

Review article: direct-acting antivirals for the treatment of HCV during pregnancy and lactation - implications for maternal dosing, foetal exposure, and safety for mother and child

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Summary

Background: With the global efforts to eradicate hepatitis C virus (HCV), treatment during pregnancy is becoming a priority for research as this, and maternal cure should reduce vertical transmission. However, as information on the efficacy and safety of direct-acting antivirals (DAAs) in pregnancy is generally lacking, treatment of HCV infection during pregnancy is not currently recommended.

Aim: To provide an overview of current knowledge regarding maternal exposure, placental handling and safety of DAAs during pregnancy and lactation

Methods: A literature search was performed focusing on the effect of pregnancy on maternal exposure to DAAs, the placental handling of DAAs, the safety of DAAs for mother and child during pregnancy and the safety of DAAs during lactation.

Results: Exposure to all DAAs studied is likely to be altered during pregnancy, mostly related to pregnancy-induced effects on drug absorption and metabolism. Although animal studies show that most DAAs are reported to cross the placenta and transfer into breast milk, most DAA combinations show a favourable safety profile. Because of the rapid viral decline after treatment initiation, and to avoid the critical period of organogenesis, treatment may be started at the end of the second trimester or early third trimester.

Conclusions: Treatment of HCV infection during pregnancy is realistic, as DAAs are highly effective and treatment duration is relatively short. There is an urgent need to study DAAs during pregnancy and lactation to contribute to the goal of HCV elimination.

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The Handling Editor for this article was Professor Grace Wong, and this uncommissioned review was accepted for publication after full peer-review.

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1 | INTRODUCTION

In 2015, there were an estimated 71 million persons chronically infected with hepatitis C virus (HCV), resulting in 1.34 million deaths that year.¹ With the global efforts of the World Health Organization to eradicate HCV by 2030, it is important to identify individuals at risk and provide treatment as soon as possible after diagnosis.² While the majority of infections among adults in many settings are linked to injection drug use, the most important source of paediatric HCV infection is vertical transmission of the virus, responsible for approximately 60% of paediatric HCV cases globally.^{3,4} Among pregnant women, estimates of HCV prevalence have ranged from 0.1% to 8% from different countries and settings.⁵⁻⁸

1.1 | Vertical transmission of HCV

A large meta-analysis performed by Benova et al reported a 5.8% risk of vertical transmission of HCV, resulting in 1700 HCV-infected newborns in the USA yearly.^{9,10} In addition to high maternal HCV viral load, the review states that maternal HIV co-infection increased the risk of vertical transmission of HCV to around 10%.^{9,11,12} However, the majority of the co-infected pregnant women included were not taking antiretroviral therapy, and a recent study suggested that those on antiretroviral therapy have a similar risk of transmitting HCV to those with HCV mono-infection.¹³ The prevalence of HCV and HIV co-infection among pregnant women varies across settings. One study in Rwanda reported that 3.9% of pregnant women with HCV were co-infected with HIV.¹⁴ In a Western/Central European cohort of pregnant women living with HIV, 12% were co-infected with HCV.^{14,15} In addition to high maternal HCV viral load and having HIV, membrane rupture for more than 6 hours before delivery and internal foetal monitoring (uterine or foetal scalp) have been reported to contribute to an increased risk of vertical HCV transmission.¹⁶ Currently, most studies suggest that the risk of transmission may be reduced by elective caesarean section, particularly in the case of HCV/HIV co-infection.¹⁷⁻¹⁹ Based on timing of positive HCV RNA test results in the newborn, timing of transmission is thought to occur during intrauterine, peripartum and postpartum periods.²⁰ Transmission may be most frequent during the peripartum period (estimated 40%-50%) when there is blood-blood contact during delivery. In this case, the child will be born HCV-RNA negative, but detectable RNA levels are expected after the first 3 days of life. It is estimated that intrauterine transmission accounts for approximately 30% of the cases, based on HCV-RNA positivity at or shortly after delivery.²¹ The exact mechanisms by which intrauterine transmission occurs are not well understood, but may include trophoblast-mediated endocytosis of HCV and/or transcytosis of viral particles.²² Postpartum transmission via breastfeeding is rare, as the proportion of children acquiring HCV is similar among those who were breastfed compared to those who were not.¹⁷

1.2 | Testing and consequences of HCV in the newborn

Although vertical transmission seems to be the most important source of paediatric HCV infection, a retrospective cohort study showed that many children of women with chronic HCV are not screened and therefore many paediatric HCV cases will be missed.²³ A critical reason for the low proportion of exposed infants who are screened is related to the delay in diagnosis, as HCV antibody testing can only be performed at or after 18 months of age, and the chance of loss to follow-up in the intervening period is high.²⁴ Testing for HCV-RNA positivity in the newborn is generally not routinely performed, but should be recommended in infants born to HCV-RNA positive mothers.²⁵ The majority (80%) of children acquiring HCV through vertical transmission do not clear the infection spontaneously, resulting in chronic paediatric HCV infection.²⁶ Although liver injury from chronic HCV infection generally progresses slowly early in life, serious liver damage can occur during childhood and beyond.²⁷⁻²⁹ One centre reported five children (out of 91 included patients, mean age: 9 years) with an accelerated course of HCV and early development of decompensated liver disease requiring liver transplantation, two of whom subsequently died.³⁰ In addition to concerns about the physical health of the child with HCV, there may be high levels of distress in the family.³¹ Treatment regimens based on direct-acting antivirals (DAAs) for children with chronic HCV ≥ 12 years of age or ≥ 35 kilograms were approved by the FDA in April 2017.³² Phase I and II trials of several DAA combinations for children aged 3-12 years are currently ongoing [ClinicalTrials.gov: NCT03067129, NCT03080415, NCT03487848, NCT03022981]. Unfortunately, there will be no treatment available prior to the age of 3 in the near future as this is not requested by the European Medicines Agency (EMA). Therefore, treatment of children with vertically acquired HCV may be complicated as loss to follow-up in healthcare later in life is likely to be high, as is the case in some settings for HIV.^{33,34}

1.3 | Effect of HCV on pregnancy outcome

In addition to the risk of vertical HCV transmission, maternal HCV infection may increase the risk of adverse pregnancy outcomes. Recently, a protocol has been published for a study which will undertake an extensive systematic review of pregnancy outcomes in women with HCV; results are expected soon.³⁵ Only a small proportion of available studies have sufficient power to adjust for potential confounding variables such as tobacco, alcohol and drug use. These studies report an association between maternal HCV infection and the risk of gestational diabetes and intrahepatic cholestasis of pregnancy.^{36,37} In addition, an increased risk of preterm birth was reported and children born to women living with HCV were more likely to have a lower birth weight and to be small for gestational age.³⁸⁻⁴¹

1.4 | Considerations for HCV treatment during pregnancy

Diagnosis and treatment of HCV in pregnant women is becoming a priority area of research as this has potential, not only to cure the mother, but also to prevent vertical transmission.^{42,43} Until recently, ribavirin was a cornerstone of HCV therapy. As this drug is known to be teratogenic and embryotoxic in all animal species studied, its use—and consequently all classical forms of HCV therapy—during pregnancy has been contra-indicated.⁴⁴ However, new, potentially much safer combinations of DAAs drugs are now available that are ribavirin free. The relative short duration of treatment (8–12 weeks) and the rapid viral load decline following treatment initiation makes treatment and cure of women with chronic HCV late in pregnancy realistic.^{24,45} Testing and treatment during pregnancy seems a unique opportunity, as loss to follow-up of mother and child postpartum is high in many low and middle income country settings, and pregnant women are engaged in healthcare during this period, being highly motivated to take actions to ensure their own health and the health of their unborn child.^{23,46,47} In 2018, the American Association for the Study of Liver Disease (AASLD)/Infectious Diseases Society of America (IDSA) guidelines recommended universal HCV screening in pregnancy which was already suggested by other countries such as France and Pakistan a few years earlier.^{24,48,49} It is, however, not being implemented widely thus far as other guidelines, such as from the Centers for Disease Control and Prevention and the Society for Maternal-Foetal Medicine, have not yet adopted the recommendation. It is estimated that such a screening strategy, followed by treatment after pregnancy, would be cost-effective for maternal treatment and would identify around 300 newborns with vertical HCV in the USA annually.⁵⁰ However, pregnant women may experience psychological stress as treatment start has to be postponed to the postpartum period. A recent survey showed that among women with (a history of) HCV, 60% were willing to undergo HCV therapy during pregnancy given the fact that it would reduce the risk of vertical transmission, and despite the lack of safety data.⁵¹

Despite recent interest and major advancements in available treatment options, data on DAAs in this population are limited to three abstracts on either intentional or accidental exposure during pregnancy

in a small number of women.^{52–54} There are a number of important aspects to consider prior to implementation of DAA therapy during pregnancy, which we review here. These are: (a) The effect of pregnancy on maternal exposure to DAAs; (b) The placental handling of DAAs; (c) Safety of DAAs for mother and child during pregnancy; (d) Safety of DAAs during the lactation period. Implementation and costs of antenatal HCV screening are also important but will not be considered here. We identify research gaps on the potential use of DAAs in pregnant and breastfeeding women living with HCV.

2 | EFFECT OF PREGNANCY ON MATERNAL EXPOSURE TO DIRECT-ACTING ANTIVIRALS

Pregnancy-associated anatomical and physiological changes may influence drug pharmacokinetics (PK), in some cases leading to the need for dose adjustments.⁵⁵ To date, only one abstract is available on sofosbuvir/daclatasvir in pregnancy and two abstracts on sofosbuvir/ledipasvir.^{52–54} Although all women included in these three studies had a rapid HCV RNA response to therapy, no results from PK analysis are reported (yet). Because of absence of available clinical PK data to date, the effect of pregnancy-induced alterations on drug disposition may be predicted based on their PK properties. For each DAA, we discuss the impact of pregnancy on maternal DAA exposure by considering the potential effect on drug absorption, distribution, metabolism and excretion, as well as potential drug-drug interactions (DDIs) with combination antiretroviral therapy (cART) for treatment of HIV. The literature search strategy can be found in Appendix S1. The expected pregnancy-induced changes in maternal DAA exposure are described below and summarised in Table 1.

2.1 | Absorption

Pregnancy-induced alterations of gastrointestinal function, such as delayed-gastric emptying, prolonged gastrointestinal transit time and reduced gastric acidity, can either increase or decrease drug absorption.^{55,56} Ledipasvir and velpatasvir show pH-dependent absorption, with a decreased solubility at a higher pH. Reduced gastric

TABLE 1 Overview safety and pharmacokinetic data of DAAs in pregnancy

DAA combination	Genotype	Hypothetical change in maternal exposure (mechanism)	Safety concerns based on animal data	Priority to be studied in clinical trials in pregnancy
SOF/DAC	Genotype 1-4	↓ DAC exposure (CYP3A4 induction)	Yes	High
SOF/LDV	Genotype 1, 4-6	↓ LDV exposure (gastric pH increase)	No	Moderate
SOF/VEL SOF/VEL/VOX	Pan-genotypic	↓ VEL exposure (gastric pH increase) ↓ VEL/VOX exposure (CYP3A4 induction)	Uncertain	High
GZR/ELB	Genotype 1,4	↓ GZR/ ELB exposure (CYP3A4 induction)	No	Moderate
GLE/PIB	Pan-genotypic	↓ GLE exposure (CYP3A4 induction)	Uncertain	High

Abbreviations: DAC, daclatasvir; ELB, elbasvir; GLE, glecaprevir; GZR, grazoprevir; LDV, ledipasvir; PIB, pibrentasvir; SOF, sofosbuvir; VEL, velpatasvir; VOX, voxilaprevir.

acidity during pregnancy may therefore result in lower exposure.^{57,58} During pregnancy, women often suffer from nausea and heartburn for which antacids and/or proton pump inhibitors (PPIs) may be prescribed.⁵⁹ It has been shown that velpatasvir and ledipasvir exposure in healthy volunteers treated with PPIs such as omeprazole, is reduced up to 40%.^{60,61} Therefore, co-administration of PPIs with velpatasvir or ledipasvir during pregnancy should be avoided if possible.^{57,58}

2.2 | Distribution

Apart from physiological changes (eg body volume and tissue perfusion), physicochemical factors (eg drug lipophilicity and molecular weight) determine drug distribution. For example, the increase in body fat during pregnancy is likely to increase the volume of distribution of highly lipophilic drugs, such as DAAs, which in turn may result in lower peak plasma levels, prolonged half-life and lower amplitude of plasma concentrations at steady state. However, little information is available to estimate the contribution of the increased fat mass to the decrease in plasma levels often observed during pregnancy.^{55,62} All DAAs, except sofosbuvir, show a high degree of plasma protein binding.⁶³ Particularly for these highly protein bound drugs, an increase in the unbound fraction may be expected due to decreased plasma levels of the main drug-binding plasma proteins albumin and α 1-acid glycoprotein during pregnancy. For most drugs, the total concentration decreases during pregnancy while the unbound concentrations are unaffected. Therefore, it is crucial to measure the unbound plasma concentration in pregnancy, next to total plasma concentrations, to reliably identify the effect of pregnancy on the pharmacologically active unbound concentration. This should be taken into account in future studies on DAA pharmacokinetics in pregnancy.⁶⁴

2.3 | Metabolism

Pregnancy-induced changes in the activity of drug-metabolising enzymes including cytochrome P450 (CYP) and the uridine diphosphate glucuronosyltransferase (UGT) family have been observed. While the mechanism of the observed changes has not been identified, accumulated data suggest that the changes are regulated by rising concentrations of hormones.⁵⁵ Increased CYP3A4 capacity in liver and/or intestine is expected to have the most profound impact on DAA pharmacokinetics compared to other metabolising enzymes.⁶⁵ Tracy et al reported that CYP3A activity increased by 35%–38% during pregnancy⁶⁶ and, except for sofosbuvir/ledipasvir, exposure to all DAA combinations may be affected to some extent by induction of CYP3A-mediated metabolism. The use of potent CYP3A inducers in combination with DAAs that are metabolised by CYP3A4 is currently contra-indicated, as this may reduce DAA efficacy, possibly resulting in virological failure.⁶⁵ The moderate pregnancy-induced increase in CYP3A4 activity may have less profound effects compared to the effects of concomitant use of strong CYP3A inducers on DAA exposure, but dose adjustments of DAAs during pregnancy

may have to be considered. For some DAA combinations, only exposure to a single component may be affected by pregnancy-induced changes. For example, exposure to velpatasvir and voxilaprevir, but not to sofosbuvir, is influenced by CYP3A activity. However, a dose adjustment of individual components is complicated since all DAA combination treatments are available as fixed-dose combinations, except for sofosbuvir and daclatasvir, which are available as separate formulations. Data from phase IV trials suggest that sustained virological response is not related to plasma concentrations of glecaprevir in nonpregnant patients on high-dose proton pump inhibitors (PPIs), implying that the levels were well above the therapeutic threshold. A slight decrease in glecaprevir exposure, caused by moderate CYP3A4 induction due to pregnancy, is therefore expected to be of less clinical relevance.^{67,68} Regarding daclatasvir, the recommended daclatasvir dose of 60 mg QD is increased to 90 mg QD when co-administered with moderate inducers of CYP3A4, as reductions in exposure of 25% have been observed frequently for CYP3A4 substrates.⁶² A moderate increase in CYP3A activity due to pregnancy may also require an increase in daclatasvir dose. However, the clinical relevance of increased CYP3A4 metabolism for daclatasvir in pregnancy is unknown as its oral clearance is significantly lower in women than in men, resulting in higher exposure in women.⁶⁹

2.4 | Excretion

Elimination of DAAs (except for sofosbuvir) occurs mainly via biliary excretion as parent drug. Pregnancy may alter the expression of drug transporters in metabolising and eliminating organs, but there is little quantitative information on the influence of pregnancy on transporter activity in the basolateral and canalicular membrane of hepatocytes, and the resulting effect on DAA excretion. Due to this lack of knowledge, no pregnancy physiologically-based pharmacokinetic (PBPK) models have been published which simulate the role of biliary drug excretion.⁷⁰ Sofosbuvir is mainly renally eliminated as its pharmacologically inactive metabolite GS-331007 (78%) and to a lesser extent as unchanged sofosbuvir (3.5%). Because pregnancy leads to an increase in renal blood flow and glomerular filtration rate, renal clearance of sofosbuvir may be increased during pregnancy. It is, however, unclear whether this could influence plasma levels to the point of requiring dose adjustment.^{55,71}

2.5 | Drug-drug interactions (DDIs) in case of maternal viral co-infection

For the treatment of maternal hepatitis B co-infection, tenofovir disoproxil fumarate (TDF) is preferred.⁷² As TDF may also be part of combination antiretroviral therapy (cART) for treatment of HIV, literature on DDIs between cART and DAAs can be consulted.⁶⁵ DDIs between HCV and cART are an important consideration in the treatment of (pregnant) HCV/HIV co-infected women,^{14,15} and are well described in the literature.^{65,73} However pregnancy-induced alterations could also influence either HCV and/or HIV drug

exposure as a third factor, making the translation of DDIs from the nonpregnant patient population to pregnant women complicated. Here we do not elaborate on drug combinations that are already contra-indicated in the nonpregnant population, but focus on specific DDIs that may be of concern due to the possible effects of pregnancy on drug exposure. A first example is efavirenz, commonly used as part of cART, but known to decrease daclatasvir exposure via induction of CYP3A4, with an area under the plasma concentration-time curve (AUC) geometric mean ratio (GMR) with 90% CI of 0.68 (0.60, 0.78).⁷⁴ The recommended daclatasvir dose is therefore increased (90 mg instead of 60 mg once daily) in patients using efavirenz. In pregnant women, an increase of daclatasvir dose may also be warranted as pregnancy also affects CYP3A4 activity, resulting in lower daclatasvir plasma levels compared to nonpregnant patients. In addition, use of efavirenz with ledipasvir results in a reduction of ledipasvir exposure (AUC GMR [90% CI] of 0.66 [0.59, 0.75]); the pregnancy-related increase in gastric pH is likely to also decrease ledipasvir exposure.⁵⁷ Lastly, concomitant use of darunavir/ritonavir with sofosbuvir/velpatasvir/voxilaprevir results in higher voxilaprevir due to inhibition of organic-anion-transporting polypeptide (OATP)-1B1, P-glycoprotein (P-gp) and CYP3A, with an AUC GMR (90% CI) of 2.43 (2.15, 2.75), but is considered to be not clinically relevant in the nonpregnant population.⁷⁵ During pregnancy twice daily darunavir, instead of once daily, is recommended and therefore concomitant use of darunavir/ritonavir and sofosbuvir/velpatasvir/voxilaprevir should be contra-indicated.

According to the guidelines, dolutegravir has low potential for DDIs and may therefore seem of particular interest for use in women living with HCV and HIV.⁶⁵ However, a recent report highlighted an increased incidence of neural tube defects associated with dolutegravir use around the time of conception. Further safety data are awaited to confirm or refute this finding and in the meantime dolutegravir use around the time of conception should be avoided,⁷⁶ although if used after the first trimester, there is no increased risk of neural tube defects. As the choice for HCV as well as cART is mainly dependent on local drug availability, which is limited in low-income countries, it might not be possible to prescribe the combination of preference. Based on available data regarding possible DDIs between DAAs and cART, and taking potential effects of pregnancy on their pharmacokinetics into consideration, the choice of combination treatment should be made by local physicians.

3 | PLACENTAL HANDLING OF DIRECT-ACTING ANTIVIRALS

Drug transport across the placental barrier is a major determinant of foetal exposure and toxicity. However, for some conditions foetal exposure to maternally administered drugs could potentially provide pre-exposure prophylaxis and thereby reduce the chance of vertical transmission, as has been hypothesised for HIV.⁷⁷

3.1 | Placental handling in human pregnancy

For ethical reasons, pregnant women have historically often been excluded from clinical trials in the drug development process, resulting in a gap of knowledge regarding both maternal and foetal drug exposure throughout gestation. However, recent reports on the importance of conducting pharmacological research in pregnancy and possible research strategies highlight that times are changing.^{78,79} To our knowledge, information on DAA exposure during pregnancy is currently limited to three conference abstracts. However, none of these studies collected data on foetal exposure (eg as umbilical cord blood concentrations) as treatment was either discontinued or completed during pregnancy and it is therefore not known whether or how well these DAAs cross the human placental barrier *in vivo*.

3.2 | Placental handling in pre-clinical research

Studies on placental handling of DAAs are solely based on developmental toxicology studies in animal models. As shown in Table 2, placental transfer of sofosbuvir, daclatasvir, glecaprevir, pibrentasvir, grazoprevir and elbasvir has been observed in rats. Placental transfer of grazoprevir and elbasvir has, in addition to rats, also been observed in rabbits, but to a minimal extent. However, because of interspecies differences in placental anatomy, placental transfer data from animal studies is of poor translational value. Compared to the placenta of rabbit, rat and mouse, the structure of the human placenta differs in gross shape, histology of the maternofoetal interface and type of maternofoetal interdigitation, which may all affect placental drug transfer.⁸⁰

3.3 | Prediction of placental drug handling *ex vivo*

To predict transfer of drugs across the human placenta *in vivo*, data from animal studies may be combined with information on drug-specific physicochemical characteristics. Comparing DAAs based on their specific physicochemical properties provides information on potential changes in their pharmacokinetics during pregnancy (Chapter 2) and a similar approach can yield estimates of placental transfer, and hence provides a rough estimate of foetal exposure. A review by Giaginis et al summarised the factors affecting transport of drugs across the placental barrier.⁸¹ In general, maternofoetal exchange increases with gestational age because of physiological changes, eg reduced membrane thickness and increased uterine blood flow, inherent to the increased foetal demand of oxygen and nutrients.⁸⁰ Passive diffusion is the major route of placental transport and is responsible for rapid transfer of lipophilic drugs with a molecular weight of <500 Da. Larger molecules may also be subjected to passive diffusion, which is a relatively slow process⁸¹; all DAAs are highly lipophilic, indicated by a log P >2.5 (except for sofosbuvir, log P = 1.62), favouring effective passive diffusion. On the other hand, their high molecular weight (all >500 Da) may hamper or at least slow the process. In addition, the degree of ionisation and protein binding also influence the rate and extent of placental transfer.

TABLE 2 Safety data from reproductive teratogenicity studies of DAAs in pregnancy

DAA therapy		Prenatal and postnatal development		Placental transfer		Lactation
DAA combination	Drug	Safety concerns?	Tested animal species (Dose and duration)	Transfer across placenta	Tested animal species (% of maternal plasma levels)	Transfer into milk ^a (% of maternal plasma levels)
SOF/DAC	SOF ^b	No	Rats: 10x RHD, GD6-18, GD6-LD20 Rabbits: 28x RHD, GD6-19	Yes	Rats	Yes (80%)
	DAC	Yes ^c	Rats: 4x RHD, GD7-19 Rabbits: 16x RHD, GD6-15	Yes	Rats	Yes (170%-200%)
SOF/LDV	SOF ^b	No	Rats: 10x RHD, GD6-18, GD6-LD20 Rabbits: 28x RHD, GD6-19	Yes	Rats	Yes (80%)
	LDV	Possible ^c	Rats: 4x RHD, GD6-18 Rabbits: 2x RHD, GD7-20	Unknown	Not tested	Yes
SOF/VEL SOF/VEL/VOX	SOF ^b	No	Rats: 10x RHD, GD6-18, GD6-LD20 Rabbits: 28x RHD, GD6-19	Yes	Rats	Yes (80%)
	VEL	Possible ^d	Rats: 6x RHD, GD6-17, GD6-LD20 Rabbits: 0.5-0.7x RHD, GD7-20 Mice: 31x RHD, GD6-15	Not evident	Rats	Yes (173%)
	VOX	No	Rats: 141x RDH, GD6-LD20 Rabbits: 4x RHD, GD7-19	Unknown	Not tested	Yes
GZR/ELB	GZR	No	Rats: 117x RHD, GD6-20, GD6-LD20 Rabbits: 41x RHD, GD7-20	Yes	Rats (89%) Rabbits (7%)	Yes (400%)
	ELB	No	Rats: 10x RHD, GD6-20, GD6-LD20 Rabbits: 18x RHD, GD7-20	Yes	Rabbits (0.8%) Rats (2.2%)	Yes (87%)
GLE/PIB	GLE	Possible ^e	Rats: 53x RHD, GD6-18, GD6-LD20 Rabbits: 0.07x RHD, GD7-19	Yes	Rats	Yes (<8%)
	PIB	No	Rabbits: 1.5x RHD GD7-19 Mice: 51x RHD GD6-15, GD6-LD20	Yes	Mice	Yes (150%)

Abbreviations: DAC, daclatasvir; ELB, elbasvir; GD, gestation day; GLE, glecaprevir; GZR, grazoprevir; LD, lactation day; LDV, ledipasvir; PIB, pibrentasvir; RHD, recommended human dose; SOF, sofosbuvir; VEL, velpatasvir; VOX, voxilaprevir.

^aTransfer into milk was studied in rats.

^bExposure to predominant circulating metabolite of sofosbuvir (GS-331007).

^cAt a high dose (4.6-fold RHD), an increased incidence of skeletal variations (vertebrae, sterneae, ribs) in rats was observed. These effects are likely related to a decrease in maternal body weight gain and decreased food intake.

^dA possible teratogenic effect was indicated in rabbits where an increase in total visceral malformations was seen in exposed animals at AUC exposures up to 0.7-fold RHD for SOF/VEL and 0.5-fold RHD for SOF/VEL/VOX.

^eMaternal toxicity with some embryofoetal toxicity precluded the ability to evaluate glecaprevir in the rabbit at human clinical exposures.

Protein binding will contribute to trapping of drug in the foetal or maternal circulation, and as maternal and foetal plasma protein concentrations differ and change with advancing gestational age, the maternal-to-foetal ratio of total drug plasma concentration may vary accordingly.⁸² Next to passive diffusion, drug transport across the placental barrier may also be carrier-mediated, either as facilitated diffusion or via active transporters. All DAAs included in this review are ATP-binding cassette (ABC) transporter substrates of P-gp (ABCB1) and/or Breast Cancer Resistance Protein (BCRP/ABCG2). As these efflux transporters are expressed at the apical side of the syncytiotrophoblast layer, they possibly play a role in reducing foetal exposure. Xenobiotics interacting with these transporters may also influence placental transfer of DAAs.⁸³ Since placental transporter expression changes during pregnancy, placental transfer may be also dependent on timing of treatment during pregnancy. A reduction in P-gp mRNA and protein levels from first trimester towards term has

been reported, likely related to the general decrease in foetal protection after the critical period of organogenesis. Therefore, there is a greater potential of P-gp substrates (eg most DAAs), to reach the unborn child with advancing gestational age. Literature on BCRP expression throughout gestation is inconsistent.⁸⁴

As outlined above, different factors either facilitate or impede drug transport across the placental barrier. Hence, it is difficult to estimate the extent of placental transport of a specific drug at a specific time point during pregnancy. In addition to in vitro techniques using immortalised cell lines or tissue explants, computer-assisted modelling attempts are useful to explore the contribution of the physicochemical properties to placental transport.^{85,86} The dual side placental perfusion model has proven to be a valid experimental method to study the transport of xenobiotics ex vivo and is currently used extensively to investigate placental passage.⁸⁷ As stated before, it is hypothesised that the extent of placental drug transfer

increases towards term.⁸⁰ Therefore, data from ex vivo placental perfusion experiments using term placentas potentially overestimate foetal exposure during earlier phases of pregnancy.⁸⁷ For a variety of drugs studied, transfer across term placentas ex vivo shows good correlations with in vivo maternal and cord blood concentration. Hence, data from ex vivo placental perfusion experiments may also be used to rank the various DAAs with regard to their potential to cross the placenta.⁸⁸

4 | SAFETY OF DIRECT-ACTING ANTIVIRALS DURING PREGNANCY

In the absence of conclusive evidence from DAA exposure during human pregnancy, assessments of DAA safety are based on data derived from animal reproduction toxicology studies. Table 2 summarises the results of these pre-clinical studies on embryofoetal toxicity, teratogenicity, placenta transfer and breast milk. The literature search strategy can be found in Appendix S1. Although the majority of the adverse effects of drugs are related to direct foetal exposure because of placental transfer, drugs may also affect the developing foetus indirectly by disturbing placental function.⁸⁹ However, the species-specific placental physiology, as well as immunological and endocrinological differences hamper the translation of placental drug effects from animal studies.⁹⁰ A large registry of infants intrauterine-exposed to DAAs is needed to assess long-term effects in humans. Such an approach has been undertaken for HIV, the Antiretroviral Pregnancy Registry, and has been proven to be successful in monitoring effects of intrauterine exposure to antiretrovirals.⁹¹ Adding HCV to an existing pregnancy registry may be an option worth considering.

4.1 | Sofosbuvir/daclatasvir

The only data available on sofosbuvir/daclatasvir in human pregnancy include one study on accidental sofosbuvir/daclatasvir exposure around the time of conception (n = 7). No adverse birth outcomes were reported but one infant tested HCV positive at 18 months with low viral load, which is not unexpected as all women discontinued therapy early, before week 9 of gestation.⁵³

Sofosbuvir administration showed no adverse effects in pre-clinical reproduction toxicology studies using rabbits at exposure levels comparable to 10-fold the recommended human dose (RHD). As sofosbuvir could not be detected in rodent plasma probably due to high esterase activity, assessment of reproductive toxicity tests in rats are based on exposure to the major (inactive) metabolite GS-331007. At GS-331007 exposure levels following a 10-fold RHD, no effect on intrauterine development or any malformations were seen in rats.^{92,93} As sofosbuvir was detectable in human plasma, data from rodent studies regarding sofosbuvir exposure should be interpreted with caution. For daclatasvir, embryofoetal toxicity (external and/or visceral malformations) in rabbits and rats was reported by the EMA. However, exposure in rats and rabbits was 4.6

and 16-fold RHD respectively.⁹⁴ Remarkably, the Food and Drug Administration (FDA) reported no concerns for embryofoetal toxicity in rats when exposed to 6x RHD and in rabbits when exposed to 22-fold RHD.⁹⁵

In the general patient population, this DAA combination has a favourable safety profile. The most frequently reported adverse reactions were fatigue, headache and nausea.^{71,74} A special warning for the use of sofosbuvir (in combination with either daclatasvir or ledipasvir) and amiodarone was based on observed bradycardia in several patients.⁹⁶

4.2 | Sofosbuvir/ledipasvir

Data on sofosbuvir/ledipasvir use during pregnancy are limited to two conference abstracts: one study performed in India included pregnant women living with HCV who requested treatment because of anxiety about vertical transmission (n = 15), and DAAs were started during the second and early third trimester⁵⁴; and the other, previously mentioned, is a phase I trial of sofosbuvir/ledipasvir started during the second trimester of pregnancy (n = 8) from the USA.⁵² Both studies reported no safety concerns; there were no cases of vertical transmission to date in the USA study, but the number is yet to be reported for the Indian study. Considering the small number of women in the two studies, a lack of vertical transmission would not be unusual even in the absence of treatment.

The decision to study sofosbuvir/ledipasvir in a clinical setting is supported by a favourable embryofoetal safety profile based on pre-clinical studies. As stated earlier in this review, sofosbuvir use seems safe for the developing offspring in rats and rabbits. At exposure levels of 3.4-fold RHD, minor effects of ledipasvir on fertility of female rats were reported. However, this was not seen at 2-fold RHD and effects were likely related to non-adverse maternal toxicity.⁹⁷ The FDA reported that there are no clear adverse effects on foetal development in rats and rabbits at 4-fold and 2.3-fold RHD respectively. However, a lower body weight of the offspring in rats at an exposure level of 4-fold RHD is reported by the EMA and at slightly higher exposure levels (4.6-fold RHD), an increased incidence of skeletal variations was observed.^{57,98} In the absence of other toxicity findings, this effect on the offspring may be related to non-adverse maternal toxicity.

In terms of adverse events, fatigue and headache were reported in adult patients treated with ledipasvir/sofosbuvir.⁵⁷

4.3 | Sofosbuvir/velpatasvir (±voxilaprevir)

The EMA reports a possible teratogenic effect (visceral malformations) due to velpatasvir exposure of 0.7-fold RHD in pregnant rabbits; however, according to the FDA label, this is written as being of "no significant effect". Mice and rat studies found no embryofoetal adverse effects at 23-fold RHD and 4-fold RHD respectively. There was no evidence of placental transfer of velpatasvir as it could not be detected in litter after a single dose of 30 mg/kg on gestation day 13 or 18. Maternal voxilaprevir administration did not result in

adverse embryofetal effects in rats (141-fold RHD) and rabbits (4-fold RHD). No data on placental transfer of voxilaprevir in animals have been reported.⁹⁹⁻¹⁰²

The most common adverse effects seen in clinical studies were headache, fatigue and nausea. When combined with voxilaprevir, diarrhoea and nausea were also reported as common adverse events.^{58,75}

4.4 | Grazoprevir/elbasvir

Grazoprevir and elbasvir reproduction studies have failed to reveal any adverse effects in rats (10-fold RHD) and rabbits (18-fold RHD).^{103,104}

In patients with HCV, reported adverse reactions were fatigue and headache with a special warning for plasma liver enzyme (ALT) elevations. The rate of late ALT elevations during treatment was directly related to plasma exposure to grazoprevir and generally occurred from approximately 8 weeks after start of treatment. These late ALT elevations were typically asymptomatic and resolved with ongoing therapy with grazoprevir/elbasvir or after completion of therapy.¹⁰⁵

4.5 | Glecaprevir/pibrentasvir

Registration files state that either glecaprevir administration in rats (63-fold RHD) or pibrentasvir administration in mice (100-fold RHD) did not result in reproductive toxic effects. However, this conclusion was considered questionable because maternal toxicity with some embryofetal toxicity precluded the ability to evaluate glecaprevir in rabbits at human clinical exposures.^{106,107}

In clinical studies, the most commonly reported adverse reactions were fatigue and headache. Occasionally, elevations of total bilirubin levels have been reported in patients using glecaprevir/pibrentasvir. The effect is more pronounced with higher glecaprevir plasma levels and is likely due to glecaprevir-mediated inhibition of bilirubin transport and metabolism.¹⁰⁸ Although maternal bilirubin elevations are asymptomatic and transient, the effects on the foetus may be questionable as unconjugated bilirubin can cross the placental barrier.¹⁰⁹ Therefore, it may be hypothesised that high maternal bilirubin levels may increase the risk of neonatal jaundice.

5 | SAFETY OF DIRECT-ACTING ANTIVIRALS DURING THE LACTATION

As studies have shown that avoidance of breastfeeding does not seem to reduce the chance of vertical HCV transmission, breastfeeding is considered safe among women with chronic HCV, except for women with cracked nipples.¹¹⁰ Since breastfeeding is currently not contra-indicated in these patients living with HCV, it is important to gather information of the potential use and safety of DAAs during the lactation period.

To evaluate safety of drug use during the lactation period the following aspects should be considered: the effect of drugs on milk

production; drug concentrations in milk; and the effects of exposure on the breastfed child. In the absence of human data, data on DAA exposure in milk are limited to rat studies. They should be interpreted with caution due to species-specific differences in lactation physiology such as mammary gland anatomy, storage and release of milk into ducts, protein and fat composition of milk and the expression of drug transporters in mammary tissue, as these factors play a major role in the extent passage of drugs into milk.¹¹¹ Data obtained from rat studies showed that DAAs are transferred into milk, but no effects on growth and development were observed in nursing pups exposed to DAAs via milk.^{97,99,104,107} Maternal plasma-to-milk ratios have been reported to differ considerably between DAAs in rat studies. Whereas glecaprevir concentrations in milk are <8% of maternal plasma levels, grazoprevir milk concentrations exceed maternal plasma concentrations (400%). This disparity in extent of milk transfer is, however, difficult to explain based on the physicochemical differences and transporter profiles of the two compounds.¹¹² Grazoprevir and glecaprevir have a comparable molecular weight with a similar degree of plasma protein binding. Moreover, glecaprevir is known to be a BCRP substrate, whereas grazoprevir is not. As this transporter is considered to contribute to excretion of drugs into milk,¹¹³ the proportion of glecaprevir transferred to milk is expected to be high, but extensive plasma protein binding impedes its transfer into breastmilk.

6 | DISCUSSION

There are multiple reasons to either consider or defer DAA treatment during pregnancy as reviewed extensively by others.^{7,114,115} Although the AASLD/IDSA guidelines recommend universal screening of pregnant women,²⁴ no DAA regimen is currently approved for treatment during pregnancy because of insufficient human safety and efficacy data and treatment is therefore delayed until after delivery. The high chance of loss to follow-up of both mother and her HCV-exposed child in many settings, together with loss of health-care insurance after pregnancy may complicate adequate maternal and paediatric treatment, highlighting the pregnancy period as a unique window of opportunity to both cure the mother and prevent vertical transmission of HCV.^{46,116}

Standard dosing regimens of currently used DAAs may be sub-optimal for the pregnant patient population as pregnancy-induced pharmacokinetic changes may influence maternal drug exposure, hence efficacy of the drugs. The expected increased elimination of DAAs, both because of a potentially increased biliary excretion as well as induction of metabolising enzymes, may potentially lead to subtherapeutic levels. This pregnancy-induced effect is expected to be less pronounced for sofosbuvir/ledipasvir and glecaprevir/pibrentasvir compared to other DAA combinations. Instead of adjusting the dose—which is rarely done in clinical practice—a DAA combination less prone to pregnancy-induced effects could be chosen, if available.

Apart from data on maternal exposure to DAAs, early data on placental handling and subsequent foetal exposure are important to study possible placental toxicity of DAAs as well as the potential of

DAA to provide foetal pre-exposure prophylaxis. Several *ex vivo* and *in vitro* models may provide insight into pharmacokinetics, including placental transfer of drugs.^{87,117} The *ex vivo* placental perfusion model, using human term placentas yet unexposed to drugs, can be helpful in studying the initial phase of placental DAA handling and may provide an estimation of foetal exposure. Subsequently, pregnancy-PBPK modelling can be used as a tool to assess foetal plasma levels upon maternal administration of different dosing regimens.¹¹⁸ In the view of potential pre-exposure prophylaxis, foetal exposure to DAAs may, next to maternal viral load reduction, contribute to the reduced risk of vertical transmission. In contrast to HIV, research has yet not focused on the use of DAAs for pre-exposure prophylaxis in the general population. Future research is needed to clarify the role of foetal exposure in reducing the chance of vertical transmission.

Most DAAs are reported to cross the placental barrier in either rats and/or rabbits when administered early during pregnancy. In clinical practice, it is more likely that treatment will be started late in pregnancy to avoid the critical period of foetal organogenesis. Therefore, data from animal reproductive toxicity studies are difficult to extrapolate to the human clinical situation as there is a difference in timing of treatment and because of the large interspecies variability in placental anatomy, both affecting the extent of placental passage. Based on animal studies, it is likely that postpartum exposure to DAAs may occur via breastfeeding. Nowadays, breastfeeding is not contra-indicated in women with chronic HCV. However, this advice may change if breastfeeding women are treated with DAAs in the future, given that fact that all DAAs are detected in milk of rats, with grazoprevir levels in milk being 400% of maternal levels.

In order to decide on the timing of treatment, it is not only important to assess the most critical window of possible teratogenic effects of drug exposure (generally the earlier phase of pregnancy), but also to consider the timing of vertical transmission of HCV. As peripartum blood-blood contact may be the most important source of vertical transmission, maternal HCV RNA should be undetectable during delivery. Ideally, treatment would be completed before delivery. In that case, taking into account that women living with HCV may deliver preterm,⁴⁰ the optimal time period to start DAA treatment may be at the end of the second trimester (at around week 23/24 of gestation) or early third trimester (at around 27/28 weeks of gestation), in case of a 12- or 8 week treatment period respectively, and may have to be extended until after delivery to complete treatment. For late presenters (>28 weeks of gestation), treatment may still be effective as DAAs cause a rapid viral decline, resulting in undetectable HCV RNA in just 2-4 weeks.¹¹⁹

The choice for a specific DAA combination should be based on safety data from animal reproductive studies and safety and efficacy data from the nonpregnant patient population. Further research on safety, PK and efficacy in pregnant women is warranted prior to implementation of treatment in this population. Research on the potential effect of maternal DAA use on the state of foetal-directed immune tolerance is of particular importance in this population as DAAs are thought to improve the proliferative potential of HCV-specific T cell response again which may decrease immune tolerance.¹²⁰

Furthermore, foetal exposure should be assessed, eg by measuring umbilical cord blood concentrations, when women continue treatment until after delivery. This information is needed to assess the potential of DAAs for pre-exposure prophylaxis. Furthermore, an international registry is needed to provide a safety net to detect adverse effects after intrauterine or postpartum DAA exposure.

Next to safety and efficacy data, various other factors have to be taken into account to decide which HCV treatment regimen should be preferred. Firstly, genotype specificity of DAAs plays an important role as the phase I study on sofosbuvir/ledipasvir in pregnancy had to exclude a third of the pregnant women for participation because of genotype 2 or 3 infection.⁵² As genotyping is costly, not feasible in all settings and delays treatment start, future research may focus particularly on the use of the pan-genotypic DAA combinations glecaprevir/pibrentasvir and sofosbuvir/velpatasvir (with or without voxilaprevir) during pregnancy. Furthermore, the use of co-medication may determine the DAA regimen of first choice. In the case of HCV/HIV co-infection, EFV should not be used in combination with any DAA and when boosted PIs are part of cART, only sofosbuvir/ledipasvir or sofosbuvir/velpatasvir should be used concomitantly. If women use proton pump inhibitors (PPIs) during pregnancy, neither sofosbuvir/ledipasvir nor sofosbuvir/velpatasvir should be prescribed. In case of concomitant use of strong CYP3A4 inducers, eg rifampicin, sofosbuvir/ledipasvir should be advised. Lastly, local drug availability and costs may determine which drug will be prescribed, despite the fact that this DAA regimen may not be the regimen of first choice based on animal safety data, genotype specificity or potential for DDIs. An important example that needs to be taken into consideration is the widespread use of sofosbuvir/daclatasvir in Egypt, which is one of the countries with the highest HCV prevalence worldwide.¹²¹ Women becoming pregnant using daclatasvir are advised to stop their treatment because of the lack of knowledge regarding safety and efficacy,⁵³ despite not knowing whether cessation of treatment during pregnancy, likely resulting in HCV disease relapse, may be less advantageous than continuing treatment. Given the paucity of data and the potential exposure to daclatasvir during conception or early pregnancy, research is needed on daclatasvir efficacy in human pregnancy and global pregnancy registry databases are warranted to assess its safety.

Ideally, a pan-genotypic, safe and effective DAA combination would be available to all pregnant women living with HCV, diagnosed by a (cost-effective) universal screening programme. However, cost-effectiveness of specific DAA combinations, local drug availability and preferences of pregnant women themselves and their treating physicians play a dominant role and these factors have to be taken into consideration.

7 | CONCLUSION

Treatment of HCV with DAAs during pregnancy and breastfeeding is not currently recommended because of lack of data on safety, leaving pregnant women diagnosed with HCV untreated until after

delivery (which in itself maybe distressing for the mother and deter her from breastfeeding). In our opinion, this window of opportunity to simultaneously improve maternal health and prevent vertical transmission should not be missed. There is an urgent need to study DAAs in pregnant and breastfeeding women to target these patient populations as well as their HCV-exposed children and to contribute to the HCV elimination goal of 2030.

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REFERENCES

- WHO. Global hepatitis report 2017. <https://apps.who.int/iris/bitstream/handle/10665/255016/9789241565455-eng.pdf?sequence=1>. Accessed September 2018.
- WHO. Combating hepatitis B and C to reach elimination by 2030. May 2016 http://apps.who.int/iris/bitstream/handle/10665/206453/WHO_HIV_2016.04_eng.pdf?sequence=1. Accessed September 2018.
- Squires JE, Balistreri WF. Hepatitis C virus infection in children and adolescents. *Hepatol Commun*. 2017;1:87-98.
- WHO. Guidelines for the screening, care and treatment of persons with chronic hepatitis C infection April 2016. [/apps.who.int/iris/bitstream/handle/10665/205035/9789241549615_eng.pdf?sequence=1](https://apps.who.int/iris/bitstream/handle/10665/205035/9789241549615_eng.pdf?sequence=1). Accessed September 2018.
- Hofstraat S, Falla AM, Duffell EF, et al. Current prevalence of chronic hepatitis B and C virus infection in the general population, blood donors and pregnant women in the EU/EEA: a systematic review. *Epidemiol Infect*. 2017;145:2873-2885.
- Benhammou V, Tubiana R, Matheron S, et al. HBV or HCV coinfection in HIV-1-infected pregnant women in France: prevalence and pregnancy outcomes. *J Acquir Immune Defic Syndr*. 2018;77:439-450.
- Spera AM, Eldin TK, Tosone G, Orlando R. Antiviral therapy for hepatitis C: Has anything changed for pregnant/lactating women? *World J Hepatol*. 2016;8:557-565.
- Bigna JJ, Kenne AM, Hamroun A, et al. Gender development and hepatitis B and C infections among pregnant women in Africa: a systematic review and meta-analysis. *Infect Dis Poverty*. 2019;8:16.
- Benova L, Mohamoud YA, Calvert C, Abu-Raddad LJ. Vertical transmission of hepatitis C virus: systematic review and meta-analysis. *Clin Infect Dis*. 2014;59:765-773.
- Ly KN, Jiles RB, Teshale EH, et al. Hepatitis C virus infection among reproductive-aged women and children in the United States, 2006 to 2014. *Ann Intern Med*. 2017;166:775-782.
- Thomas D, Villano S, Riester K, et al. Perinatal transmission of hepatitis C virus from human immunodeficiency virus type 1-infected mothers. Women and Infants Transmission Study. *J Infect Dis*. 1998;177:1480-1488.
- Ohto H, Terazawa S, Sasaki N, et al. Transmission of hepatitis C virus from mothers to infants. *N Engl J Med*. 1994;330:744-750.
- Checa Cabot CA, Stoszek SK, Quarleri J, et al. Mother-to-child transmission of hepatitis C virus (HCV) among HIV/HCV-Coinfected women. *J Pediatric Infect Dis Soc*. 2013;2:126-135.
- Mutagoma M, Balisanga H, Sebuho D, et al. Hepatitis C virus and HIV co-infection among pregnant women in Rwanda. *BMC Infect Dis*. 2017;17:167.
- Landes M, Newell M-L, Barlow P, et al. Hepatitis B or hepatitis C coinfection in HIV-infected pregnant women in Europe. *HIV Med*. 2008;9:526-534.
- Prasad MR, Honegger JR. Hepatitis C virus in pregnancy. *Am J Perinatol*. 2013;30:149-159.
- European Paediatric Hepatitis CVN. Effects of mode of delivery and infant feeding on the risk of mother-to-child transmission of hepatitis C virus. *BJOG*. 2001;108:371-377.
- Gibb DM, Goodall RL, Dunn DT, et al. Mother-to-child transmission of hepatitis C virus: evidence for preventable peripartum transmission. *Lancet*. 2000;356:904-907.
- Elrazek A, Saab S, Foad M, et al. Ongoing transmission of HCV: should cesarean section be justified? data mining discovery. *J Transl Int Med*. 2017;5:27-33.
- Mok J, Pembrey L, Tovo PA, Newell ML. When does mother to child transmission of hepatitis C virus occur? *Arch Dis Child Fetal Neonatal Ed*. 2005;90:F156-F160.

21. Tosone G, Maraolo AE, Mascolo S, et al. Vertical hepatitis C virus transmission: main questions and answers. *World J Hepatol.* 2014;6:538-548.
22. Mavilia MG, Wu GY. Mechanisms and prevention of vertical transmission in chronic viral hepatitis. *J Clin Transl Hepatol.* 2017;5:119-129.
23. Chappell CA, Hillier SL, Crowe D, et al. Hepatitis C virus screening among children exposed during pregnancy. *Pediatrics.* 2018;141:e20173273.
24. AASLD/IDSA. HCV guidance: recommendations for testing, managing, and treating hepatitis C. 2018. https://www.hcvguidelines.org/sites/default/files/full-guidance-pdf/HCVGuidance_May_24_2018b.pdf. Accessed November 2018.
25. Resti M, Bortolotti F, Vajro P, Maggiore G, Committee of Hepatology of the Italian Society of Pediatric G, Hepatology. Guidelines for the screening and follow-up of infants born to anti-HCV positive mothers. *Dig Liver Dis.* 2003;35:453-457.
26. European Paediatric Hepatitis CVN. Three broad modalities in the natural history of vertically acquired hepatitis C virus infection. *Clin Infect Dis.* 2005;41:45-51.
27. Jara P, Resti M, Hierro L, et al. Chronic hepatitis C virus infection in childhood: clinical patterns and evolution in 224 white children. *Clin Infect Dis.* 2003;36:275-280.
28. Bortolotti F, Verucchi G, Cammà C, et al. Long-term course of chronic hepatitis C in children: from viral clearance to end-stage liver disease. *Gastroenterology.* 2008;134:1900-1907.
29. Modin L, Arshad A, Wilkes B, et al. Epidemiology and natural history of hepatitis C virus infection among children and young people. *J Hepatol.* 2019;70:371-378.
30. Rumbo C, Fawaz RL, Emre SH, et al. Hepatitis C in children: a quaternary referral center perspective. *J Pediatr Gastroenterol Nutr.* 2006;43:209-216.
31. Rodrigue JR, Balistreri W, Haber B, et al. Impact of hepatitis C virus infection on children and their caregivers: quality of life, cognitive, and emotional outcomes. *J Pediatr Gastroenterol Nutr.* 2009;48:341-347.
32. Balistreri WF, Murray KF, Rosenthal P, et al. The safety and effectiveness of ledipasvir-sofosbuvir in adolescents 12 to 17 years old with hepatitis C virus genotype 1 infection. *Hepatology.* 2016;66:371-378.
33. Carlucci JG, Liu Y, Friedman H, et al. Attrition of HIV-exposed infants from early infant diagnosis services in low- and middle-income countries: a systematic review and meta-analysis. *J Int AIDS Soc.* 2018;21:e25209.
34. Kiyaga C, Narayan V, McConnell I, et al. Retention outcomes and drivers of loss among HIV-exposed and infected infants in Uganda: a retrospective cohort study. *BMC Infect Dis.* 2018;18:416.
35. Parent S, Salters K, Awendila L, Ti L. Hepatitis C and pregnancy outcomes: a systematic review protocol. *BMJ open.* 2018;8:e024288.
36. Reddick KL, Jhaveri R, Gandhi M, et al. Pregnancy outcomes associated with viral hepatitis. *J Viral Hepat.* 2011;18:e394-e398.
37. Wijarnpreecha K, Thongprayoon C, Sanguankeo A, et al. Hepatitis C infection and intrahepatic cholestasis of pregnancy: a systematic review and meta-analysis. *Clin Res Hepatol Gastroenterol.* 2017;41:39-45.
38. Connell LE, Salihu HM, Salemi JL, et al. Maternal hepatitis B and hepatitis C carrier status and perinatal outcomes. *Liver Int.* 2011;31:1163-1170.
39. Huang QT, Hang LL, Zhong M, et al. Maternal HCV infection is associated with intrauterine fetal growth disturbance: a meta-analysis of observational studies. *Medicine (Baltimore).* 2016;95:e4777.
40. Huang QT, Huang Q, Zhong M, et al. Chronic hepatitis C virus infection is associated with increased risk of preterm birth: a meta-analysis of observational studies. *J Viral Hepat.* 2015;22:1033-1042.
41. Pergam SA, Wang CC, Gardella CM, et al. Pregnancy complications associated with hepatitis C: data from a 2003–2005 Washington state birth cohort. *Am J Obstet Gynecol.* 2008;199:38 e1-39.
42. Aebi-Popp K, Duppenhaler A, Rauch A, et al. Vertical transmission of hepatitis C: towards universal antenatal screening in the era of new direct acting antivirals (DAAs)? short review and analysis of the situation in Switzerland. *J Virus Erad.* 2016;2:52-54.
43. Benova L, Awad SF, Miller FD, Abu-Raddad LJ. Estimation of hepatitis C virus infections resulting from vertical transmission in Egypt. *Hepatology.* 2015;61:834-842.
44. Sinclair SM, Jones JK, Miller RK, et al. The ribavirin pregnancy registry: an interim analysis of potential teratogenicity at the midpoint of enrollment. *Drug Saf.* 2017;40:1205-1218.
45. Feld JJ, Jacobson IM, Hézode C, et al. Sofosbuvir and velpatasvir for HCV genotype 1, 2, 4, 5, and 6 infection. *N Engl J Med.* 2015;373:2599-2607.
46. Towers CV, Fortner KB. Infant follow-up postdelivery from a hepatitis C viral load positive mother. *J Matern Fetal Neonatal Med.* 2019;32:3303-3305.
47. Kuncio DE, Newbern EC, Johnson CC, Viner KM. Failure to test and identify perinatally infected children born to hepatitis C virus-infected women. *Clin Infect Dis.* 2016;62:980-985.
48. Bottero J, Brouard C, Roudot-Thoraval F, et al. 2014 French guidelines for hepatitis B and C screening: a combined targeted and mass testing strategy of chronic viruses namely HBV, HCV and HIV. *Liver Int.* 2016;36:1442-1449.
49. Umar M, Khaar HT, Akhter TS, et al. Diagnosis, management and prevention of hepatitis C in Pakistan 2017. *J Ayub Med Coll Abbottabad.* 2016;28(4 Suppl 1):S839-S882.
50. Chaillon A, Rand EB, Reau N, Martin NK. Cost-effectiveness of universal hepatitis C virus screening of pregnant women in the United States. *Clin Infect Dis.* 2019.
51. Kushner T, Cohen J, Tien PC, Terrault NA. Evaluating women's preferences for hepatitis C treatment during pregnancy. *Hepatol Commun.* 2018;2:1306-1310.
52. Chappell CA, Krans EE, Bunge K, et al. A phase I study of ledipasvir/sofosbuvir in pregnant women with hepatitis C virus. Presented at CROI 2019. 2019.
53. El-Sayed MH, Elakel W, Elsharkawy A, et al. DAA therapy in women of child bearing age: Accidental conception during therapy and pregnancy outcome. Vienna: Austria; 2019. Presented at The International Liver Congress by the European Association for the Study of the Liver, April 10–14.
54. Yattoo NG. Treatment of chronic hepatitis C with ledipasvir/sofosbuvir combination during pregnancy. Presented at 27th Annual Conference of APASL, March 14–18, 2018, New Delhi, India.
55. Abduljalil K, Furness P, Johnson TN, et al. Anatomical, physiological and metabolic changes with gestational age during normal pregnancy: a database for parameters required in physiologically based pharmacokinetic modelling. *Clin Pharmacokinet.* 2012;51:365-396.
56. Chiloiro M, Darconza G, Piccioli E, et al. Gastric emptying and orocecal transit time in pregnancy. *J Gastroenterol.* 2001;36:538-543.
57. European Medicines Agency. Harvoni: Summary of Product Characteristics. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003850/WC500177995.pdf. Accessed March 2018.
58. European Medicines Agency. Eplclusa: Summary of product characteristics. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/004210/WC500211151.pdf. Accessed March 2018.
59. Lupattelli A, Spigset O, Twigg MJ, et al. Medication use in pregnancy: a cross-sectional, multinational web-based study. *BMJ Open.* 2014;4:e004365.
60. Mogalian E, Shen G, Moorehead L, et al. Drug-Drug Interaction Profile of Sofosbuvir/Velpatasvir Fixed-Dose Combination

- International Liver Congress, Barcelona, Spain, 13–17 April, 2016 (Poster # FRI-168)2016.
61. U.S. Food and Drug Administration. Harvoni: Clinical Pharmacology Biopharmaceutics Review(s). Available from: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/205834Orig1s000ClinPharmR.pdf. Accessed March 2018.
 62. Feghali M, Venkataramanan R, Caritis S. Pharmacokinetics of drugs in pregnancy. *Semin Perinatol*. 2015;39:512-519.
 63. Zajac M, Muszalska I, Sobczak A, et al. Hepatitis C - New drugs and treatment prospects. *Eur J Med Chem*. 2019;165:225-249.
 64. Schalkwijk S, Greupink R, Burger D. Free drug concentrations in pregnancy: bound to measure unbound? *Br J Clin Pharmacol*. 2017;83:2595-2598.
 65. EASL Recommendations. Treatment of Hepatitis C. 2018. <https://easl.eu/wp-content/uploads/2018/10/HepC-English-report.pdf>.
 66. Tracy TS, Venkataramanan R, Glover DD, Caritis SN. Temporal changes in drug metabolism (CYP1A2, CYP2D6 and CYP3A Activity) during pregnancy. *Am J Obstet Gynecol*. 2005;192:633-639.
 67. Flamm S, Reddy KR, Zadeikis N, et al. Efficacy and pharmacokinetics of glecaprevir and pibrentasvir with concurrent use of acid-reducing agents in patients with chronic HCV infection. *Clin Gastroenterol Hepatol*. 2018;17:527-535.
 68. Lin CW. Exposure-Response Analyses of Virologic Response to Glecaprevir and Pibrentasvir in HCV Subjects from Phase 2 and 3 Studies. AASLD The Liver Meeting; 20–24 October 2017; Washington, DC 2017.
 69. U.S. Food and Drug Administration. Daklinza: Clinical Pharmacology and Biopharmaceutics review(s). http://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/206843Orig1s001s003ClinPharmR.pdf. Accessed March 2018.
 70. Ke AB, Greupink R, Abduljalil K. Drug dosing in pregnant women: challenges and opportunities in using physiologically based pharmacokinetic modeling and simulations. *CPT Pharmacometrics Syst Pharmacol*. 2018;7:103-110.
 71. European Medicines Agency. Sovaldi: summary of product characteristics. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002798/WC500160597.pdf. Accessed March 2018.
 72. Aslam A, Campoverde Reyes KJ, Malladi VR, et al. Management of chronic hepatitis B during pregnancy. *Gastroenterol Rep (Oxf)*. 2018;6:257-262.
 73. Rice DP Jr, Faragon JJ, Banks S, Chirch LM. HIV/HCV antiviral drug interactions in the era of direct-acting antivirals. *J Clin Transl Hepatol*. 2016;4:234-240.
 74. European Medicines Agency. Daklinza: summary of product characteristics. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003768/WC500172848.pdf. Accessed March 2018.
 75. European Medicines Agency. Vosevi: summary of product characteristics. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/004350/WC500235373.pdf. Accessed March 2018.
 76. Zash R, Makhema J, Shapiro RL. Neural-tube defects with dolutegravir treatment from the time of conception. *N Engl J Med*. 2018;379:979-981.
 77. McCormack SA, Best BM. Protecting the fetus against HIV infection: a systematic review of placental transfer of antiretrovirals. *Clin Pharmacokinet*. 2014;53:989-1004.
 78. Eke AC, Dooley KE, Sheffield JS. Pharmacologic research in pregnant women - time to get it right. *N Engl J Med*. 2019;380:1293-1295.
 79. Illamola SM, Bucci-Rechtweg C, Costantine MM, et al. Inclusion of pregnant and breastfeeding women in research - efforts and initiatives. *Br J Clin Pharmacol*. 2018;84:215-222.
 80. Zaidi MT, Arshad M, Vasenwala SM, et al. Histomorphometry of preterm and term human placentas. *Int J Morphol*. 2013;31:409-413.
 81. Giaginis C, Theocharis S, Tsantili-Kakoulidou A. Current toxicological aspects on drug and chemical transport and metabolism across the human placental barrier. *Expert Opin Drug Metab Toxicol*. 2012;8:1263-1275.
 82. Syme MR, Paxton JW, Keelan JA. Drug transfer and metabolism by the human placenta. *Clin Pharmacokinet*. 2004;43:487-514.
 83. Joshi AA, Vaidya SS, St-Pierre MV, et al. Placental ABC transporters: biological impact and pharmaceutical significance. *Pharm Res*. 2016;33:2847-2878.
 84. Walker N, Filis P, Soffientini U, et al. Placental transporter localization and expression in the Human: the importance of species, sex, and gestational age differences dagger. *Biol Reprod*. 2017;96:733-742.
 85. Hewitt M, Madden JC, Rowe PH, Cronin MT. Structure-based modelling in reproductive toxicology: (Q)SARs for the placental barrier. *SAR QSAR Environ Res*. 2007;18:57-76.
 86. Giaginis C, Tsantili-Kakoulidou A, Theocharis S. Assessing drug transport across the human placental barrier: from in vivo and in vitro measurements to the ex vivo perfusion method and in silico techniques. *Curr Pharm Biotechnol*. 2011;12:804-813.
 87. Hutson JR, Garcia-Bournissen F, Davis A, Koren G. The human placental perfusion model: a systematic review and development of a model to predict in vivo transfer of therapeutic drugs. *Clin Pharmacol Ther*. 2011;90:67-76.
 88. Pacifici GM. Transfer of antivirals across the human placenta. *Early Human Dev*. 2005;81:647-654.
 89. Sachdeva P, Patel BG, Patel BK. Drug use in pregnancy; a point to ponder!. *Indian J Pharm Sci*. 2009;71:1-7.
 90. Malassine A, Frenzo JL, Evain-Brion D. A comparison of placental development and endocrine functions between the human and mouse model. *Hum Reprod Update*. 2003;9:531-539.
 91. Tilson HH, Doi PA, Covington DL, et al. The antiretrovirals in pregnancy registry: a fifteenth anniversary celebration. *Obstet Gynecol Surv*. 2007;62:137-148.
 92. European Medicines Agency. Sovaldi: Assessment report. https://www.ema.europa.eu/documents/assessment-report/sovaldi-epar-public-assessment-report_en.pdf. Accessed March 2018.
 93. U.S. Food and Drug Administration. Sofosbuvir: Pharmacology Review(s). https://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/204671Orig1s000PharmR.pdf.
 94. European Medicines Agency. Daklinza: Assessment report. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/003768/WC500172849.pdf. Accessed March 2018.
 95. U.S. Food and Drug Administration. Daclatasvir: Pharmacology Review(s). https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/206843Orig1s000PharmR.pdf. Accessed March 2018.
 96. European Medicines Agency. Sovaldi: summary of product characteristics. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002798/WC500160597.pdf. Accessed March 2018.
 97. U.S. Food and Drug Administration. Harvoni: Pharmacology Review(s). https://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/205834Orig1s000PharmR.pdf. Accessed March 2018.
 98. European Medicines Agency. Harvoni: Assessment report. https://www.ema.europa.eu/documents/assessment-report/harvoni-epar-public-assessment-report_en.pdf. Accessed March 2018.
 99. U.S. Food and Drug Administration. Vosevi: Pharmacology Review(s). https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/209195Orig1s000PharmR.pdf. Accessed March 2018.
 100. U.S. Food and Drug Administration. Eplclusa: Pharmacology Review(s). https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/208341Orig1s000PharmR.pdf. Accessed March 2018.

101. European Medicines Agency. Eplclusa: Assessment Report. https://www.ema.europa.eu/documents/assessment-report/eplclusa-epar-public-assessment-report_en.pdf. Accessed March 2018.
102. European Medicines Agency. Vosevi: Assessment report. https://www.ema.europa.eu/documents/assessment-report/vosevi-epar-public-assessment-report_en.pdf. Accessed March 2018.
103. European Medicines Agency. Zepatier: Assessment report. https://www.ema.europa.eu/documents/assessment-report/zepatier-epar-public-assessment-report_en.pdf. Accessed March 2018.
104. U.S. Food and Drug Administration. Zepatier: Pharmacology Review(s). https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/208261Orig1s000PharmR.pdf. Accessed March 2018.
105. European Medicines Agency. Zepatier: Summary of Product Characteristics. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/004126/WC500211235.pdf. Accessed March 2018.
106. U.S. Food and Drug Administration. Mavyret: Pharmacology Review(s). https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/209394Orig1s000PharmR.pdf. Accessed March 2018.
107. European Medicines Agency. Maviret: Assessment report. https://www.ema.europa.eu/documents/assessment-report/maviret-epar-public-assessment-report_en.pdf. Accessed March 2018.
108. European Medicines Agency. Maviret: Summary of Product Characteristics. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/004430/WC500233677.pdf. Accessed March 2018.
109. McDonagh AF. Movement of bilirubin and bilirubin conjugates across the placenta. *Pediatrics*. 2007;119:1032-1033; author reply 3.
110. Cottrell EB, Chou R, Wasson N, et al. 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;158:109-113.
111. Wang J, Johnson T, Sahin L, et al. Evaluation of the safety of drugs and biological products used during lactation: workshop summary. *Clin Pharmacol Ther*. 2017;101:736-744.
112. Newton ER, Hale TW. Drugs in breast milk. *Clin Obstet Gynecol*. 2015;58:868-884.
113. Ito N, Ito K, Ikebuchi Y, et al. Prediction of drug transfer into milk considering breast cancer resistance protein (BCRP)-mediated transport. *Pharm Res*. 2015;32:2527-2537.
114. Bernstein HB, Dunkelberg JC, Leslie KK. Hepatitis C in pregnancy in the era of direct-acting antiviral treatment: potential benefits of universal screening and antepartum therapy. *Clin Obstet Gynecol*. 2018;61:146-156.
115. Kushner T, Terrault NA. Hepatitis C in pregnancy: a unique opportunity to improve the hepatitis C cascade of care. *Hepatol Commun*. 2019;3:20-28.
116. Association AP. Medicaid for Pregnant Women [updated September 2, 2016]. <http://americanpregnancy.org/planning/medicaid-for-pregnant-women/>
117. Myren M, Mose T, Mathiesen L, Knudsen LE. The human placenta—an alternative for studying foetal exposure. *Toxicol In Vitro*. 2007;21:1332-1340.
118. Schalkwijk S, Buaben AO, Freriksen J, et al. Prediction of fetal darunavir exposure by integrating human ex-vivo placental transfer and physiologically based pharmacokinetic modeling. *Clin Pharmacokinet*. 2018;57:705-716.
119. Loggi E, Galli S, Vitale G, et al. Monitoring the treatment of hepatitis C with directly acting antivirals by serological and molecular methods. *PLoS ONE*. 2017;12:e0187755.
120. Martin B, Hennecke N, Lohmann V, et al. Restoration of HCV-specific CD8+ T cell function by interferon-free therapy. *J Hepatol*. 2014;61:538-543.
121. Keating GM. Daclatasvir: a review in chronic hepatitis C. *Drugs*. 2016;76:1381-1391.

SUPPORTING INFORMATION

Additional supporting information will be found online in the Supporting Information section at the end of the article.

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