An Observational Study of Mother-Infant Outcomes Following Antenatal Exposure to Direct-Acting Antivirals:

The Treatment in Pregnancy for Hepatitis C (TiP-HepC) Registry

Study Protocol

Version 1.0
October 2021

Primary Investigators:
Neil Gupta, Coalition for Global Hepatitis Elimination, The Task Force for Global Health
John Ward, Coalition for Global Hepatitis Elimination, The Task Force for Global Health

Contact: ngupta-consultant@taskforce.org

Table of Contents

Acronyms and Abbreviations

DAA: Direct Acting Antivirals

DCV: Daclatasvir

GLE: Glecaprevir

GT: Genotype

HCV: Hepatitis C Virus

LDV: Ledipasvir

LMIC: Low- and middle-income country

M&E: Monitoring and evaluation

PIB: Pibrentasvir

PWID: People who inject drugs

SOF: Sofosbuvir

SVR12: Sustained Virologic Response at 12 weeks

VEL: Velpatasvir

VOX: Voxilaprevir

1. Abstract

Clinical interventions to reduce the risk of vertical transmission of hepatitis C virus (HCV) infection from mother to infant are highly limited. Direct-acting antiviral (DAA) medications have demonstrated excellent safety and efficacy in non-pregnant individuals, but there is a lack of data regarding the safety of these medications in pregnant women and the effectiveness of these medications in reducing mother-to-child transmission. Therefore, although HCV screening during pregnancy is now recommended in many countries, there is no approved treatment for HCV during pregnancy. We propose an observational study to assess outcomes of mother-infant pairs exposed to DAAs during pregnancy within a global clinical case registry. Data regarding the exposures and outcomes of mother-infant pairs exposed to DAAs during pregnancy will be solicited and collected from clinical providers, healthcare facilities, HCV treatment programs, and other clinical practices worldwide. Data will be shared and maintained within a secure database, and cumulative data will be analyzed at pre-determined six-month intervals. The primary outcome will be the number and proportion of mother-infant pairs with adverse pregnancy or birth outcomes. The results of this study will inform HCV treatment decisions by clinical providers and programs worldwide.

2. Introduction and Study Justification

In 2016, approximately 6% of all women who were tested for HCV during pregnancy in the United States were HCV antibody-positive (Schillie 2018). That year, there were 14,417 live births delivered by HCV-positive women, which comprised 0.38% of all live births in the US (Schillie 2018). Globally, the HCV prevalence among pregnant women varies widely (0.06%-7%) depending on regional and local epidemiology and risk factors (Kushner 2020). Approximately 5.8% of infants born to HCV-infected mothers will acquire HCV infection with higher rates of transmission among women with HIV co-infection (Benova 2014). The primary route for the vertical transmission of HCV is believed to be the perinatal exposure of the infant to maternal blood, though in utero transmission also occurs (Mok 2005).

Hepatitis C virus (HCV) testing for pregnant women is now recommended in many countries and universal HCV screening for pregnant women was adopted in the United States in 2020 (Schillie 2020). No clinical interventions have been proven to reduce perinatal HCV transmission, but current and clinical practice guidelines include recommendations for the avoidance of potentially invasive procedures during delivery (ie, chorionic villus sampling, fetal scalp monitoring, episiotomy) (Cottrell 2013, SMFM 2021). The effect of virologic suppression or cure of HCV infection during pregnancy on the risk of mother-to-child HCV transmission has not been directly studied. Previous HCV treatment regimens were contra-indicated in pregnancy due to the inclusion of ribavirin and other teratogenic drugs. More recently, interferon- and ribavirin-free direct-acting antiviral (DAA) medications have raised the potential for HCV treatment during pregnancy to prevent perinatal transmission of HCV and allow for treatment of women during pregnancy. Over half of women reported a preference for HCV treatment during pregnancy if it reduced the probability of vertical transmission to the infant (Kushner 2018). In addition to potentially reducing vertical transmission to the infant during the current pregnancy, treatment during pregnancy can increase the number of women

treated for HCV, and decrease the likelihood of being infected during subsequent pregnancies. Many vulnerable women are at high-risk for loss-to-follow-up following delivery and many women living with HCV may only be eligible for health insurance during pregnancy and immediately postpartum.

Several DAA regimens have demonstrated excellent safety and efficacy profiles in non-pregnant individuals across multiple or all HCV genotypes, achieving cure in >95% of people in as few as 8 weeks of once-daily oral treatment. However, there are limited data regarding the safety and efficacy of DAAs in pregnancy. A phase I pharmacokinetic study of sofosbuvir/ledipasvir (SOF/LDV) in 9 pregnant women demonstrated similar drug levels to non-pregnant individuals with excellent safety and efficacy profile, and a similar study of sofosbuvir/velpatasvir (SOF/VEL) is currently enrolling participants (Chappell 2020). A prospective study of 15 women treated with SOF/LDV in India reported no adverse events (Yattoo 2018). No other trials have been conducted or registered for pregnant individuals to date. The frequency and outcomes for women who become pregnant while on DAA treatment have been rarely reported. Currently, there is only one published study reporting outcomes of mother-infant pairs of women who became pregnant while on DAA treatment; among 100 women, 9 of whom completed 12 weeks of treatment with various regimens, no major adverse events were reported (Abdallah 2021).

Given the paucity of data regarding the safety and efficacy of DAA treatment in pregnancy, the American College of Obstetrics and Gynecology and Society for Maternal-Fetal Medicine recommend that DAAs "only be initiated in the setting of a clinical trial during pregnancy and that people who become pregnant while taking a direct-acting antiviral should be counseled in a shared decision-making framework about the risks and benefits of continuation." (SMFM 2021). The Infectious Diseases Society of America and the American Association for the Study of Liver Diseases (IDSA/AASLD) advise that "treatment can be considered during pregnancy on an individual basis after a patient-physician discussion about the potential risks and benefits". Treatment for HCV in pregnancy therefore remains an off-label use of DAA medications and clinical practices remain highly variable by providers and programs. The frequency, geographic distribution, safety profile or effectiveness of HCV treatment during pregnancy for mother-infant pairs have not been evaluated or reported.

3. Objectives & Hypotheses

The primary objective of this observational study is to assess the safety of DAA treatment in mother-infant pairs with exposure to DAA medications during pregnancy within a clinical case registry. The secondary objectives of this study are to describe the frequency and distribution of known cases of DAA exposure during pregnancy and to assess the effectiveness of DAA treatment in pregnancy in achieving HCV cure for mothers and reducing the transmission of HCV from mother to infant.

4. Methodology

4.1 Study Design

This is an observational study of the outcomes of mother-infant pairs exposed to DAA treatment during pregnancy in routine clinical practice using de-identified data from a convenience sample of health facilities, public health, government, and private entities globally. Data regarding the demographics, baseline clinical status, timing and type of DAA exposure, and pregnancy/birth outcomes of mother-infant pairs exposed to DAAs during pregnancy will be solicited from clinical providers, health facilities, HCV treatment programs, and other clinical practices or programs prescribing DAA treatment. Data will be coded, standardized, and pooled in a common database for analysis.

4.2 Inclusion and exclusion criteria

The following inclusion criteria are required to be included in the study database:

- Documented pregnancy with:
    - Estimated date of conception by documentation of either 1) date of last menstrual period or 2) ultrasound evaluation
    - Actual date of delivery
- Documented chronic HCV infection prior to or during pregnancy (positive test for HCV RNA or HCV core antigen)
- Documented DAA exposure occurring within 30 days of the estimated date of conception and before the pregnancy outcome (ie, fetal demise, spontaneous abortion, live delivery, etc). Eligible DAA drugs are listed in Appendix 1. (DAA exposures that include ribavirin or interferon will be excluded given their established harm during pregnancy.)

4.3 Outcomes and Data variables

The primary outcomes measured in the study are adverse pregnancy and birth outcomes documented at the time of the outcome of the pregnancy (primary endpoint). Primary adverse pregnancy outcomes include preterm delivery (<37 weeks gestational age), stillbirth or fetal demise, and maternal death. Primary adverse birth outcomes include low birth weight (<2500g), small for gestational age, need for neonatal intensive care, and presence of congenital anomaly. Secondary outcomes of the study are the proportion of women achieving HCV cure by HCV PCR test 12 weeks following last DAA treatment (SVR12) and the proportion of infants with evidence of chronic HCV infection after 2 months of age by HCV PCR or after 18 months of age by anti-HCV antibody seropositivity. The study variables to be collected are listed and defined in Appendix 2.

4.4 Data collection

Clinical providers, health facilities, HCV treatment programs, and other clinical practices prescribing DAA treatment will be invited to contribute data based on the inclusion criteria described above. Participating centers and programs will be identified through systematic email and phone outreach to the following sources:

- Coalition for Global Hepatitis Elimination program registration database
- Coalition for Global Hepatitis Elimination contact mailing list
- Coalition for Global Hepatitis Elimination partner programs and contributors
- Coalition for Global Hepatitis Elimination technical advisory board members

- Professional societies in hepatology, infectious diseases, and obstetrics-gynecology
- Contact authors for relevant studies identified in comprehensive literature review search
- Research networks in fields of viral hepatitis, HIV, and obstetrics-gynecology
- National and local hepatitis care and treatment programs
- Referrals from World Health Organization and regional offices
- Drug manufacturers of included drugs
- Other referrals

Potential participating centers will be contacted via email (Appendix 3) and provided a project summary (Appendix 4) as well as full study protocol for consideration of participation. To participate, sites will be required to have data regarding at least one patient meeting study inclusion criteria. The study variables will be shared with the participating center in excel format for data entry and sharing. The participating center will remove all personally identifiable information (PII) from the data. The study team will provide a sequential unique Registry Identification Number (RIN) to the participating center to label each record based on the participating facility name, date of study inclusion, and sequential order. The RIN will be linked to each subject by the participating center and this key maintained under password protection by the participating center (and not shared with the study team). Data from a participating center will be transmitted electronically to the study team via a password-protected secure data sharing system. Participating centers contributing routinely-collected clinical data coded by unique identifier to the registry will not be engaged in any research conducted using this registry and are not required to meet regulatory requirements stipulated by the Office for Human Research Protection Guidance (OHRP 2011).

After the data is submitted from a participating center, the data will be inspected and cleaned by the study team and entered into the study dataset. In the case of missing or incomplete data, the participating center may provide additional data to the study team by RIN. The study dataset will be stored in a password-protected cloud-based software platform hosted by the Task Force for Global Health and only accessible to authorized study team members. Participating centers will be requested to maintain the link of RIN to each subject for ten years, after which the participating center will be requested to delete the linkage from study records.

Data collection will be open-ended without a pre-determined end date. Participating centers may provide additional cases meeting the inclusion criteria at any time. Participating centers will also be contacted and requested to contribute additional data at regular time intervals. Cumulative data analysis will occur at regular pre-determined time intervals (see Data Analysis).

In the initial phase of the study, data will be collected a single point in time after the primary endpoint (pregnancy/birth outcomes) from participating centers. In future phases of the study, the study team may contact participating centers for follow-up data collection regarding secondary endpoints (up to 18 months of age of the child) regarding registered cases using the unique Registry Identification Number. An amendment to this protocol will be submitted for approval prior to contacting participating centers for any follow-up data on invidiuals linked by the Registry Identification Number.

4.5 Data analysis

We will report the following descriptive results in tabular format:

1. Number of facilities identified with data on documented exposure to DAAs during pregnancy
2. Number of women identified with documented exposure to DAAs during pregnancy and median time of exposure during the gestational period
3. Number and proportion of mother-infant pairs with documented exposure to DAAs during pregnancy with adverse pregnancy outcome (ie, fetal demise, spontaneous abortion, preterm delivery)
4. Number and proportion of mother-infant pairs with documented exposure to DAAs during pregnancy and with adverse birth outcome (ie, low birth weight, small for gestational age, need for intensive care) or congenital anomaly noted at birth
5. Proportion of women with exposure to DAA during pregnancy who completed DAA treatment
6. Proportion of women with exposure to DAA during pregnancy who completed DAA treatment and achieved SVR12
7. Proportion of infants born to women with exposure to DAA during pregnancy with evidence of exposure and chronic infection reflecting HCV vertical transmission after 2 months of infant age by positive HCV PCR result or after 18 months of age by anti-HCV antibody positivity

Data analysis will occur on a pre-determined date at regular six month intervals. Data analysis will be cumulative and include all entries within the data set.

4.6 Dissemination of Findings

The findings from this analysis will be disseminated through submission of a conference abstract(s) and manuscript for peer-reviewed publication. The findings also will be shared with participating centers and inform technical guidance for clinical guidelines. The findings will be discussed and disseminated within the TiP-HCV Community of Practice.

5. Limitations

This is an observational study to report real-life occurences and outcomes of mother-infant exposures to DAAs and will rely on routinely collected clinical data from multiple centers. Therefore, there will be several limitations. Firstly, the data on characteristics and outcomes of mother-infant pairs will likely be incomplete and highly variable among participating centers. Measurement and reporting of HCV status, adverse pregnancy/birth outcomes or congenital anomalies will not be standardized or necessarily validated. This will preclude rigorous comparison of data among participating centers, types of facilities, types of providers, DAA regimens, countries, and regions. Secondly, our search process for participating samples will result in only a sample of participating centers with data meeting the inclusion criteria. Our results will therefore reflect a convenience sample of DAA-exposed mother-infant pairs and is not intended to be exhaustive of all existing cases. The sampled data will not allow for sufficient power to assess for significant differences in mother-infant safety or efficacy outcomes from the background population nor estimation of overall prevalence of clinical outcomes.

6. Ethical Issues

6.1 Confidentiality

Consistent with Section 301(d) of the Public Health Service Act, a Certificate of Confidentiality (CoC) applies to this research because this research is funded, conducted, or supported by CDC and the activity constitutes biomedical, behavioral, clinical, or other research. Therefore, CDC and any of its collaborators, contractors, grantees, investigators or collaborating institutions that receive "identifiable, sensitive information" as defined by subsection 301(d) of the Public Health Service Act will not:

- Disclose or provide, in any Federal, State, or local civil, criminal, administrative, legislative, or other proceeding "identifiable, sensitive information" that was created or compiled for purposes of the research, unless such disclosure or use is made with the consent of the individual to whom the information, document, or biospecimen pertains; or
- Disclose "identifiable, sensitive information" or provide ISI to any other person not connected with the research.

In accordance with subsection 301(d) of the Public Health Service Act, disclosure will be permitted only when:

- Required by Federal, State, or local laws (e.g., as required by the Food, Drug and Cosmetic Act or required by state laws requiring the reporting of communicable diseases to State and local health departments), excluding instances of disclosure in any Federal, State, or local civil, criminal, administrative, legislative, or other proceeding;
- Made with the consent of the individual to whom the information, document, or biospecimen pertains; or
- Made for the purposes of other scientific research that is in compliance with applicable Federal regulations governing the protection of human subjects in research.

CDC and its collaborators and contractors conducting this research will establish and maintain effective internal controls (e.g., policies and procedures) that provide reasonable assurance that the research is managed in compliance with subsection 301(d) of the Public Health Service Act. CDC will ensure: 1) that any investigator or institution not funded by CDC who receives a copy of identifiable, sensitive information protected by this Certificate, understands that it is also subject to the requirements of the Certificate; and 2) that any subrecipient that receives CDC funds to carry out part of this research involving a copy of identifiable, sensitive information protected by a Certificate understands that it is subject to subsection 301(d) of the PHS Act. Therefore, all study staff will receive training on the importance of protecting the confidentiality of human research subjects and of personal information acquired, including the collection of biological specimens.

6.2 Informed Consent

Exception to the informed consent process is requested as this study reasonably meets all criteria for waiver of informed consent under 45 CFR 46.116(d), which are:

- This research involves no more than minimal risk to the subjects included in the registry (see 6.4 Risk versus Benefits).
- This waiver will not adversely affect the rights and welfare of the subjects included in the registry.
- The research could not practicably be carried out without the waiver.
- If requested by a participating center, subjects would be provided with additional pertinent information about the registry(see Appendix 4).

6.3 HIPAA Privacy Rule Authorization

A waiver of HIPAA Privacy Rule authorization is requested as the disclosure and use of protected health information in this study will involve no more than a minimal risk to the privacy of individuals based on the presence of the following criteria 45 CFR 164.512(b):

- This study protocol describes a plan to protect identifiers from improper use and disclosure (see section 4.4 Data Collection).
- This study protocol describes a plan to destroy the identifiers at the earliest opportunity consistent with conduct of the research (see section 4.4 Data Collection).
- The study protocol provides written assurances that the protected health information will not be reused or disclosed to any other person or entity
- This study could not practicably be conducted without the waiver and could not practicably be conducted without access to and use of the PHI.

6.4 Risks versus Benefits

All patient data will include a coded unique identification number which will be linked to the Registry Identification Number. Therefore, there exists the risk of linkage of individual registry case records with the patient identity. To minimize this risk, all data from the participating center will be transmitted via a password-protected secure data sharing system, andthe study database (registry) will be maintained within a password protected secure cloud-based data warehouse and accessible only to study team members. There is no direct benefit to the individual patients from whom data is contributed to the study. However, the results of this study will improve the understanding of the safety and effectiveness of HCV treatment for pregnant individuals and better inform decision-making by providers and programs treating HCV infection in pregnant individuals.

7. Investigators & Funding Sources

The study will be conducted by the Coalition for Global Hepatitis Elimination at the Taskforce for Global Health. The study Primary Investigators (Neil Gupta, John Ward) will have primary responsibility for study design, data collection, data interpretation, and study dissemination. The study team will hire a data analyst to construct and manage the study dataset, including data acquisition, cleaning, merging, and analysis. The study is funded by the U.S. Centers for Disease Control and Prevention (award # CDC-RFA-GH21-2102); CDC team members will provide technical assistance for the study, but will not participate in data collection or analysis. The study team of the Task Force for Global Health retains final decision making for study design, methodology, interpretation, and dissemination of the study.

Study Team Members:
Neil Gupta, Coalition for Global Hepatitis Elimination, Task Force for Global Health
John Ward, Coalition for Global Hepatitis Elimination, Task Force for Global Health
Henry Njuguna, Coalition for Global Hepatitis Elimination, Task Force for Global Health

CDC Team Members:
Carolyn Wester, Division of Viral Hepatitis, U.S. Centers for Disease Control and Prevention
Paige Armstrong, Division of Viral Hepatitis, U.S. Centers for Disease Control and Prevention
Senad Handanagic, Division of Viral Hepatitis, U.S. Centers for Disease Control and Prevention
Shaun Shadaker, Division of Viral Hepatitis, U.S. Centers for Disease Control and Prevention
Nancy Glass, Division of Viral Hepatitis, U.S. Centers for Disease Control and Prevention

8. Project Timeline

Activities	Sept '21	Oct '21	Nov '21	Dec '21	Jan '22	Feb '22	Mar '22	Apr '22	May '22	June '22
Protocol and data collection tool development	X									
IRB approval		X	X							
Solicitation of participating centers	X	X	X	X	X	X				
Study database development			X	X						
Data sharing, merger, and cleaning				X	X	X	X	X		
Data analysis								X		

Data interpretation and results dissemination						X	X	X

9. References

AASLD & IDSA. HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C, v2021.1.

AbdAllah M, Alboraie M, Abdel-Razek W, Hassany M, Ammar I, Kamal E, Alalfy M, Okasha A, El Akel W, Shaaban E, Elbaz T. Pregnancy outcome of anti-HCV direct-acting antivirals: Real-life data from an Egyptian cohort. Liver International. 2021 Jul;41(7):1494-7.

Benova L, Mohamoud YA, Calvert C, Abu-Raddad LJ. Vertical transmission of hepatitis C virus: systematic review and meta-analysis. Clinical infectious diseases. 2014 Sep 15;59(6):765-73.

Chappell CA, Scarsi KK, Kirby BJ, Suri V, Gaggar A, Bogen DL, et al. Ledipasvir plus sofosbuvir in pregnantwomen. with hepatitis C virus infection: a phase 1 pharmacokinetic study. Lancet Microbe 2020;1(5):e200–e208.

Cottrell EB, Chou R, Wasson N, Rahman B, Guise JM. Reducing risk for mother-to-infant transmission of hepatitis C virus: a systematic review for the U.S. Preventive Services Task Force. Ann Intern Med 2013;158(2):109–113.

Kushner T, Cohen J, Tien PC, Terrault NA. Evaluating women's preferences for hepatitis C treatment during pregnancy. Hepatol Commun 2018;2(11):1306–1310.

Kushner T, Reau N. Changing epidemiology, implications, and recommendations for hepatitis C in women of childbearing age and during pregnancy. Journal of Hepatology 2021 vol. 74 j 734–741

Mok J, Pembrey L, Tovo PA, Newell ML, European Paediatric Hepatitis CVN. When does mother to child transmission of hepatitis C virus occur? Arch Dis Child Fetal Neonatal Ed 2005;90(2):F156–F160.

Office for Human Research Protections. National Health Registry Activities and 45 CFR part 46 (2011). Available from: www.hhs.gov/ohrp/regulations-and-policy/guidance/regarding-application-of-45-cfr-46-to-national-health-registry/index.html. Accessed on Oct 15, 2021.

OCR HIPAA Privacy. Disclosures for Public Health Activities [45 CFR 164.512(b)]. 2002. Available from: www.hhs.gov/sites/default/files/ocr/privacy/hipaa/understanding/special/publichealth/publichealth.pdf. Accessed on Oct 15, 2021.

Schillie SF, Canary L, Koneru A, Nelson NP, Tanico W, Kaufman HW, et al. Hepatitis C virus in women of childbearing age, pregnant women, and children. Am J Prev Med 2018;55(5):633–641.

Schillie S, Wester C, Osborne M, Wesolowski L, Ryerson AB. CDC recommendations for hepatitis C screening among adults—United States, 2020. MMWR Recommendations and Reports. 2020 Apr 3;69(2):1.

Society of Maternal Fetal Medicine (SMFM). Society for Maternal-Fetal Medicine Consult Series #56: Hepatitis C in pregnancy – updated guildelines. September 2021.

Yattoo G. Treatment of chronic hepatitis C with ledipasvir/sofosbuvir combination during

pregnancy. Hepatol Int. 2018;12(Suppl. 2):S292–3.

Appendix 1: Direct-acting antivirals included in registry (combinations also permitted)

Daclatasvir
Elbasvir
Glecaprevir
Grazoprevir
Ledipasvir
Ombitasvir
Paritaprevir
Pibrentasvir
Ravidasvir
Simprevir
Sofosbuvir
Velpatasvir

Appendix 2. Data Set Variables

Variable	Field Type	Description
SETTING		
Registry Identification Number	Alphanumeric	Provided by the study team to the participating center
Country	Text field / drop down country list	Country where patient care occurred
Facility Type	Select: • Prenatal facility • Hepatitis treatment facility • Other	Facility where patient was treated with DAA OR facility where patient data is stored?
Clinician Type	Select: • Obstetrician/Gynecologist • Nurse Midwife • Other prenatal provider • Infectious Disease clinician • Hepatologist • Internist • Other clinician	Type of clinician providing primary responsibility of care and DAA treatment decision
MATERNAL INFORMATION		
Maternal Age	Numeric field	Age in years of the patient at the time of first recorded antenatal visit
Maternal birth year	Numeric field	
Esimated date of conception (EDC)	Date field	
Mode of estimation for EDC	Select: Second trimester ultrasound First trimester ultrasound Last menstrual period Other estimation by clinician or patient	Note, if multiple modalities for estimation available, prioritize response in order of: 1. Second trimester ultrasound 2. First trimester ultrasound 3. Last menstrual period 4. Other estimation by clinician or patient
If EDC by ultrasound, provide date of ultrasound	Date field	Report latest (highest gestational age) ultrasound available If known
If EDC by last menstrual period, provide date of last menstrual period	Date field	
HCV Genotype	Select: • 1a • 1b • 1 subtype unknown • 2 • 3 • 4 • 5 • 6 • 7 • Other • unknown	
HCV viral load (IU/mL)	Numeric	Most recent HCV PCR result prior to treatment. Enter “999” for positive result on qualitative test.
HCV viral load date	Date field	Most recent HCV PCR result prior to treatment
Cirrhosis status	Select: • No cirrhosis • Compensated cirrhosis • Decompensated cirrhosis	Cirrhosis status of patient prior to initation of treatment. Cirrhosis is defined by METAVIR F4 equivalent.

	• Unknown	
Mode of Cirrhosis assessment	Select: Biopsy Transient elastography Non-invasive tests (APRI score) Ultrasound Clinical exam	
HBV status (HBsAg)	Select from: • HBsAg+ • HBsAg- • Vaccinated • Unknown	
HIV status	Select from: • HIV positive • HIV negative • Unknown	Status of HIV co-infection: whether patient was HIV positive or negative, or unknown
If HIV-positive, antiretroviral treatment during pregnancy period	Alphanumeric	
Current or recent intravenous drug use (in 12 months prior to pregnancy)	Select from: • Yes • No • Unknown	
Tobacco use during pregnancy	Select from: • Yes • No • Unknown	
Current or recent use of other recreational drugs	Select from: • Marijuana • Cocaine • Methamphetamines • Opioids • None • Unknown	
Opioid maintenance therapy during pregnancy	Select from: • Yes • No • Unknown	
Pre-existing maternal conditions or diagnoses #1	Alphanumeric (ICD-10 code)	See: https://icd.who.int/browse10/2016/en#/
Pre-existing maternal conditions or diagnoses #2	Alphanumeric (ICD-10 code)	See: https://icd.who.int/browse10/2016/en#/
Pre-existing maternal conditions or diagnoses #3	Alphanumeric (ICD-10 code)	See: https://icd.who.int/browse10/2016/en#/
Concurrent medications in pregnancy	Alphanumeric	List all medications taken for chronic conditions during pregnancy
DAA Exposure		
DAA medication 1		
Drug name	Select: Appendix 2 drop down	
Drug dosage (total DAILY dose)	Numeric entry	Provide total daily dose in mg
Drug start date	Date field	
Drug end date	Date Field	
Discontinued due to pregnancy?	Select: Yes No Unknown	
DAA medication 2		
Drug name	Select: Appendix 2 drop down	

Drug dosage (total DAILY dose)	Numeric entry	Provide total daily dose in mg
Drug start date	Date field	
Drug end date	Date Field	
Discontinued due to pregnancy?	Select: Yes No Unknown	
DAA medication 3		
Drug name	Select: Appendix 2 drop down	
Drug dosage (total DAILY dose)	Numeric entry	Provide total daily dose in mg
Drug start date	Date field	
Drug end date	Date Field	
Discontinued due to pregnancy?	Select: Yes No Unknown	
DAA medication 4		
Drug name	See code sheet for individual drugs	
Drug dosage (total DAILY dose)	Numeric entry	Provide total daily dose in mg
Drug start date	Date field	
Drug end date	Date Field	
Discontinued due to pregnancy?	Select: Yes No Unknown	
MATERNAL OUTCOMES		
HCV treatment completed	Select: Yes No Unknown	
If HCV treatment not completed, reason for HCV treatment non-completion	Select: Discontinuation due to pregnancy Adverse Event Physician discontinued for other reason Patient discontinued for other reason Loss-to-follow-up Death Other	
If HCV treatment discontinued due to adverse event, list adverse event here	Alphanumeric	
HCV Treatment outcome	Select Cure (SVR12 achieved) Not cured (SVR12 not achieved) SVR12 not obtained	
HCV Treatment outcome date	Date field	
Prentatal test(s) conducted	Select multiple: Ultrasound Amniocentesis Chorionic Villus Sampling Cystic Fibrosis Mutation Analysis Fetal Echo First Trimester Screen MSAFP/serum markers Nuchal translucency Other	
Any fetal structural defect noted prenatally?	Select: Yes	

	No unknown	
Prenatal test where structural defect detected?	Select multiple: Ultrasound Amniocentesis Chorionic Villus Sampling Cystic Fibrosis Mutation Analysis Fetal Echo First Trimester Screen MSAFP/serum markers Nuchal translucency Other	
Pregnancy complications	Select (multiple): Fetus small for gestational age Pregnancy-induced hypertension Pre-eclampsia Eclampsia Gestational diabetes Gestational hypertension Intrahepatic cholestasis of pregnancy Other: ICD-10 code None Unknown	
Pregnancy outcome	Select: Live infant – term delivery(>37 weeks GA) Live infant – preterm delivery (34-37 weeks GA) Live infant – very preterm delivery (<34 weeks GA) Live infant – unknown term Spontaneous abortion Induced abortion Fetal demise or stillbirth Maternal death Unknown	Definitions: Preterm birth: <37weeks gestational age Very preterm birth: <34 weeks gestational age
Date of pregnancy outcome	Date field	
Type of delivery	Select: Vaginal delivery Cesarean section delivery Unknown	
Delivery complications	Select: Prolonged rupture of membranes Breech or other non-cephalic presentation Post-partum hemorrhage Maternal death Other: ICD-10 code None Unknown	
INFANT BIRTH OUTCOMES		
Date of Birth	Date field	Or date of birth outcome if fetal loss
Gender	Select: Male Female Unknown	
Birth weight	Numeric	Birth weight in grams, if known
Birth length	Numeric	Birth length in cm, if known
Birth head circumference	Numeric	Birth head circumference in cm, if known
APGAR score	Numeric (0-10)	5-minute APGAR score, if available

Neonate admitted to intensive care unit following delivery	Select: Yes No Unknown	
Congential anomaly identified	Select: Yes No Unknown	Congenital anomalies as listed in ICD-10 Section: XVII Congenital malformations, deformations and chromosomal abnormalities See: https://icd.who.int/browse10/2016/en#/XVII (example in Appendix 3).
Date of last evaluation for congenital anomaly	Date field	
Congenital anomaly #1	Alphanumeric (ICD-10 code)	See: https://icd.who.int/browse10/2016/en#/XVII
Congenital anomaly date of detection	Date field	
Type of evaluation for congenital anomaly	Select all that apply: General newborn physical exam Targeted physical exam by speciality physician Infant anatomy scan (ultrasound) Evaluation conducted, results not documented No evaluation obtained	
Congenital anomaly #2	Alphanumeric (ICD-10 code)	See: https://icd.who.int/browse10/2016/en#/XVII
Congenital anomaly date of detection	Date field	
Type of evaluation for congenital anomaly	Select all that apply: General newborn physical exam Targeted physical exam by speciality physician Infant anatomy scan (ultrasound) Evaluation conducted, results not documented No evaluation obtained	
Other neonatal or infant diagnoses (ICD-10 code) #1	Alphanumeric ICD-10	List here other pertinent neonatal or infant diagnoses. See: https://icd.who.int/browse10/2016/en#/XVII
Other neonatal or infant diagnoses (ICD-10 code) #2	Alphanumeric ICD-10	List here other pertinent neonatal or infant diagnoses. See: https://icd.who.int/browse10/2016/en#/XVII
Other neonatal or infant diagnoses (ICD-10 code) #3	Alphanumeric ICD-10	List here other pertinent neonatal or infant diagnoses. See: https://icd.who.int/browse10/2016/en#/XVII
INFANT FOLLOW-UP (If AVAILABLE)		
Infant HCV PCR test	Select: Positive Negative	PCR test after 2 months of age is preferred. If multiple PCR tests were conducted, list the most recent (oldest infant age)
Infant HCV PCR test date	Date field	
Infant HCV antibody test	Select: Positive Negative	Antibody test after 18 months of age is preferred. If multiple antibody tests, list most recent (oldest infant age).
Infant HCV antibody test date	Date field	
Infant clinical outcome	Select: No neonatal or infant death noted Neonatal death noted (0-29 days) Infant death noted (>29 days) Unknown	

Date of last assessment of infant	Date field	The most recent date for which clinical outcome of infant is document.
Other relevant infant diagnoses, including neurodevelopmental diagnoses	Alphanumeric (ICD-10 code)	List here other pertinent neonatal or infant diagnoses. See: https://icd.who.int/browse10/2016/en#/XVII
Other relevant infant diagnoses, including neurodevelopmental diagnoses	Alphanumeric (ICD-10 code)	List here other pertinent neonatal or infant diagnoses. See: https://icd.who.int/browse10/2016/en#/XVII

Appendix 3: Recruitment email for participating centers

Subject: Call for Contributors: Treatment in Pregnancy for HepC (TiP-HepC) Registry

[Date]

Dear [Name of Participating Center],

The Coalition for Global Hepatitis Elimination has recently launched the Treatment in Pregnancy for Hepatitis C (TiP-HepC) Registry. With support from the U.S. CDC, the TiP-HepC project aims to gather existing data regarding the occurrence and outcomes of mother-infant pairs exposures to direct-acting antiviral treatments during pregnancy. We are currently soliciting collaborators to contribute data to this registry.

If you have documented experience or data related to DAA exposure in pregnancy and are interested in contributing to this registry, please contact ngupta-consultant@taskforce.org.

Sincerely,

[Study Team Member Name]

Appendix 4: Project summary to be communicated to potential participating centers

Knowledge and Practice for Treatment in Pregnancy for Hepatitis C

TiP-HepC Project Summary – August 2021

Background: Hepatitis C virus (HCV) antenatal screening is now recommended in the US and is increasingly the standard of care globally. However, there are no current interventions to reduce perinatal HCV transmission. Virologic suppression via the use of direct-acting antiviral (DAA) medications during pregnancy may reduce risk of mother-to-child HCV transmission, but there is very limited data regarding the safety and efficacy profile of DAAs for mother-infant pairs and off-label use of DAAs is determined on a case-by-case basis.

TiP-HepC Project: The Treatment in Pregnancy for Hepatitis C (TiP-HepC) project is an initiative of the Coalition for Global Hepatitis Elimination (CGHE) at the Taskforce for Global Health and supported by the Centers for Disease Control and Prevention.

Project Goal: The goal of the TiP-HCV project is to consolidate and leverage existing data and engage a community of practice among relevant stakeholders to prospectively inform appropriate decision-making for HCV treatment in pregnancy.

Project Objectives: The objectives of the TiP-HCV project are to:

1. Compile the existing knowledge, evidence, and initiatives related to HCV treatment in pregnancy. This includes sharing, aggregation, and analysis of existing data within HCV treatment programs globally demonstrating outcomes of mother-infant pairs exposed to DAA treatment during pregnancy or breastfeeding as a result of either intentional treatment or incidental exposures.

2. Plan prospective data sharing through a multi-country safety and effectiveness registry for mother-infant pairs exposed to DAAs. No current standardized or unified registry exists to monitor mother-infant outcomes following exposure to DAAs.

3. Build a community of practice and advocacy coalition dedicated to treatment for HCV in pregnant women. CGHE will develop an online knowledge hub and convene stakeholders using the knowledge generated through this project and profiling other efforts in the field.

Request for Collaboration: CGHE is seeking partners and collaborators for the TiP-HCV project to:

- Contribute existing data on outcomes of mothers and infants exposed to DAA medications in pregnancy
- Provide ideas, support, or case enrollment for a prospective registry to document outcomes of mothers and infants exposed to DAA medications in pregnancy
- Join a “Community of Practice” to learn about current evidence and efforts in the treatment of HCV for pregnancy women

Contact: Dr. Neil Gupta, Coalition for Global Hepatitis Elimination, ngupta-consultant@taskforce.org