index [APRI] or fibrosis-4 index [FIB-4]) and an ultrasound scan of the liver and spleen should be undertaken where there is suspicion of advanced liver disease. It is important where cirrhosis is found to be present that there is close liaison with the hepatologist because of a significantly increased rate of complications. Additionally, acute liver failure can occur on reactivation of HBV disease if anti-HBV treatment is discontinued [8]. However, in the absence of decompensated disease and with cART incorporating anti-HBV drugs and close monitoring, most women with cirrhosis do not have obstetric complications from their HBV infection.

Because of the risk of antiretroviral-related hepatotoxicity and a hepatitis flare from immune reconstitution, it is important to repeat LFTs at 2 and 4 weeks after initiation of ART and periodically thereafter. Through pregnancy, LFTs are routinely monitored at each antenatal clinic appointment as a marker for potential obstetric complications (HELLP, pre-eclampsia, acute fatty liver, etc.), particularly in the final trimester. Finally, in those diagnosed late and not receiving HBV treatment incorporated into cART, LFT flares may be seen shortly after delivery, which in some cases relates to HBeAg seroconversion and reappearance or a marked increase in HBV DNA levels. Where acute infection is suspected, testing for anti-HBc IgM is recommended. Acute HBV is uncommon during pregnancy and each case needs to be managed with specialist advice. Data suggest that lamivudine as part of cART does not completely protect against the development of acute HBV infection, although it is unlikely that this is also the case with tenofovir DF with or without lamivudine/emtricitabine [9]. Although there is a theoretical risk of high HBV DNA levels and the linked association with increased risk of vertical transmission combined with the potential for acute hepatitis and threat to maternal and fetal health, it is assumed that this would be mitigated by the patient already being on cART incorporating tenofovir DF and either emtricitabine or lamivudine. Where the woman is not on cART, a tenofovir DF-based ART regimen should be commenced immediately.

7.1.3	Because there is no evidence of any adverse effect on maternal or neonatal health if women become pregnant while taking ART dually active against HBV, treatment should be continued.	1C

For tenofovir DF, emtricitabine and lamivudine, the APR [10] and the Development of Antiretroviral Therapy Study [11] have not identified any increase in prevalence of congenital abnormality or any specific pattern of anomaly, even when administered in the first trimester. Hence, when a woman conceives on an anti-HBV viral agent as part of ART (tenofovir DF, lamivudine or emtricitabine), as for HIV management, cART should be continued as the potential risk to the fetus from drug exposure is outweighed by that of a hepatitis flare or liver disease progression if the drug(s) were to be discontinued in addition to HIV virological rebound and risk of vertical transmission of HIV. Because entecavir has activity against HIV, it is not recommended unless given with active cART in a woman with both HBV and HIV. Moreover, it has been found to have significant carcinogenic potential in animal studies and therefore its use as an antiviral drug for HBV during pregnancy should be avoided. Lamivudine has been extensively used, as has tenofovir DF and to a lesser extent emtricitabine, for the treatment of HIV mono-infection during pregnancy, and a combination of lamivudine and telbivudine has been used in HBV mono-infected pregnant women and all have been found to be safe. Although experience with tenofovir alafenamide in pregnancy is limited, animal data do not indicate direct or indirect harmful effects with respect to reproductive toxicity [12]. New data from IMPACT 2010 has shown use of tenofovir alafenamide to be safe after the first trimester of pregnancy, therefore it may be considered to treat HIV and HBV co-infection after the first trimester[13]. There is no evidence of any adverse effect on maternal health if women become pregnant while taking tenofovir DF, lamivudine or emtricitabine; these drugs are recommended as NRTI choices in national [14,15] and international guidelines [16].

7.1.4	Tenofovir DF and emtricitabine or lamivudine should form the backbone of an antiretroviral regimen in treatment-naïve patients with wild-type HIV/HBV co-infection and no contraindication to any of these drugs.	1B
7.1.5	If tenofovir DF is not currently part of cART it should be added or tenofovir alafenamide /emtricitbine can be added after the first trimester.	1B
7.1.6	Lamivudine/emtricitabine may be omitted from the antiretroviral regimen and tenofovir DF given as the sole anti-HBV agent if there is clinical or genotypic evidence of	1C

	lamivudine/emtricitabine-resistant HBV or HIV.	
7.1.7	Lamivudine or emtricitabine should not be used as the only active drug against HBV in cART because of the likelihood of emergent HBV resistance to these agents.	1B
7.1.8	Emtricitabine has potentially increased antiviral benefits compared to lamivudine, appears to be equally safe during pregnancy and hence is the preferred option to be given with tenofovir DF in women with HBV and HIV.	2D

All women living with both HBV and HIV should receive cART containing tenofovir DF, or if after the first trimester tenofovir alafenamide, in combination with emtricitabine or lamivudine treatment during pregnancy. Although lamivudine and emtricitabine are potent anti-HBV agents, HBV monotherapy is associated with a high likelihood of HBV resistance in co-infected persons and hence therapy with either of these drugs, without a second anti-HBV active drug, is not recommended. Tenofovir DF is effective at suppressing HBV DNA in mono- and co-infected patients whether they are HBeAg positive or negative, and independent of the presence of lamivudine-resistant virus [17]. More recently, tenofovir alafenamide has also been shown to have non-inferior efficacy and improved renal and bone toxicity compared to tenofovir DF in the management of HBV mono-infection [18,19]. Phenotypic HBV resistance has not been ascribed to tenofovir DF in people with both HBV and HIV with up to 5 years of follow-up and has only been demonstrated *in vitro* in treated individuals with suboptimal control [20] as represented by detectable HBV DNA levels. In combination with lamivudine or emtricitabine, tenofovir DF has been demonstrated to be effective at suppressing HBV DNA and may induce HBeAg seroconversion. Combining lamivudine/emtricitabine with tenofovir DF may also reduce the risk of breakthrough HBV viraemia [14], however the biggest advantage is that currently emtricitabine is co-formulated with tenofovir DF and therefore convenient for dosing.

Emtricitabine is structurally similar to lamivudine but has a longer intracellular half-life and is more potent *in vitro* and *in vivo* as monotherapy in the treatment of naïve patients with HIV and HBV [21]. It also selects for resistance for both HBV and HIV less rapidly and less often than lamivudine [21]. Although not currently approved for HBV treatment, it induces a sharp reduction of HBV DNA in both mono- and co-infected patients. In patients with both HBV and HIV naïve to antivirals, combining emtricitabine with tenofovir DF has been shown in a randomised controlled trial to be more effective than emtricitabine alone (median time-weighted average concentration decrease was −5.32 $\log_{10}$ IU/mL in the tenofovir DF/emtricitabine group *vs* −3.25 IU/mL in the emtricitabine group; *P*=0.036) [22]. Further studies comparing emtricitabine/lamivudine with lamivudine alone produced similar results [23].

Nevirapine should be not be started in any individual with HBV and HIV. Zidovudine should, if possible, be avoided in viral hepatitis co-infection because of the association with hepatic steatosis. In a retrospective analysis of patients with HCV and HIV, a strong association with hepatic steatosis was found with didanosine and stavudine, however there was also a trend with zidovudine (OR 2.65; 95% CI 0.95–7.41) [24].

Liver enzymes should be monitored frequently after starting cART because of the possibility of an inflammatory flare from immune reconstitution (see recommendation 7.2.2).

7.1.9	In all HAV non-immune women with HBV and HIV, HAV vaccine is recommended, after the first trimester as per the normal schedule (0 and 6 months);	1A
	unless the CD4 cell count is <300 cells/mm^3, when an additional dose (0, 1 and 6 months) may be indicated.	1D

Immunisation for HAV uses inactivated vaccine. Data for HAV vaccine in pregnancy are limited. Nevertheless, several guidelines indicate that pregnancy is not a contraindication for HAV immunisation, including in pregnant women with both HBV and HIV [25]. Patients with higher CD4 cell counts and on cART generally show improved responses to HAV vaccination. People living with HIV with CD4 cell counts <300 cells/mm^3 should receive three instead of the standard two doses of HAV vaccine.

7.1.10	cART active against both HBV and HIV should be continued postpartum in all women with HBV and HIV.	1A
7.1.11	Hepatitis flares that occur after delivery should be managed conservatively with careful monitoring.	2D

Inflammatory flares may be severe, particularly in persons with cirrhosis, and can occur as a result of viral escape and HBV viraemia if drugs with anti-HBV activity are stopped. In a randomised controlled trial comparing lamivudine with placebo for reducing vertical transmission of HBV in women with HBV mono-infection, an immediate increase in HBV DNA levels was observed on discontinuation of lamivudine postpartum [26]. Similarly, hepatitis flares among patients with HBV and HIV have been reported upon the discontinuation of lamivudine, emtricitabine and tenofovir DF. In the Swiss HIV observational cohort, liver enzyme elevation occurred in 29% of patients who discontinued lamivudine and in 5% this was severe with three patients presenting with fulminant hepatitis [27] at a median time of 6 weeks after discontinuation.

Pregnancy induces a state of relative immune suppression. Postpartum flares of liver inflammation have been described for HBV, HCV and autoimmune hepatitis. Although rarely leading to fulminant hepatitis, careful monitoring of flares is needed in the postpartum period. HBeAg positivity is a common predictor of flares, most of which are asymptomatic and resolve within 12 months [28].

HBV-active antiviral therapy does not appear to protect against the development of a postpartum flare and does not lead to anti-HBe seroconversion in HBeAg-positive women [29].

7.1.12	In the absence of obstetric complications, normal vaginal delivery can be recommended if the woman has fully suppressed HIV viral load on cART, irrespective of HBV viral load.	1C
7.1.13	Neonatal immunisation with or without hepatitis B immunoglobulin (HBIG) should commence within 24 hours of delivery. The national infant HBV schedule should then be followed.	1A

No data exist to support any benefit from PLCS in women with both HBV and HIV and no robust randomised controlled trial has been conducted in women with HBV alone. In a meta-analysis of women with HBV alone (four randomised trials all from China including 789 people) where routine HBV neonatal vaccine and HBIG were used, there was strong evidence that PLCS versus vaginal delivery could effectively reduce the rate of vertical transmission of HBV (RR 0.41; 95% CI 0.28–0.60) [30]. However, methodological concerns including lack of information on randomisation procedure, lack of allocation concealment and lack of blinding make the role of PLCS for preventing vertical transmission of HBV uncertain. A more recent meta-analysis including 10 eligible studies confirmed that there may not be additional benefit beyond appropriate vaccination and HBIG use [31].

Another meta-analysis suggested that oral antiviral therapies in pregnancy, including lamivudine, telbivudine and tenofovir DF, reduce the rates of vertical HBV transmission [32].

Although HBV DNA levels are increased as a result of HIV, the efficacy of oral nucleos(t)ide inhibitors in reducing the rate of vertical transmission in mono-infection, the efficacy of lamivudine, tenofovir DF and emtricitabine as part of cART in reducing HBV DNA in non-pregnant individuals with HBV and HIV, and the use of tenofovir DF with either lamivudine or emtricitabine as standard practice in co-infected patients collectively provide further reason against recommending PLCS in those pregnant women with HBV and HIV.

Immunoprophylaxis with HBV vaccine with or without HBIG given to the neonate has been shown in separate meta-analyses of randomised controlled trials to significantly reduce vertical transmission from women with HBV alone.

HBIG should be given to the neonate if:

- maternal HBV DNA concentration is $>10^6$ IU/mL
- and/or the woman is HBeAg positive
- or anti-HBe negative

- or anti-HBe status is unknown [33].

In the absence of neonatal immunisation with HBV vaccine with or without HBIG, the rate of vertical transmission from a pregnant woman with HBV alone is 70–90% if the woman is both HBsAg and HBeAg positive and 10–40% if HBsAg positive but HBeAg negative. By co-administering vaccination (effectiveness of vaccine *vs* placebo RR: 0.28; 95% CI 0.2–0.4) and HBIG (effectiveness of HBIG/vaccine *vs* vaccine alone RR: 0.54; 95% CI 0.41–0.73), transmission rates can be reduced to between 0% and 14%. The most important determinant of prophylaxis failure has been shown to be maternal serum HBV DNA levels.

Failure of birth-dose vaccine and HBIG in up to 9% of infants despite appropriate post-delivery immunoprophylaxis occurs mainly because of infection *in utero* [34].

The strongest evidence of prevention of vertical transmission is for the use of birth-dose vaccination and HBIG in neonates born to high viraemic and HBeAg-positive mothers.

A randomised controlled trial of tenofovir DF given to HBV mono-infected mothers (in addition to birth-dose vaccine and HBIG for the neonate) showed a significant reduction in vertical transmission in the tenofovir DF group [35]. All mothers randomly assigned to the tenofovir DF group received therapy from week 32 onwards. Only mothers with HBV DNA >200 000 IU/L showed transmission of infection.

The inference, therefore, is that while birth-dose vaccination plus HBIG remains the cornerstone for prevention of vertical transmission of HBV, additional tenofovir DF with/without lamivudine is of benefit in mothers with very high viral loads and a reduction in viral load to <200 000 IU/L at birth is of additional benefit.

Therefore, maternal cART together with prompt post-delivery neonatal immunoprophylaxis is the ideal approach for preventing vertical transmission of HBV. This recommendation may change, therefore clinicians should refer to the Green Book [33] for the most up-to-date recommendations.

7.2 Hepatitis C virus (HCV)

It is recommended practice that all pregnant women with active HCV (HCV RNA positive) and HIV should be managed jointly with a clinician experienced in the management of these co-infections, and that those with advanced cirrhosis be managed in a tertiary centre with a hepatologist.

Antenatal prevalence of HCV mono-infection ranges from less than 1% to about 2.5%, increasing to 3–50% in co-infection with the wide range reflecting the proportion of women who are injecting drug users or from high HCV prevalence areas in the cohorts studied [36,37]. Several meta-analyses and systematic reviews have shown that the overall rate of vertical transmission for HCV is approximately 5% (range 2–10%) if the woman has HCV mono-infection.

Infection with HCV and HIV is associated with a significant increase in HCV transmission (OR up to 2.82) compared to HCV mono-infection [38,39]. Conversely, the higher risk of HCV transmission seems to be ameliorated in co-infected mothers who have suppressed HIV on ART [40,41]. In addition, a higher rate of HCV vertical transmission is seen in women who have both HCV and HIV with HCV viraemia compared to those who have HCV and HIV but without HCV viraemia (OR 2.82) [38,39]. Acquisition of infection of HCV is more likely in infants acquiring HIV vertically, and vertical transmission of HIV occurs more often from women with HCV and HIV than from those with HIV alone (OR 1.82) with a modest association with HCV viral load [42].

Numerous studies have shown that the HCV viral load correlates with the risk of HCV vertical transmission and it is likely there is a linear relationship between viral load and transmission as for HIV [43-45]. Invasive obstetric procedures, internal fetal monitoring, prolonged rupture of membranes and female infant sex have also been associated with transmission but breastfeeding and CS do not pose an additional risk in women with HCV alone [40,41]. Indeed some studies have shown a lower risk of HCV transmission in infants born by CS [46,47]. However, a meta-analysis in HCV mono-infected women concluded that there was no effect of mode of delivery on risk of vertical transmission [48]. Effective cART significantly reduces the rate of HCV transmission, possibly by reducing HCV viraemia [40,49]. Lack of immune regulation during pregnancy may also facilitate HCV transmission via peripheral blood monocytes [50]. No correlation between HCV genotype or interleukin-28 polymorphisms and transmission has been identified [45,51,52]. Both intrauterine and intrapartum infection probably occur, but the relative contribution of each is uncertain. However, approximately one-third of neonates are HCV viraemic at

birth suggesting acquisition *in utero* [53].

7.2.1	On diagnosis of new HCV infection, confirmation of HCV viraemia with quantitative RNA and genotype, assessment of hepatic inflammation/fibrosis and liver function and concomitant liver disease should be performed.	1C
7.2.2	LFTs should be repeated at 2 and 4 weeks after commencing ART to detect evidence of hepatotoxicity or IRIS and then monitored regularly throughout pregnancy and postpartum.	1C

In a pregnant woman living with HIV and newly diagnosed with HCV, in addition to referral to the local designated specialist, baseline investigations are indicated including the presence and level of the virus (HCV RNA viral load), the genotype and subtype, the degree of inflammation and synthetic function (ALT, AST, albumin and INR), an assessment of fibrosis and the exclusion of additional causes of liver disease (e.g. haemochromatosis and autoimmune hepatitis). Additionally, patients should be assessed for:

- The need for HAV immunisation (HAV IgG antibody);
- The need for HBV immunisation (anti-HBs);
- HBV co-infection (HBsAg).

Liver biopsy and hepatic elastometry (FibroScan) are relatively contraindicated during pregnancy [7], therefore clinical assessment, use of blood panel-based fibrosis markers (e.g. APRI or FIB-4) and an ultrasound scan of the liver and spleen should be undertaken where there is suspicion of advanced liver disease. It is important where cirrhosis is found to be present that there is close liaison with the hepatologist because of a significantly increased rate of complications [8]. However, in the absence of decompensated disease, most women with cirrhosis do not have obstetric complications from their HCV infection.

Because of the risk of cART-related hepatotoxicity and a hepatitis flare from immune reconstitution, it is important to repeat LFTs at 2 and 4 weeks after initiation of cART. Through pregnancy, LFT results are routinely monitored at each antenatal clinic appointment as a marker for potential obstetric complications (HELLP, pre-eclampsia, acute fatty liver, etc.), particularly in the final trimester. Acute HCV infection is rare in pregnancy but HCV RNA, the initial test to become positive, should be measured where there is a sudden unexplained increase in transaminases and/or a history of exposure. Where acute HCV infection is confirmed, HCV viral load should be monitored through pregnancy. Involvement of a clinician experienced in the management of hepatitis is important both for initial care and postpartum when treatment decisions are made.

In chronic HCV infection there is unlikely to be a significant change in the HCV viral load during pregnancy. However, the prenatal viral load will give some indication of the risk of transmission and may be worth repeating near delivery. Treatment of HCV infection is not recommended during pregnancy. If pregnancy has occurred during treatment for HCV with pegylated interferon (IFN) and ribavirin, or during DAA-based therapy, there should be immediate discontinuation of all HCV treatment. Ribavirin is teratogenic (see below), and risk of teratogenicity may persist for weeks after discontinuation. Furthermore, ribavirin is able to penetrate in spermatozoa with the added risk of mutagenesis. The effects of DAAs in pregnant women are largely unknown [54]. In addition, thyroid function testing should be included as part of routine blood tests as thyroid dysfunction occurs in approximately 7% of patients on IFN therapy.

Ribavirin has been assigned to category X by the FDA and is not recommended for use in pregnancy. Significant teratogenic and/or embryocidal effects have been demonstrated in all animal species exposed to ribavirin. It is contraindicated in pregnancy and in the male partners of women who are pregnant. In the Ribavirin Registry, 6.1% of women who received ribavirin at some point during their pregnancy had offspring with birth defects [55]. Given the evidence from animal data, women with co-infection should discontinue HCV therapy as soon as pregnancy is confirmed. Extreme care must be taken to avoid pregnancy during therapy and for the 6 months after completion of therapy in both female patients and in female partners of male patients who are taking ribavirin therapy. At least two reliable forms of effective contraception must be utilised. The outcome of an exposed pregnancy should be reported prospectively to the Ribavirin Pregnancy Registries (email: pregnancyregistries@increasearch.com).

There are limited data on the possible teratogenicity of DAA-based IFN-free therapy without ribavirin. The