Cumulative Review of Sofosbuvir/Velpatasvir exposure in pregnant women with Hepatitis C from a Pharmacovigilance Safety Database

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Conclusions

There were no new or significant safety concerns identified from this cumulative review of SOF/VEL use in pregnancy for the treatment of chronic Hepatitis C virus (HCV) using a pharmacovigilance database comprised mainly of spontaneously reported cases. These cumulative findings contribute to the growing knowledge of safety of HCV treatment during pregnancy, which includes the treatment of maternal HCV at a time of high healthcare engagement, reducing HCV-associated pregnancy morbidity, and potentially reducing the risk of perinatal HCV transmission.

Plain Language Summary

Why was this study done?
HCV infections are increasing among women of childbearing age. Treating HCV during pregnancy has the potential to help prevent the virus from being passed to the baby. However, there is limited information about the safety of using antiviral medicines like sofosbuvir/velpatasvir (SOF/VEL) during pregnancy.

What did we do?
We reviewed individual case safety reports from a global safety database collected between 2016 and 2024. These reports included information from women who became pregnant while taking SOF/VEL for HCV. The goal was to understand pregnancy outcomes and any related complications as a result of SOF/VEL use.

What did we find?
337 pregnancies (335 cases) were reported;
123 (36.5%) pregnancies had known outcomes:
- **74 (60.2%) live births**: Most babies were born healthy and full-term. A few had birth defects or were born early, but none of these defects or early births were linked to the medicine.
- **49 (39.8%) abortions**: Some were spontaneous, others were induced and often related to other health complications or drug use.

No cases of the virus being passed from mother to baby were reported. Only 20 women (27.8%) completed treatment during pregnancy, and sustained virological response was confirmed in 8 cases (2.4%).

What does this mean?
So far, the data do not show any safety concerns with using SOF/VEL during pregnancy. However, more safety data are needed to support this. The ongoing STORC study investigating the use of SOF/VEL during pregnancy is expected to yield more answers.

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Introduction

- HCV prevalence in women of childbearing age and pregnant individuals has increased tenfold over the past 20 years, paralleling rising infection rates among young adults. With an estimated 494 maternal HCV cases per 100,000 pregnancies, over 29,000 HCV-infected births occur annually[1].
- Preventing mother-to-child transmission (MTCT) of the virus is critical, and treatment of women of childbearing age should be prioritized. Mothers infected with HCV have shown a 7.2% risk of perinatal transmission, and this risk increases to 12.1% in pregnant people with HIV[2,3].
- At least 19 countries, including the USA and Canada, recommend Universal HCV screening in pregnancy[3].
- While no direct-acting antivirals (DAAs) are currently approved for use in pregnancy, DAAs have shown a favorable safety profile in animal studies, unlike interferon-based regimens, which consistently caused embryocidal and teratogenic effects[1].
- There is growing clinical experience with sofosbuvir-based, fixed-dose DAA combinations in pregnancy—case series, systematic reviews, registries, and studies supporting the need for evidence-based treatment guidance.
- The STORC (Safety, Tolerability and Outcomes of SOF/VEL in treatment of Chronic hepatitis C virus) study is currently ongoing and evaluating the safety, tolerability, and outcomes of SOF/VEL use during pregnancy, since there are limited data on its use in pregnancy[5].
- Emerging clinical experience on fixed dose combination DAAs are summarized in Table 1.

Table 1: Emerging Clinical Experience on DAAs

Drug	Clinical Experience
Ledipasvir/Sofosbuvir	Completed Phase I clinical trial: 12-Week treatment in second trimester, 9 pregnant women, no neonatal or maternal safety concerns, no MTCT.
Sofosbuvir/Velpatasvir (SOF/VEL)	▪ Completed Phase I clinical trial: 12-week treatment, 10 pregnant women. Three serious adverse events were reported, no neonatal or maternal safety concerns reported, no MTCT[4]. ▪ Ongoing Phase 4 clinical trial (STORC): 12-week treatment in second trimester, ~80 pregnant women, single-arm, multicenter[5].
Sofosbuvir + Daclatasvir	▪ Case series of 11 women who became pregnant, 7 discontinued after 4 weeks and 1 after 8 weeks; 1 MTCT; no safety concerns. ▪ Real life data from an Egyptian cohort, included 9/100 pregnant women who completed 12-week treatment, all delivered normal babies with no major adverse events reported[6].
All DAAs	▪ TiP-HepC (Treatment in Pregnancy for Hepatitis C) registry; Ongoing observational registry (n=37 participants) collecting clinical data and case reports to evaluate pregnancy and birth outcomes following DAA exposure[7]. ▪ Multiple case series have been reported via literature with data on sofosbuvir-based therapies for pregnant women and infants with severe chronic hepatitis C[8]. ▪ Systematic review protocols: active reviews retrieving pregnancy outcomes data in HCV-positive women from databases including MEDLINE, EMBASE, CINAHL, clinicaltrials.gov, Cochrane Library, and conference abstracts[9].

Aim

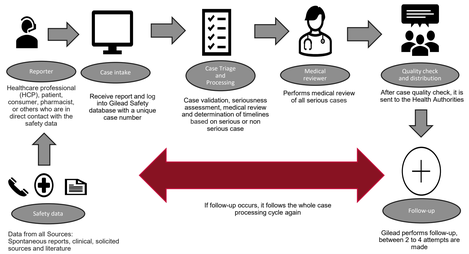
To address gaps in existing clinical evidence of SOF/VEL use during pregnancy, this study investigated pregnancy outcomes in women with chronic HCV who became pregnant while receiving SOF/VEL and were reported to a global pharmacovigilance database.

Methods

DESIGN

This is a cumulative review of safety data reported from spontaneous reports, clinical, solicited sources and literature from Feb 2016 to June 2024 in the Gilead Pharmacovigilance Database. The Gilead Pharmacovigilance Database contains safety data stored in the form of Individual Case Safety Reports (ICSRs) with a unique identification number. Figure 1 below displays how ICSRs are processed from intake of data through to reporting to the relevant Health Authorities.

Figure 1: Processing of Individual Case Safety Reports



Methods

DATA SOURCES

These safety data include pregnancy exposures and outcomes from the following sources:
- Spontaneous sources (via spontaneous reporting systems which allow healthcare professionals and patients to report suspected adverse drug reactions)
- Clinical studies (Gilead-sponsored clinical and post-marketing studies on the safety and effectiveness of the product)
- Solicited [nonclinical] from organized data collection systems (like patient registries, post-marketing surveillance programs, etc.)
- Clinical literature (published articles and other clinical research findings)
- Spontaneous literature (published case reports)

DATA ANALYSIS

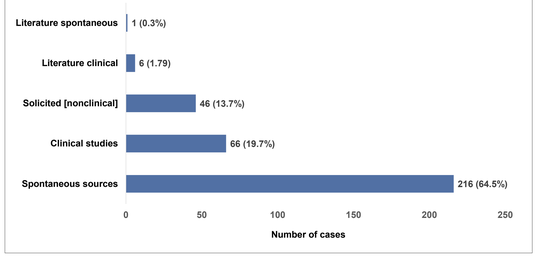
All cases reported with SOF/VEL use at any time (trimester) during pregnancy from Feb 2016 to June 2024 were identified and characterized based on the following:
- Data sources
- Pregnancy outcomes including congenital anomalies
- Timing of treatment exposure
- Whether SOF/VEL treatment was completed or treatment was discontinued
- If sustained virologic response (SVR) was achieved
- Geographical distribution
- Maternal age (at the time of the report)

Results

DATA SOURCES

From the SOF/VEL international birth date (28 June 2016, US) to 27 June 2024, there were 335 pregnancy cases (337 pregnancy outcomes, including 2 twin pregnancies) reported to the Gilead Pharmacovigilance Database. Of the total reported cases of SOF/VEL use in pregnancy, 64.5% were from spontaneous sources (Figure 2).

Figure 2: Sources of Pregnancy data

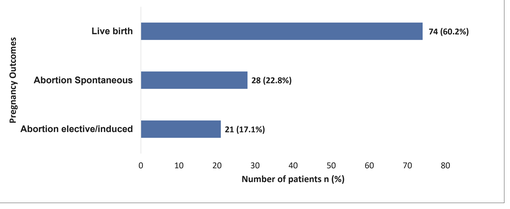


PREGNANCY OUTCOMES

The 335 pregnancy reports described pregnancy outcomes (2 twin pregnancies) with the following outcomes:
- 214 **(63.5%)** – with either unknown/not reported outcome (n=195) or pending (n=19)
- 123 **(36.5%)** – with documented outcomes

Pregnancy outcomes among the 123 reported cases with known outcomes are presented in Figure 3.
Live births were reported in 74 (60.2%) cases. Of these, 72 (58.5%) were full term births (gestational age ≥ 37 weeks) and 2 (1.6%) were preterm births. Of the full-term births, 16 (21%), were delivered via caesarean section. Spontaneous abortions (nonviable intrauterine pregnancy occurs within 12 weeks and 6 days of gestation) were reported in 28 (22.8%) cases. The remaining 21 cases (17.1%) reported elective or induced abortions (intentional interruption of pregnancy through medical or surgical procedures before the 20th week of gestation)

Figure 3: Known Pregnancy outcomes after SOF/VEL exposure



Results

PREGNANCIES WITH DOCUMENTED OUTCOMES:

- **Live Births**

Of the 74 live births, 63 (85.1%) were reported as full-term (greater than 37-weeks gestation) with 16 (21.6%) delivered by caesarean section, 9 (12.1%) were congenital anomalies and the remaining 2 (2.7%) were reported as premature births (at 30 and 33-weeks gestation).

- **Congenital anomalies**:**

Ten congenital anomalies (8.1%, 10/123) were reported, of which 9 anomalies were reported among the 74 live births and 1 anomaly under spontaneous abortion. The anomalies reported in 9 live births are listed in Table 2 below. None of the congenital anomaly cases reported to the global pharmacovigilance database were assessed as causally related to SOF/VEL use after medical review. Also, two cases had first trimester exposure, when fetal development is most vulnerable—highlighting timing as key in assessing anomaly risk.

Table 2: Congenital anomalies among live births

Country	Data Source	Trimester of SOF/VEL initiation	Congenital anomaly reported
Brazil	Spontaneous	Unknown	Kidney malformation
Canada	Study IN-CA-337-2100	First	Fallot's tetralogy, Congenital ureteric anomaly, Congenital hydronephrosis
US	Spontaneous	First	Fetal growth restriction, Limb asymmetry
	Study IN-US-342-5634	Second	Talipes
	Study IN-US-342-5634	Second	Cryptorchism
	STORC study	Third	Congenital megacolon
	STORC study	Second	Retrognathia
	STORC study	Third	Pyloric stenosis
	STORC study	Third	Periauricular skin tag

- **Spontaneous abortions:**

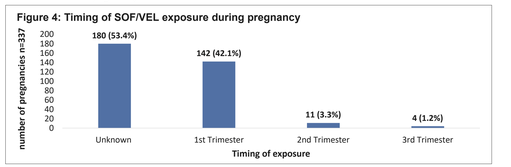
A total of 28 (28/123, 22.7%) spontaneous abortion cases were reported. In 9 cases, possible explanations were provided including pre-existing history of abortions, abortion due to ectopic pregnancy, polycystic ovaries, history of drug abuse (alcohol, substance and tobacco use), concomitant medications (gabapentin, clonidine, methadone, fentanyl, etc.) and underlying conditions (hepatic failure, depression). None of the spontaneous cases reported to the Global Pharmacovigilance Database were assessed as causally related to SOF/VEL use.

**Congenital anomalies defined by World Health Organization (WHO) as structural or functional anomalies that occur during intrauterine life affecting 3–6% of births globally.

TIMING OF TREATMENT EXPOSURE

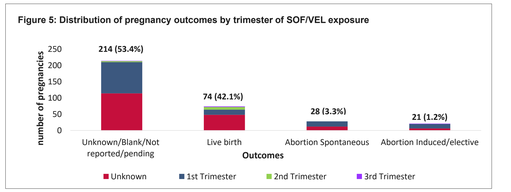
Timing of treatment exposure was unknown in 180 cases which was 53% of reported pregnancies. Of the remaining cases, 142 (42%) reported initiation in the first trimester, 11 (3.3%) in the second, and 4 (1.2%) in the third trimester (Figure 4).

Figure 4: Timing of SOF/VEL exposure during pregnancy



Of the 74 live births, the timing of initiation was not documented for 48 cases. Among the remaining 26, initiation occurred during the first trimester in 16 cases, the second trimester in 8, and the third trimester in 2.

Figure 5: Distribution of pregnancy outcomes by trimester of SOF/VEL exposure



TREATMENT DISCONTINUATION OR COMPLETION

Information on treatment discontinuation or completion was available for 72 (21.4%) cases. Among these, treatment was discontinued in 52 (72.2%) cases, of which 32 occurred in the first trimester. Treatment was completed in 20 (27.8%) cases, of which 7 occurred in the first trimester.

SVR achieved
SVR data were often incomplete and successful treatment completion was rarely documented. Overall, only **8 (2.4%)** of 337 pregnancies reported a confirmed SVR.

Vertical transmission
Vertical transmission refers to the transfer of a virus, bacteria from an infected parent to their embryo, fetus, or baby. This transmission can occur either before birth (antenatal) through the placenta, during birth (perinatal) via contact with maternal fluids, or after birth (postnatal) through breastfeeding.
None of the reported pregnancies reported any vertical transmission.

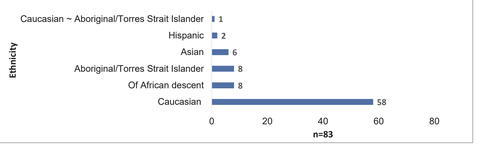
MATERNAL AGE

Maternal age was reported in **153** of the 335 cases. The median age was **31 years** (range: 17-52).

ETHINICITY

Ethnicity data were available for **83** of 335 cases. Among these, 58 (70%) identified as **Caucasian**.

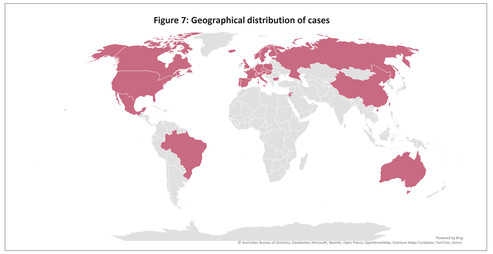
Figure 6: Ethnic distribution of pregnant individuals in the study



GEOGRAPHICAL DISTRIBUTION

Cases were reported from 30 countries, with the highest numbers from the United States (188, 62%), Canada (30, 8.9%), Australia (18, 5.3%) and UK (17, 5.1%). Others included France (13), China (11), Italy (10), and Spain (7). Several countries reported fewer than five cases each, including Poland, Taiwan, Belgium, Israel, Sweden, Switzerland, Brazil, Finland, Germany, and the Russian Federation. The remaining countries reported a single case from each: Austria, Bulgaria, Czech Republic, Estonia, Hungary, Iceland, Jordan, Mexico, Norway, Portugal, Singapore, and Slovakia. Figure 7 shows the geographical distribution of the reported pregnancy cases.

Figure 7: Geographical distribution of cases



Discussion

- Although there are no currently approved treatments for HCV in pregnancy, 337 pregnancies with SOF/VEL exposure during pregnancy were reported to a global pharmacovigilance database from 2016 to 2024.
- Most reported cases had unknown/not reported or pending outcome information. Of the 123 cases with reported pregnancy outcomes, 74 were live births (including 9 congenital anomalies), 28 were spontaneous abortions (including 1 congenital anomaly) and 21 were induced abortions. The frequency of spontaneous abortion and induced abortion was similar to the background rates in the US[10].
- Overall, of the 123 cases with documented pregnancy outcomes, 10 (8.1%) reported congenital anomalies. Two first trimester exposures highlight timing in anomaly risk.
- Of the 74 live births, 85.1% had normal outcomes.
- Spontaneous reporting systems play a critical role in signal detection; however, they are inherently prone to bias, often overrepresenting adverse outcomes. This is especially evident in pregnancy, where normal outcomes are frequently underreported, and establishing causality is challenging due to confounding clinical conditions and incompletely reported data[11]. Overall, in the data presented, spontaneous abortions and congenital anomaly cases were either confounded by alternative etiology or had insufficient information to determine causality.
- There is a need for clear clinical guidance on managing pregnancy during antiviral treatment and assessing safety profiles for DAAs in pregnancy. Ongoing studies like STORC are essential to establish this guidance and bridge any gaps to ensure maternal and fetal safety.

Strengths and Limitations

STRENGTHS

- Large cumulative dataset from 2016 to 2024: 335 cases (337 pregnancies), providing substantial data for analysis
- Real-world evidence: Captures outcomes outside controlled clinical settings.
- Causality: Physician review conducted for select clinical and serious spontaneous cases. No reported adverse events showed a causal link to SOF/VEL.
- Global representation: Cases from USA, Europe, Canada, Asia, and Australia.

LIMITATIONS

- Under-reporting: Adverse events may be under-represented due to limitations in spontaneous reporting systems, leading to incomplete safety data.
- Reporting bias: Spontaneous reporting systems may disproportionately capture more severe cases, potentially skewing the overall safety profile[11].
- High rate of unknown or pending outcomes: 63.5% of cases lacked outcome data. Limited detail on congenital anomalies; some cases lacked sufficient clinical information, including timing of exposure.