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

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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
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 individuals 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 (i.e., 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 (i.e., 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 occurrences 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, and the 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
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Henry Njuguna, Coalition for Global Hepatitis Elimination, Task Force for Global Health

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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**

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<th>Sept '21</th>
<th>Oct '21</th>
<th>Nov '21</th>
<th>Dec '21</th>
<th>Jan '22</th>
<th>Feb '22</th>
<th>Mar '22</th>
<th>Apr '22</th>
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<td>Protocol and data collection tool development</td>
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<td>Study database development</td>
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<td>Data sharing, merger, and cleaning</td>
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<td>Data analysis</td>
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<td>Data interpretation and results dissemination</td>
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9. References


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

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<th>Field Type</th>
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<td>Registry Identification Number</td>
<td>Alphanumeric</td>
<td>Provided by the study team to the participating center</td>
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<td>Country</td>
<td>Text field / drop down country list</td>
<td>Country where patient care occurred</td>
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<tr>
<td>Facility Type</td>
<td>Select:</td>
<td>Facility where patient was treated with DAA OR facility where patient data is stored?</td>
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<tr>
<td></td>
<td>• Prenatal facility</td>
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<td></td>
<td>• Hepatitis treatment facility</td>
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<td>• Other</td>
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<tr>
<td>Clinician Type</td>
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<td>Type of clinician providing primary responsibility of care and DAA treatment decision</td>
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<td>• Obstetrician/Gynecologist</td>
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<td>• Nurse Midwife</td>
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<td>• Other prenatal provider</td>
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<td>• Infectious Disease clinician</td>
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<td>• Hepatologist</td>
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<td>• Internist</td>
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<td>• Other clinician</td>
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<td><strong>MATERNAL INFORMATION</strong></td>
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<td>Maternal Age</td>
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<td>Age in years of the patient at the time of first recorded antenatal visit</td>
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<td>Maternal birth year</td>
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<td>Estimated date of conception (EDC)</td>
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<td>Mode of estimation for EDC</td>
<td>Select:</td>
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<td>Other estimation by clinician or patient</td>
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<td>HCV viral load (IU/mL)</td>
<td>Numeric</td>
<td>Most recent HCV PCR result prior to treatment. Enter “999” for positive result on qualitative test.</td>
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<td>HCV viral load date</td>
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<td>Most recent HCV PCR result prior to treatment</td>
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<td>Cirrhosis status</td>
<td>Select:</td>
<td>Cirrhosis status of patient prior to initiation of treatment. Cirrhosis is defined by METAVIR F4 equivalent.</td>
</tr>
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<td>• No cirrhosis</td>
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<tr>
<td></td>
<td>• Compensated cirrhosis</td>
<td></td>
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<tr>
<td></td>
<td>• Decompensated cirrhosis</td>
<td></td>
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</tbody>
</table>
| **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#/](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#/](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#/](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 |
<table>
<thead>
<tr>
<th>Drug dosage (total DAILY dose)</th>
<th>Numeric entry</th>
<th>Provide total daily dose in mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug start date</td>
<td>Date field</td>
<td></td>
</tr>
<tr>
<td>Drug end date</td>
<td>Date Field</td>
<td></td>
</tr>
<tr>
<td>Discontinued due to pregnancy?</td>
<td>Select:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Unknown</td>
<td></td>
</tr>
</tbody>
</table>

**DAA medication 3**

<table>
<thead>
<tr>
<th>Drug name</th>
<th>Select:</th>
<th>Appendix 2 drop down</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug dosage (total DAILY dose)</td>
<td>Numeric entry</td>
<td>Provide total daily dose in mg</td>
</tr>
<tr>
<td>Drug start date</td>
<td>Date field</td>
<td></td>
</tr>
<tr>
<td>Drug end date</td>
<td>Date Field</td>
<td></td>
</tr>
<tr>
<td>Discontinued due to pregnancy?</td>
<td>Select:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Unknown</td>
<td></td>
</tr>
</tbody>
</table>

**MATERNAL OUTCOMES**

<table>
<thead>
<tr>
<th>HCV treatment completed</th>
<th>Select:</th>
<th>Yes</th>
<th>No</th>
<th>Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>If HCV treatment not completed, reason for HCV treatment non-completion</td>
<td>Select:</td>
<td>Discontinuation due to pregnancy</td>
<td>Adverse Event</td>
<td>Physician discontinued for other reason</td>
</tr>
<tr>
<td>If HCV treatment discontinued due to adverse event, list adverse event here</td>
<td>Alphanumeric</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCV Treatment outcome</td>
<td>Select</td>
<td>Cure (SVR12 achieved)</td>
<td>Not cured (SVR12 not achieved)</td>
<td>SVR12 not obtained</td>
</tr>
<tr>
<td>HCV Treatment outcome date</td>
<td>Date field</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prenatal test(s) conducted</td>
<td>Select multiple:</td>
<td>Ultrasound</td>
<td>Amniocentesis</td>
<td>Chorionic Villus Sampling</td>
</tr>
<tr>
<td>Any fetal structural defect noted prenatally?</td>
<td>Select:</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prenatal test where structural defect detected?</td>
<td>Select multiple: Ultrasound Amniocentesis Chorionic Villus Sampling Cystic Fibrosis Mutation Analysis Fetal Echo First Trimester Screen MSAFP/serum markers Nuchal translucency Other</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnancy complications</td>
<td>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</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Date of pregnancy outcome</td>
<td>Date field</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type of delivery</td>
<td>Select: Vaginal delivery Cesarean section delivery Unknown</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delivery complications</td>
<td>Select: Prolonged rupture of membranes Breech or other non-cephalic presentation Post-partum hemorrhage Maternal death Other: ICD-10 code None Unknown</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**INFANT BIRTH OUTCOMES**

<table>
<thead>
<tr>
<th>Date of Birth</th>
<th>Date field</th>
<th>Or date of birth outcome if fetal loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Select: Male Female Unknown</td>
<td></td>
</tr>
<tr>
<td>Birth weight</td>
<td>Numeric</td>
<td>Birth weight in grams, if known</td>
</tr>
<tr>
<td>Birth length</td>
<td>Numeric</td>
<td>Birth length in cm, if known</td>
</tr>
<tr>
<td>Birth head circumference</td>
<td>Numeric</td>
<td>Birth head circumference in cm, if known</td>
</tr>
<tr>
<td>APGAR score</td>
<td>Numeric (0-10)</td>
<td>5-minute APGAR score, if available</td>
</tr>
<tr>
<td>Field</td>
<td>Instructions</td>
<td></td>
</tr>
<tr>
<td>----------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Neonate admitted to intensive care unit following delivery</td>
<td>Select: Yes, No, Unknown.</td>
<td></td>
</tr>
</tbody>
</table>
| Congenital 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](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:  
| Other neonatal or infant diagnoses (ICD-10 code) #2                  | Alphanumeric ICD-10  
List here other pertinent neonatal or infant diagnoses. See:  
| Other neonatal or infant diagnoses (ICD-10 code) #3                  | Alphanumeric ICD-10  
List here other pertinent neonatal or infant diagnoses. See:  
| 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. |
<table>
<thead>
<tr>
<th>Date of last assessment of infant</th>
<th>Date field</th>
<th>The most recent date for which clinical outcome of infant is documented.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other relevant infant diagnoses, including neurodevelopmental diagnoses</td>
<td>Alphanumeric (ICD-10 code)</td>
<td>List here other pertinent neonatal or infant diagnoses. See: <a href="https://icd.who.int/browse10/2016/en/#/XVII">https://icd.who.int/browse10/2016/en/#/XVII</a></td>
</tr>
<tr>
<td>Other relevant infant diagnoses, including neurodevelopmental diagnoses</td>
<td>Alphanumeric (ICD-10 code)</td>
<td>List here other pertinent neonatal or infant diagnoses. See: <a href="https://icd.who.int/browse10/2016/en/#/XVII">https://icd.who.int/browse10/2016/en/#/XVII</a></td>
</tr>
</tbody>
</table>
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