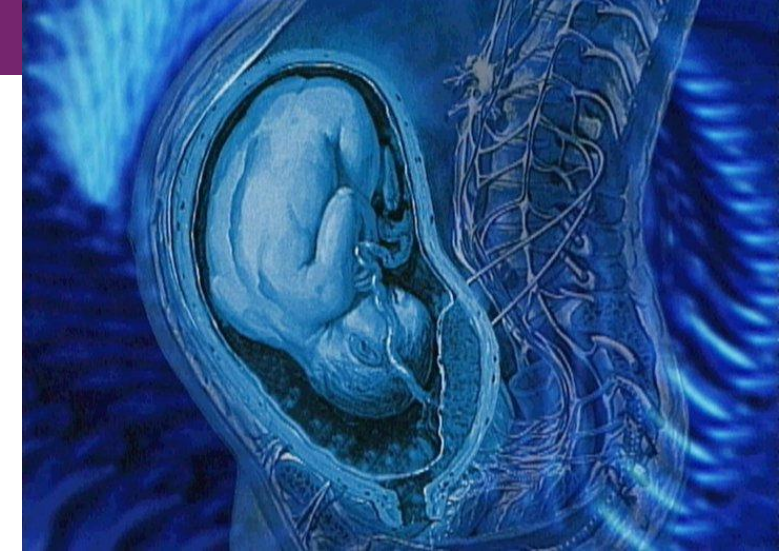
Impact of HCV on Pregnancy: Neonatal Outcomes

- Intrauterine growth restriction
 - OR: 1.53 [1.40-1.68]
- Low birth weight
 - OR 1.97 [1.43-2.71]
- 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**

Risk of Transmission

- 5.8 (95% CI 4.2-7.80) (HIV negative)
- 10.8 (95% CI 7.6-15.2) (HIV co-infected)
- Consequence of Transmission
 - Long term outcomes show that HCV acquired in infancy progresses slowly
 - Significant fibrosis is <5% after 10-20 years
 - Cirrhosis in 1%
- Majority of children grow and develop normally with no symptoms
- So there is no rush to treat...however...



Benova L., et al. *CID*. 2014;
Jara et al *CID* 2003;
Goodman et al *Hepatology* 2008

Hepatitis C- few studies report higher rate of liver disease

- 2 studies from Italy on progression of those patients with HCV since infancy
 - infection greater than 10 years = more likely to have moderate to severe fibrosis on biopsy
 - 5-10% cirrhosis overall
- Another study from St. Jude with much worse outcomes, but infection was via blood transfusion
 - 80% had chronic active hepatitis
 - 70% had fibrosis on biopsy
 - 9% had cirrhosis
 - 3 died of liver failure or HCC

What about extrahepatic outcomes?

- Early study done in 2001 from Australia looked at 19 children with chronic HCV
- Performed Child Health Questionnaire for children and parents
- Children with HCV scored lower in many outcomes: physical, emotional, parent stress and time

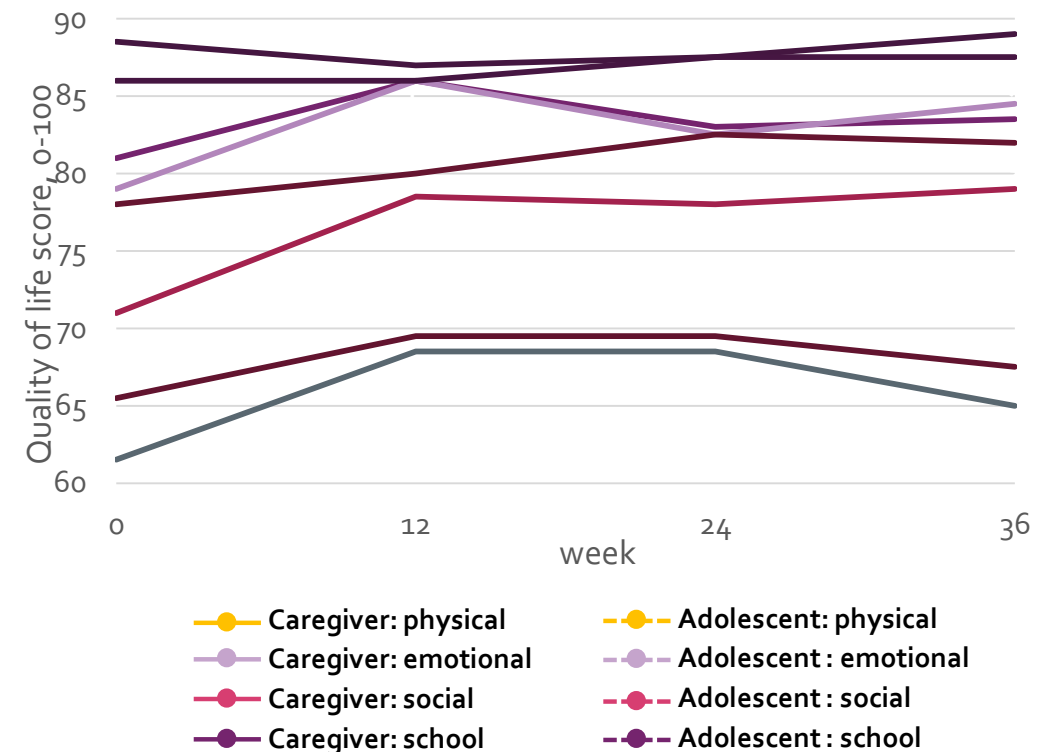
Mean (\pm SD) values and effect sizes for Child Health Questionnaire (CHQ) PF-50 scales and summary scores

| Scale item | Normal (<i>n</i> = 3119) | Hepatitis C (<i>n</i> = 19) | Effect size | <i>P</i> -value |
|-------------------------------|------------------------------|---------------------------------|----------------|-----------------|
| Physical functioning | 93.8 \pm 16.3 | 85.4 \pm 19.5 | 0.57 | <0.05 |
| Limitations–emotional | 93.4 \pm 17.8 | 76.6 \pm 34.7 | 0.93 | <0.001 |
| Limitations–physical | 93.6 \pm 18.2 | 83.3 \pm 27.8 | 0.59 | <0.05 |
| Bodily pain/discomfort | 81.6 \pm 18.9 | 84.2 \pm 15.4 | –0.09 | 0.55 |
| Behavior | 77.9 \pm 15.1 | 70.1 \pm 20.7 | 0.49 | <0.05 |
| Mental health | 80.4 \pm 12.6 | 72.1 \pm 16.0 | 0.62 | <0.05 |
| Self-esteem | 79.2 \pm 16.3 | 72.4 \pm 18.6 | 0.36 | 0.07 |
| General health | 77.1 \pm 16.0 | 49.9 \pm 16.5 | 1.66 | <0.001 |
| Parent impact–emotional | 80.3 \pm 20.5 | 45.6 \pm 31.3 | 1.63 | <0.001 |
| Parent impact–time | 91.1 \pm 16.9 | 77.8 \pm 24.0 | 0.77 | <0.001 |
| Family activities | 85.4 \pm 16.7 | 74.5 \pm 23.5 | 0.60 | <0.05 |
| Physical summary score | 49.6 \pm 10.7 | 45.3 \pm 10.8 | 0.44 | <0.05 |
| Psychosocial summary score | 50.1 \pm 10.3 | 44.0 \pm 11.8 | 0.53 | <0.05 |

Quality of life gets better with treatment

- As part of the LDV/SOF adolescent study, HRQL surveys of both children and parents were performed
- HRQL slightly improved with therapy and SVR in the adolescents
- Caregiver reports significantly improved.
- Open-label with no control group, so concern is for bias in these results

Health-related quality of life scores in adolescents with chronic hepatitis C infection during and after treatment with 12-week-long LDV/SOF. * $P < 0.05$ when compared to the baseline level.



Are these all
avoidable?

Treatment during pregnancy could prevent perinatal transmission

Parents will have significantly less stress and guilt, and those moms will feel that they contributed to that outcome by getting treated to cure themselves and prevent transmission to their child

Risk Factors for Perinatal Transmission

- HCV Viremia
 - + HCV RNA (Granocsky MO, et al. *Pediatrics*. 1998; Resti M, et al. *BMJ*. 1998)
 - Possibly with higher HCV viral loads (Ohto H, et al. *NEJM*.1994; Mast EE et al. *J Infect Dis*. 1994; Ceci O, et al. *J Pediatr Gastro Nutr*. 2001)
- HIV co-infection (Benova L., et al. *CID*. 2014)
- IV Drug Use (Resti M, et al. *J Infect Dis*. 2002)
 - PBMC infection (Resti M, et al. *Clin Infect Dis*. 2002; Azzari C, et al. *Blood*. 2000)
- Possible Risk Factors
 - Prolonged rupture of membranes (Spencer JD, et al. *J Viral Hepat*. 1997; Cottrell EB, et al. *Ann Intern Med*. 2012)
 - Maternal blood exposure (scalp electrode or vaginal laceration) (Mast EE et al. *J Infect Dis*. 1995; Steininger C, et al. *J Infect Dis*. 2003)

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 HCV 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 invasive procedures
 - Fetal scalp monitoring, amniocentesis, operative delivery

Better Scenario: HCV antivirals for maternal treatment and perinatal transmission

- Only a short course is needed for maternal cure
 - Can wait until organogenesis is complete (estimated 16 weeks, though development is ongoing)
 - Maternal cure is possible during engagement of prenatal care and before delivery
 - Unanswered question: Does maternal HCV cure ensure HCV uninfected infant?

A Phase One Study of Ledipasvir/sofosbuvir in Pregnant Women with Hepatitis C Virus

- Primary Objective

- To define the pharmacokinetics, safety of and virologic response to ledipasvir 90 mg-sofosbuvir 400mg (LDV/SOF) therapy in pregnancy

- Hypothesis

- Ledipasvir 90mg-sofosbuvir 400mg (LDV/SOF) therapy will be safe and effective in pregnant women

Inclusion and Exclusion Criteria

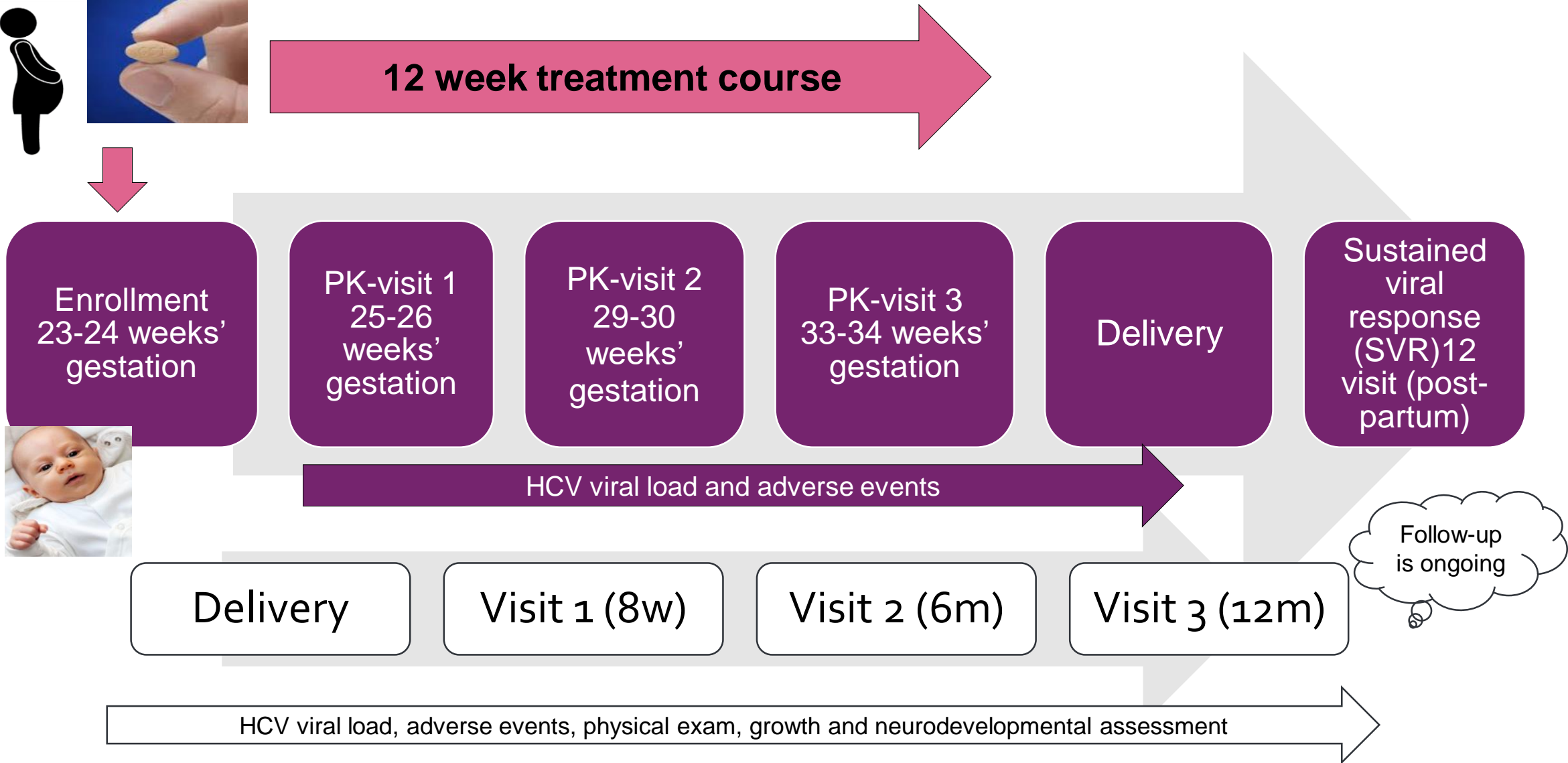
■ Inclusion

- Age 18-39 years
- Chronic HCV infection with genotype 1, 4, 5, 6
- Singleton gestation without fetal anomalies
- Negative Hepatitis B virus and HIV testing
- Delivering at Magee-Womens Hospital

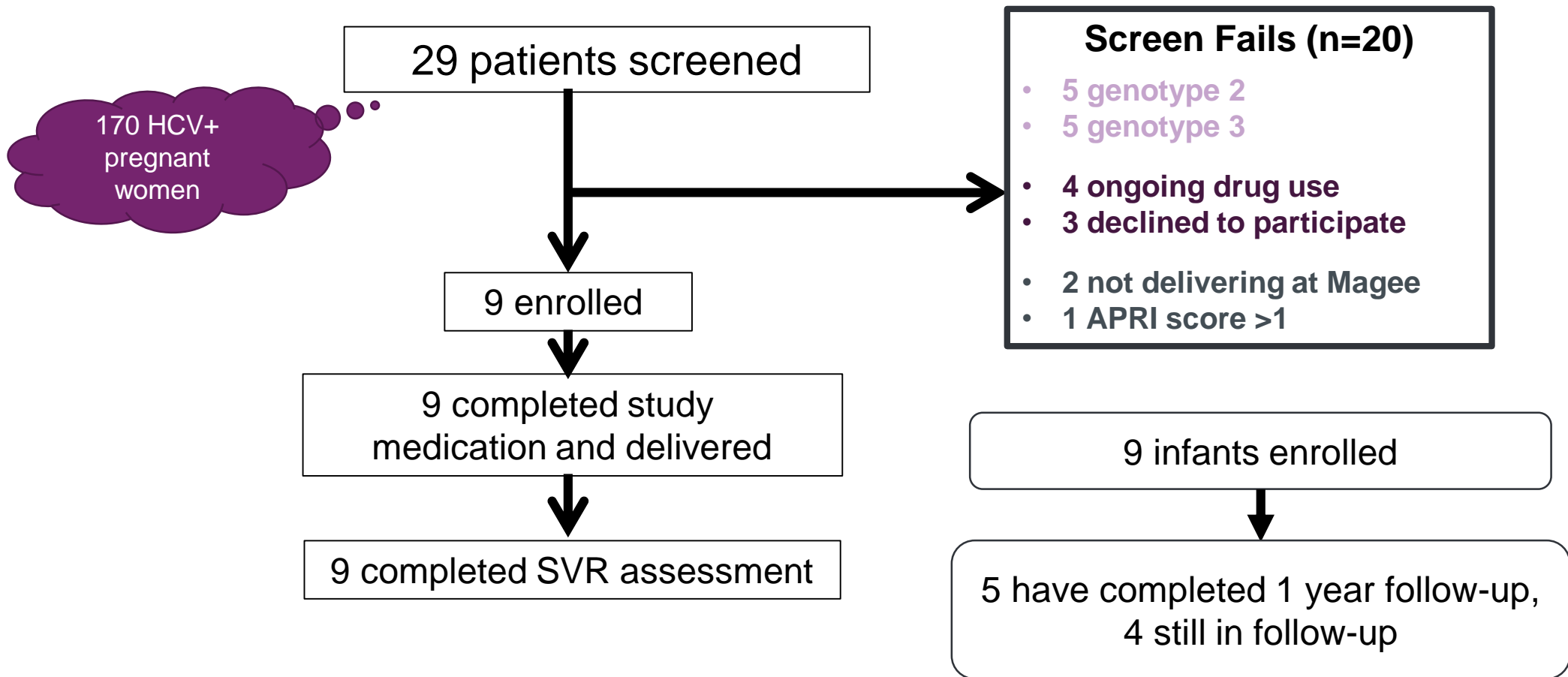
■ Exclusion

- Previous treatment with SOF or NS5A inhibitor
- History of cirrhosis
- Clinically significant drug use
- History or high risk of spontaneous preterm birth
- Significant laboratory abnormalities at screening

Study Design



Recruitment: October 2016 to October 2018



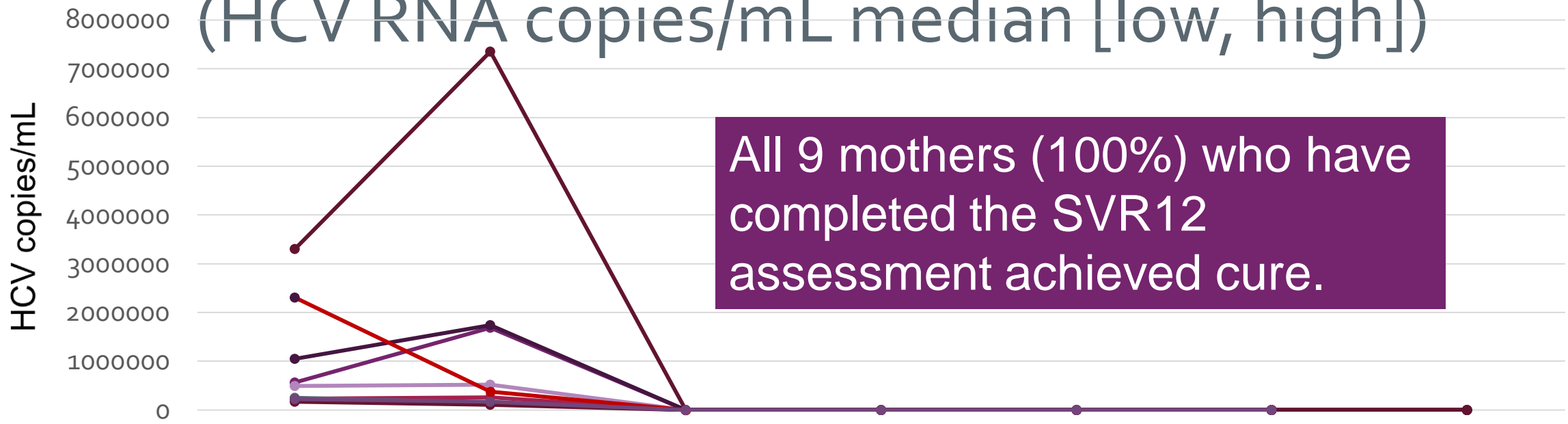
Demographic and Clinical Characteristics

| Demographic | Number (%) or Median |
|--------------|----------------------|
| Age | 31 (25, 38) |
| White Race | 9 (100%) |
| Insurance | |
| Public | 8 (89%) |
| Military | 1 (11%) |
| Education | |
| >High school | 6 (67%) |
| High School | 1 (11%) |
| <High School | 2 (22%) |

| Clinical Characteristic | Number (%) |
|--|------------|
| Tobacco Use | 7 (78%) |
| Opioid Therapy | 4 (44%) |
| Methadone | 2 (22%) |
| Buprenorphine | 2 (22%) |
| Route of HCV acquisition | |
| IV Drug Use | 8 (89%) |
| Perinatal | 1 (11%) |
| HCV RNA >6 million copies/mL at Enrollment | 1 (11%) |
| HCV Genotype 1 | 9 (100%) |

HCV Viral Response to LDV/SOF During Pregnancy

(HCV RNA copies/mL median [low, high])



All 9 mothers (100%) who have completed the SVR12 assessment achieved cure.

| Visit | Screening | Enrollment | PK-1 | PK-2 | PK-3 | Delivery | SVR ₁₂ |
|-------|-----------------------------------|-----------------------------------|------------|-----------|----------|-----------|-------------------|
| HCV | 4.9 (1.7, 33.0) × 10 ⁵ | 5.2 (1.0, 73.5) × 10 ⁵ | 12 (0, 49) | 0 (0, 12) | 0 (0, 0) | 0 (0, 12) | 0 (0, 0) |



12 weeks of treatment

12 weeks after finishing course
Undetectable = cure

Pregnancy and Delivery Outcomes

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

Conclusions

- In this first study of HCV treatment during pregnancy, LDV/SOF administration was safe for pregnant women and effective for HCV cure
 - 100% of participants were cured of HCV and all infants are negative to date
 - LDV/SOF was well tolerated in pregnant women; treatment related AEs were all mild or moderate
- No infant safety concerns to date after LDV/SOF in utero exposure.
- Further studies should consider evaluation of pan-genotypic regimen for pregnancy
- Larger studies must be conducted to confirm the safety and efficacy of HCV treatment during pregnancy

Eradication of perinatal HCV infection is possible!

- Problem:

- Risk-based screening HCV screening in pregnancy (missed maternal cases)
- Inadequate infant testing among those perinatally exposed (missed infant cases)
- No proven interventions to decrease perinatal HCV transmission

- Solution: Test for and treat HCV during pregnancy

- Gaps:

- 1) Add reflex HCV test to the new OB panel
- 2) Identify best strategies for infant testing
- 3) Evaluate safety and efficacy of DAAs in pregnancy

