BHIVA
British HIV Association

British HIV Association guidelines for the management of HIV in pregnancy and postpartum 2018

Guideline writing group

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1. Scope and purpose

The overall purpose of these guidelines is to provide guidance on best clinical practice in the treatment and management of women living with the human immunodeficiency virus (HIV) in the UK during pregnancy and postpartum, and their infants. The scope includes guidance on the use of antiretroviral therapy (ART) both to prevent vertical transmission of HIV and for the welfare of the woman and her baby, guidance on mode of delivery and recommendations in specific patient populations where other factors need to be taken into consideration, such as co-infection with other agents. The guidelines are aimed at clinical professionals directly involved with, and responsible for, the care of pregnant women living with HIV. The 2018 guidelines have identified significant developments that have either led to a change in recommendation or a change in the strength of recommendation. More detail has been added in areas of controversy, particularly breastfeeding. New data that simply support the existing data have not routinely been included in this revision. A new section on the postpartum management of women has been added. Of note, the term 'HIV' refers to HIV-1 throughout these guidelines, unless HIV-2 is specified.

1.1 Guideline development process

The British HIV Association (BHIVA) revised and updated the Association's guideline development manual in 2011 (www.bhiva.org/BHIVA-guideline-development). BHIVA has adopted the modified GRADE system for the assessment, evaluation and grading of evidence and the development of recommendations. Full details of the guideline development process including selection of the writing group and the conflict of interest policy are outlined in the manual.

The guidelines were commissioned by the BHIVA Guidelines Subcommittee; the Subcommittee nominated the Chair and Vice-chair of the writing group, who then nominated a writing group of experts in the field based on their knowledge, expertise and freedom from conflicts of interest (the conflict of interest statements of members of the writing group are available and have been published along with these guidelines on the BHIVA website). In addition, BHIVA members were asked to volunteer as authors for the guidelines, again based on their knowledge, expertise and freedom from conflicts of interest.

The scope, purpose and guideline topics were agreed by the writing group. Questions concerning each guideline topic were drafted and a systematic literature review undertaken by an information scientist. Details of the search questions (including the definition of populations, interventions, comparators and outcomes) are outlined in Appendix 1, and details of the search strategy can be found on the BHIVA website (www.bhiva.org/pregnancy-guidelines). The literature searches for the 2018 guidelines covered the period from July 2013 to July 2017 (with an additional search on ART in pregnancy from July 2017 to May 2018 in response to consultation comments), and included abstracts from selected conferences. For each topic and healthcare question, evidence was identified and evaluated by writing group members with expertise in the field. Using the modified GRADE system (see Appendix 2), members were responsible for assessing and grading the quality of evidence for predefined outcomes across studies and developing and grading the strength of recommendations. All writing group members received training in use of the modified GRADE criteria before assessing the evidence.

Owing to the lack of data from randomised controlled trials in several important areas, the writing group was unable to assign high grades (in areas such as mode of delivery); however, recommendations have been given on best practice where decisions need to be made on the balance of available evidence. Recommendations are summarised and numbered sequentially within the text.

The guidelines were published online for public consultation and external peer review was commissioned, comments from which resulted in minor revision prior to final approval by the writing group.

1.2 Patient involvement

BHIVA views the involvement of patient and community representatives in the guideline development process as both important and essential. The writing group included two patient representatives who were involved in all aspects of the guideline development.

1.3 Dissemination and implementation

The following measures have been/will be undertaken to disseminate and aid implementation of the guidelines:

- E-publication on the BHIVA website and in the journal *HIV Medicine*;
- Publication in *HIV Medicin*e;
- Shortened version including concise summary of recommendations;
- E-learning module accredited for CME;
- Educational slide set to support local and regional educational meetings;
- National BHIVA audit programme;
- Presentation of significant changes and additions at a BHIVA national conference.

1.4 Summary of guideline update and date of next review

There have been some changes in recommendations.

- Prevalence data on HIV in pregnancy: updated.
- Infant feeding: updated advice including new data on breastfeeding and the emotional impact of not breastfeeding on women. The use of cabergoline in non-breastfeeding women is also discussed.
- Psychosocial care: section 4 on The psychosocial care of women living with HIV during and after pregnancy has been expanded and its position moved within the guidelines to reflect its importance.
- Safety: new data have been included on tenofovir DF, raltegravir, rilpivirine, dolutegravir, elvitegravir and cobicistat.
- Prescribing: all women (including elite controllers) are recommended to start on treatment and remain on lifelong treatment.
- Infant post-exposure prophylaxis (PEP): length of infant PEP has been shortened where risk of vertical transmission is VERY LOW.
- Hepatitis: information has been added on tenofovir alafenamide for hepatitis B virus (HBV) infection and on direct-acting agents for hepatitis C virus (HCV) infection.
- A new section has been added on the postpartum management of women living with HIV.

We aim to revise these guidelines by 2021. In the meantime, the writing group will confer at least annually to consider new information from high-quality studies and will issue revisions or updates should clinically important and relevant data become available.

2. Recommendations and auditable outcomes

2.1 Recommendations

Section 4. The psychosocial care of women living with HIV during and after pregnancy

4.1 Psychosocial issues around HIV and pregnancy

4.1.1	Antenatal HIV care should be delivered by a multidisciplinary team (MDT).	1D
4.1.2	We recommend that pregnant women living with HIV are offered peer support where available.	1B

4.2 Perinatal mental health assessment

4.2	Assessment of antenatal and postnatal depression should be undertaken at booking, and 4–6 weeks postpartum and 3–4 months postpartum in accordance with National Institute for Care and Health Excellence (NICE) guidelines.	1D

Section 5. Screening and monitoring of pregnant women living with HIV

5.1 Sexual health screening

5.1.1	Sexual health screening is recommended for pregnant women newly diagnosed with HIV.	1B
5.1.2	For women living with HIV and already engaged in HIV care who become pregnant, sexual health screening is suggested.	2C
5.1.3	Genital tract infections should be treated according to British Association for Sexual Health and HIV (BASHH) guidelines.	1B

5.2 Laboratory monitoring of pregnant women living with HIV

5.2.1	Pregnant women who are newly diagnosed with HIV do not require any additional baseline investigations compared with non-pregnant women living with HIV other than those routinely performed in the general antenatal clinic.	1D
5.2.2	HIV resistance testing should be completed and results available prior to initiation of treatment, except for late-presenting women (after 28 weeks). Women should be encouraged to continue combination (c)ART post-delivery but, where they chose to stop cART, a further resistance test is recommended to ensure that mutations are not missed with reversion during the off-treatment period.	1D
5.2.3	In women conceiving on cART there should be a minimum of one CD4 cell count at baseline and one at delivery.	2D
5.2.4	In women who commence cART in pregnancy, a CD4 cell count should be performed as per routine initiation of cART with the addition of a CD4 count at delivery even if starting at CD4 >350 cells/mm^3.	1C
5.2.5	In women who commence cART in pregnancy, an HIV viral load should be performed 2–4 weeks after commencing cART, at least once every trimester, at 36 weeks and at delivery.	1C

5.2.6	In women commencing cART in pregnancy, liver function tests (LFTs) should be performed as per routine initiation of cART and then with each routine blood test.	1C
5.2.7	In the event that a woman who has initiated cART during pregnancy has not suppressed plasma viral load to <50 HIV RNA copies/mL, the following interventions are recommended: • Review adherence (including a full exploration of potential impacting factors) and concomitant medication; • Perform resistance test if appropriate; • Consider therapeutic drug monitoring (TDM); • Optimise to best regimen; • Consider intensification.	1C

Section 6. Current issues on the use of ART in pregnancy and pregnancy outcomes

6.1 Conceiving on cART

6.1.1	It is recommended that women conceiving on an effective cART regimen should continue this treatment.	1B
	Exceptions are: • Non-standard regimens, for example protease inhibitor (PI) monotherapy; • Regimens that have been demonstrated to show lower pharmacokinetics in pregnancy such as darunavir/cobicistat and elvitegravir/cobicistat, or where there is an absence of pharmacokinetic data such as for raltegravir 1200 mg once daily (od) (should be administered 400 mg twice daily [bd]). These should be modified to include (depending on tolerability, resistance and prior antiretroviral history) one or more agents that cross the placenta. A woman conceiving on dolutegravir should see her physician as soon as possible to discuss current evidence on neural tube defects.	2D

6.2 Woman is not already on cART: when to start

6.2.1	All pregnant women, including elite controllers, should start ART during pregnancy and be advised to continue lifelong treatment.	1A
6.2.2	All women not on cART should commence cART: • As soon as they are able to do so in the second trimester where the baseline viral load ≤30,000 HIV RNA copies/mL; • At the start of the second trimester, or as soon as possible thereafter, in women with a baseline viral load of 30,000–100,000 HIV RNA copies/mL; • Within the first trimester if viral load >100,000 HIV RNA copies/mL and/or CD4 cell count is less than 200 cells/mm^3. All women should have commenced cART by week 24 of pregnancy.	1C

6.3 Woman is not already on cART: what to start

6.3.1	Women are recommended to start tenofovir DF or abacavir with emtricitabine or lamivudine as a nucleoside backbone.	2C

6.3.2	It is recommended that the third agent in cART should be efavirenz or atazanavir/r, as these are agents with the most safety data in pregnancy.	1C
	Rilpivirine (25 mg od), raltegravir (400 mg bd) or darunavir/r (600/100 mg bd) may be used as alternatives.	1C
	Darunavir/r should be prescribed at the twice daily dose (600/100 mg bd) if known resistance, and consideration should be given to using this higher dose if darunavir is initiated in pregnancy.	2C
	Dolutegravir (50 mg od) may be considered after 8 weeks' gestation which must be confirmed.	1C
	Zidovudine monotherapy is not recommended and should only be used in women declining cART with a viral load of <10,000 HIV RNA copies/mL and willing to have a caesarean section (CS).	1A
	PI monotherapy, tenofovir alafenamide, darunavir/cobicistat and elvitegravir/cobicistat are not recommended in pregnancy.	1C
6.3.3	It is recommended that an integrase inhibitor-based regimen be considered as the third agent of choice in patients: • With high baseline viral load (>100,000 HIV RNA copies/mL); Where cART is failing to suppress the virus.	 2C 1C

6.4 Late-presenting woman not on treatment

6.4.1	A woman who presents after 28 weeks should commence cART without delay.	1B
6.4.2	If the viral load is unknown or >100,000 copies/mL, a three- or four-drug regimen that includes raltegravir is suggested.	2D
6.4.3	Management of an untreated woman presenting in labour at term. • All women should be given a stat dose of nevirapine 200 mg;	 1B
	• and commence oral zidovudine 300 mg and lamivudine 150 mg bd;	1B
	• and raltegravir 400 mg bd;	2D
	• and receive intravenous zidovudine for the duration of labour. Please also see section 9.1.3 for HIGH-RISK neonatal management.	2D
6.4.4	In preterm labour, if the infant is unlikely to be able to absorb oral medications consider the addition of double-dose tenofovir DF to the woman's treatment described in recommendation 6.7.3 to further load the infant.	2C
6.4.5	Women presenting in labour/with spontaneous rupture of the membranes (SROM)/requiring delivery without a documented HIV result must be advised to have an urgent HIV test. A reactive/positive result must be acted upon immediately, with initiation of interventions to prevent vertical transmission of HIV without waiting for further/formal serological confirmation.	1D

6.7 Pharmacokinetics of antiretrovirals in pregnancy

6.7	No routine dose alterations are recommended for antiretrovirals during pregnancy if used at standard adult licensed doses, apart from raltegravir, which should be given as 400 mg bd.	1C
	Consider TDM particularly if combining tenofovir DF and atazanavir/r.	2C
	If dosing off licence, consider switching to standard dosing throughout pregnancy or regular TDM.	2C

6.8 Stopping ART postpartum

6.8.1	Stopping ART after delivery is not recommended; women who wish to stop ART should be counselled on the risks and managed as per the BHIVA guidelines for the treatment of HIV-positive adults with antiretroviral therapy.	1B

6.9 HIV-2

6.9.1	Case discussion with experts with experience of managing HIV-2 is recommended for all women.	1D
6.9.2	A boosted PI-based regimen such as twice daily darunavir/r is recommended in women with HIV-2.	1C

Section 7. HIV and hepatitis virus co-infections

7.1 Hepatitis B virus (HBV)

7.1.1	On diagnosis of new HBV infection, confirmation of viraemia with quantitative HBV DNA, 'e' antigen status as well as hepatitis A virus (HAV), HCV and hepatitis D virus (HDV) screening and tests to assess hepatic inflammation/fibrosis and liver function are recommended.	1C
7.1.2	LFTs should be repeated at 2 and 4 weeks after commencing ART to detect evidence of hepatotoxicity or immune reconstitution inflammatory syndrome (IRIS) and then monitored regularly throughout pregnancy and postpartum.	1C
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
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.	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 lamivudine/emtricitabine-resistant HBV.	1C
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	2D

	equally safe during pregnancy and hence is the preferred option to be given with tenofovir DF in women with HBV and HIV.	
7.1.9	In all HAV non-immune women with HBV and HIV, HAV vaccination 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
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
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

7.2 Hepatitis C virus (HCV)

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
7.2.3	Women with both HCV and HIV should not be treated for HCV with ribavirin-based directly acting antiviral (DAA) therapies, and all women who discover they are pregnant while receiving treatment should discontinue HCV therapy immediately.	1B
7.2.4	Women with both HCV and HIV of child-bearing age wishing to become pregnant should be expedited to have DAA-based HCV therapy.	2D
7.2.5	Vaccination against HBV is recommended for all women with both HCV and HIV after the first trimester, unless already immune.	1C
7.2.6	In all HAV non-immune women with both HCV and HIV, HAV vaccination 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
7.2.7	In the absence of obstetric complications, normal vaginal delivery can be recommended if the woman is receiving effective cART for HIV, irrespective of HCV viral load.	2C
7.2.8	cART should be continued postpartum in all women with both HCV and HIV regardless of HCV viraemia, fibrosis stage or CD4 cell count.	1A

Section 8. Obstetric management

8.1 Antenatal management

8.1.1	Fetal ultrasound imaging should be performed as per national guidelines regardless of maternal HIV status.	1D
8.1.2	The combined screening test for fetal aneuploidies and non-invasive prenatal testing (NIPT) for those who screen as high risk is recommended as this has the best sensitivity and specificity and will minimise the number of women who may need invasive testing.	1A
8.1.3	Invasive prenatal diagnostic testing should not be performed until after the HIV status of the woman is known, and should ideally be deferred until HIV viral load has been adequately suppressed to <50 HIV RNA copies/mL.	1C
8.1.4	If not on cART and the invasive diagnostic test procedure cannot be delayed until viral suppression is achieved, it is recommended that women should commence cART to include raltegravir and be given a single dose of nevirapine 2–4 hours prior to the procedure.	1D
8.1.5	External cephalic version (ECV) can be offered to women with plasma viral load <50 HIV RNA copies/mL.	2D

8.2 Mode of delivery

For women taking cART, a decision regarding recommended mode of delivery should be made after review of plasma HIV viral load results at 36 weeks.

8.2.1	For women with a plasma viral load of <50 HIV RNA copies/mL at 36 weeks, and in the absence of obstetric contraindications, planned vaginal delivery should be supported.	1C
8.2.2	For women with a plasma viral load of 50–399 HIV RNA copies/mL at 36 weeks, pre-labour CS (PLCS) should be considered, taking into account the actual viral load, the trajectory of the viral load, length of time on treatment, adherence issues, obstetric factors and the woman's views.	1C
8.2.3	Where the viral load is ≥400 HIV RNA copies/mL at 36 weeks, PLCS is recommended.	1C
8.2.4	In women for whom a vaginal delivery has been planned and labour has commenced, obstetric management should follow the same guidelines as for the HIV-negative population, apart from duration of ruptured membranes (see section 8.3).	1C
8.2.5	Vaginal birth after CS (VBAC) can be offered to women with a viral load <50 HIV RNA copies/mL.	1D
8.2.6	Where the indication for CS is the prevention of vertical transmission, CS should be undertaken at between 38 and 39 weeks' gestation.	1C
	Where PLCS is undertaken only for obstetric indications and plasma viral load is <50 HIV RNA copies/mL, the usual obstetric considerations apply and the CS will usually be performed after 39 weeks' gestation.	1C

8.3 Management of SROM

8.3.1	In all cases of term pre-labour SROM, delivery within 24 hours should be the aim.	1C
8.3.2	If maternal HIV viral load is <50 HIV RNA copies/mL, immediate induction or augmentation of labour is recommended in women who have pre-labour SROM, with a low threshold for treatment of intrapartum pyrexia. Obstetric management should aim for delivery within 24 hours of SROM.	1C
8.3.3	For women with SROM and a last measured plasma viral load of 50–399 HIV RNA copies/mL, immediate CS is recommended, but should take into account the actual viral load, the trajectory of the viral load, length of time on treatment, adherence issues, obstetric factors and the woman's views.	1C
8.3.4	For women with SROM and maternal HIV viral load ≥400 HIV RNA copies/mL, immediate CS is recommended.	1C
8.3.5	The management of preterm SROM at ≥34 weeks is the same as that of term SROM, except that women at 34–37 weeks' gestation will require group B streptococcus prophylaxis in line with national guidelines.	1C
8.3.6	When premature SROM occurs at <34 weeks: • Intramuscular steroids should be administered in accordance with national guidelines; • Where HIV viral load is not controlled, this should be optimised; • There should be multidisciplinary discussion about the timing and mode of delivery.	1C

8.4 Use of intrapartum intravenous infusion of zidovudine

8.4.1	Intrapartum intravenous zidovudine infusion is recommended in the following circumstances:	
	For women with a viral load >1000 HIV RNA copies/mL plasma who present in labour or with SROM or who are admitted for PLCS.	1C
	For untreated women presenting in labour or with SROM in whom the current viral load is not known;	1C
	The use of intrapartum intravenous zidovudine infusion can be considered in women on cART with a plasma HIV viral load between 50 and 1000 HIV RNA copies/mL.	1C

8.5 Place of birth

8.6.1	All women living with HIV are recommended to give birth in a facility that has direct access to paediatric care (i.e. a co-located birth centre or obstetric unit).	1D

8.6 Water birth

8.7.1	There is scant safety evidence to support water births in women living with HIV; however, women who choose a water birth should be supported to achieve this where the viral load is <50 HIV RNA copies/mL.	1D

Section 9. Neonatal management

9.1 Infant PEP

See Appendix 3 for dosing recommendations

9.1.1	VERY LOW RISK	1C
	Two weeks of zidovudine monotherapy is recommended if all the following criteria are met: • The woman has been on cART for longer than 10 weeks; AND • Two documented maternal HIV viral loads <50 HIV RNA copies/mL during pregnancy at least 4 weeks apart; AND • Maternal HIV viral load <50 HIV RNA copies/mL at or after 36 weeks.	
9.1.2	LOW RISK	1C
	Extend to 4 weeks of zidovudine monotherapy: • If the criteria in 9.1.1 are not all fulfilled but maternal HIV viral load is <50 HIV RNA copies/mL at or after 36 weeks; • If the infant is born prematurely (<34 weeks) but most recent maternal HIV viral load is <50 HIV RNA copies/mL.	
9.1.3	HIGH RISK	1C
	Use combination PEP if maternal birth HIV viral load is known to be or likely to be >50 HIV RNA copies/mL on day of birth, if uncertainty about recent maternal adherence or if viral load is not known.	
9.1.4	Neonatal PEP should be commenced as soon as possible after birth, and at least within 4 hours.	1D
9.1.5	In the context of known maternal resistance to zidovudine with VERY LOW or LOW RISK, zidovudine monotherapy is still recommended for infant PEP.	1D
9.1.6	If HIGH RISK (combination PEP indicated) and there is a history of documented maternal zidovudine and/or nevirapine resistance, seek expert advice. If advice is not immediately available, commence standard three-drug PEP (zidovudine, lamivudine and nevirapine) until guidance is provided.	1D

9.1.8 Infant PEP and HIV-2

9.1.8	If a woman is known to have HIV-2 infection, follow the above advice as for HIV infant PEP but if HIGH RISK (combination PEP indicated) nevirapine will not be effective. Seek expert advice. If advice is not immediately available, commence zidovudine, lamivudine and raltegravir until guidance is available (see Appendix 3).	2C

9.1.9 Infant PEP beyond 4 weeks

9.1.9	Infant PEP should not be given beyond 4 weeks.	1C
	PEP should not be restarted unless significant subsequent exposure (e.g. maternal viral load detectable during breastfeeding). Seek expert advice regarding need for PEP following breast milk exposure during an episode of maternal viraemia.	1D

9.2 Pneumocystis pneumonia (PCP) prophylaxis

9.2.1	Co-trimoxazole prophylaxis is recommended from 1 month of age if HIV PCR screening is positive at any stage or if the infant is confirmed to be diagnosed with HIV. This should only be stopped if HIV infection is subsequently excluded.	1C

9.3 Immunisation

9.3.1	Immunisations should be given as per the national schedule outlined in the Green Book.	1C
9.3.2	Rotavirus vaccine is not contraindicated (unless HIV diagnosis has been confirmed and infant is severely immunosuppressed).	1C
9.3.3	If there is VERY LOW or LOW RISK of HIV transmission and BCG at birth is indicated as per UK guidelines, this should not be delayed.	1D

9.4 Infant feeding

9.4.1	In the UK and other high-income settings, the safest way to feed infants born to women with HIV is with formula milk, as there is no on-going risk of HIV exposure after birth. We therefore continue to recommend that women living with HIV feed their babies with formula milk.	1D
9.4.2	Abstaining from breastfeeding can have financial and psychological repercussions for women, requiring support from the HIV MDT.	1C
	Women advised not to breastfeed for their baby's health should be provided with free formula feed to minimise vertical transmission of HIV.	1D

9.4.3 Suppression of lactation

9.4.3	Women not breastfeeding their infant by choice, or because of viral load >50 HIV RNA copies/mL, should be offered cabergoline to suppress lactation.	1C

9.4.4 Choosing to breastfeed in the UK

9.4.4	Women who are virologically suppressed on cART with good adherence and who choose to breastfeed should be supported to do so, but should be informed about the low risk of transmission of HIV through breastfeeding in this situation and the requirement for extra maternal and infant clinical monitoring.	1D
	When a woman decides to breastfeed, she and her infant should be reviewed monthly in clinic for HIV RNA viral load testing during and for 2 months after stopping breastfeeding.	1D
	Maternal cART (rather than infant pre-exposure prophylaxis [PrEP]) is advised to minimise HIV transmission through breastfeeding and safeguard the woman's health.	1D

9.5 Diagnosis of infant HIV status

9.5.1	Molecular diagnostics for HIV infection should be performed on the following occasions.	
9.5.1.1	Non-breastfed infants:	1C
	• During the first 48 hours and prior to hospital discharge; • If HIGH RISK, at 2 weeks of age; • At 6 weeks (or at least 2 weeks after cessation of infant prophylaxis*); • At 12 weeks (or at least 8 weeks after cessation of infant prophylaxis*); • On other occasions if additional risk; • HIV antibody testing for seroreversion should be checked at age 18–24 months. *BHIVA guidelines on duration of PEP have changed for VERY LOW-RISK infants, see section 8.1.	
9.5.1.2	Breastfed infants:	
	• During the first 48 hours and prior to hospital discharge;	1C
	• At 2 weeks of age;	1D
	• Monthly for the duration of breastfeeding;	1D
	• At 4 and 8 weeks after cessation of breastfeeding;	1D
	• HIV antibody testing for seroreversion should be checked at age 18–24 months.	1C

9.6 Neonatal management in maternal hepatitis co-infection

9.6.1	Follow national guidance for management of maternal HBV in pregnancy and for prevention of transmission of HIV to the infant (see also section 7.1).	1D
9.6.2	Follow usual practice for investigation and management of maternal HCV in pregnancy (see also section 7.2).	1D

9.7 HIV exposed but uninfected (HEU)

9.7.1	In light of evidence for possible increased infectious morbidity in HIV exposed but uninfected (HEU) children, timely routine vaccination should be ensured and general practitioners (GPs), health visitors and secondary care physicians should be made aware of possible increased risk in order to inform decisions when assessing risk in primary care.	1D

Section 10. Postpartum management of women

10.1 Antiretroviral therapy

10.1.1	All women are recommended to continue cART postpartum.	1A

10.2 Support services

10.2.1	Women should have their support needs assessed postpartum and be referred to appropriate services in the Trust, community and/or voluntary groups without delay.	1D

10.3 Postnatal follow-up of women

10.3.1	All women should be reviewed in the postnatal period by a named member of the MDT within 4–6 weeks.	1C

10.4 Mental health assessment and support

10.4.1	Women should have their mental health needs assessed postpartum and those assessed as having mental health issues should be referred to appropriate services in the Trust, community and/or voluntary groups without delay.	1D

10.5 Contraception

10.5.1	Contraceptive needs should be discussed with all women, and ART may be changed to optimise a woman's contraception choice as long as the ART prescribed is fully active against the viral genotype.	1D

10.6 Cervical cytology

10.6.1	Cytology should be scheduled 3 months post-delivery as per the Guidelines for the NHS Cervical Screening Programme 2016.	1C

10.7 Testing of partner and/or older children

10.7.1	For the woman newly diagnosed with HIV in pregnancy, testing of her partner and/or other children should be completed.	1D

2.2 Auditable outcomes

1	Proportion of pregnant women newly diagnosed with HIV having a sexual health screen.
2	Proportion of newly diagnosed women, requiring cART for their own health, starting treatment within 2 weeks of diagnosis.
3	Proportion of women who have commenced ART by beginning of week 24 of pregnancy.
4	Proportion of women with a baseline HIV viral load ≥30,000 HIV RNA copies/mL plasma and who do not require treatment for themselves commencing temporary cART at the beginning of the second trimester (by beginning of 16 weeks' gestation).
5	Proportion of women presenting in labour/with SROM/requiring delivery without a documented HIV result having an urgent HIV test result documented and this reactive/positive result acted upon immediately with initiation of the interventions to prevent vertical transmission without waiting for further/formal serological confirmation.
6	Proportion of women with HBV/HIV co-infection who have LFTs performed 2 weeks after commencing cART to detect evidence of antiretroviral hepatotoxicity or IRIS.
7	Proportion of women with HCV/HIV co-infection who have LFTs performed 2 weeks after commencing cART to detect evidence of antiretroviral hepatotoxicity or IRIS.
8	Proportion of women who have invasive prenatal diagnostic testing performed before their HIV status is known.
9	Proportion of emergency CSs performed and their indication.
10	Proportion of infants <72 hours old, born to untreated women living with HIV, initiating three-drug therapy within 2 hours of delivery.
11	Proportion of routine neonatal PEP commenced within 4 hours of delivery.
12	Proportion of infants born to women living with HIV who have HIV antibody testing for seroreversion performed at age 15–24 months.
13	Proportion of infants reviewed postpartum by 6 weeks.
14	Proportion of mothers reviewed postpartum by 6 weeks.
15	Proportion with documented mental health assessment at booking, and at 4–6 weeks postpartum.

3. Introduction

A key goal of managing HIV in pregnancy and postpartum is to optimise a woman's own health. Furthermore, one of the major successes in the management of individuals living with HIV has been the prevention of vertical transmission of HIV. With the widespread implementation of routine antenatal screening for HIV, vertical transmission is now a rare occurrence in the UK. Despite few recent randomised controlled trials of the use of ART in pregnancy or obstetric intervention, practice continues to evolve. This is largely informed by observational data, theoretical considerations and expert opinion.

At the outset, the aim of the writing group was to make these guidelines as clinically relevant and as practical as possible. The writing group drew up a list of questions reflecting day-to-day practice and queries. It was acknowledged that the level of evidence for many of these topics was poor but recognised that there was a need to provide guidance. These guidelines have expanded on all areas relevant to the management of HIV in pregnancy and the postpartum period. The guidelines are intended to inform and aid healthcare workers in the management of pregnancy in the context of HIV. They are not intended to be prescriptive or restrictive and it is recognised that situations will arise where the optimum management may deviate from these recommendations and new data will emerge to better inform practice. We recognise that a small number of trans and non-binary people living with HIV will also experience pregnancy. We use the term 'woman' or 'women' in these guidelines for brevity, on the understanding that guidance also applies to trans and non-binary individuals.

Particular areas of focus have been psychosocial, infant feeding, neonatal and postnatal management. We have expanded, renamed and moved the section on the psychosocial care of women living with HIV during and after pregnancy. We have emphasised the need for antenatal HIV care to be delivered by an MDT, the precise composition of which will vary. We have also recommended that assessment of antenatal and postnatal depression be undertaken at booking, and 4–6 weeks postpartum and 3–4 months postpartum in accordance with NICE guidelines. We have updated infant feeding advice to include new data on breastfeeding and the emotional impact that not breastfeeding may have on a woman. We discuss the use of cabergoline in non-breastfeeding women. Length of infant PEP has been stratified according to risk of transmission being VERY LOW, LOW or HIGH according to maternal viral load and ART. PEP has been shortened to 14 days where risk of vertical transmission is VERY LOW. We have added a section on the postpartum management of women living with HIV.

An increasing number of women are aiming for and achieving a vaginal delivery but the rate of emergency CSs has increased. It is hoped that the recommendations contained within these guidelines will enable a further increase in the proportion of vaginal deliveries and a reduction in the number of emergency CSs. Linked to this is the proposed starting gestation for women temporarily taking combination antiretroviral therapy (cART) in pregnancy, which has been brought forward depending on baseline viral load. It is anticipated that this will result in a larger proportion of women achieving a viral load <50 HIV RNA copies/mL by 36 weeks' gestation, thereby allowing them to plan for a vaginal delivery.

Additional guidance has been provided with regard to conception on cART, the choice of specific drugs or drug classes and the management of women with HBV or HCV co-infection. For the first time these guidelines have addressed the issue of continuation of cART postpartum in women. The paediatric section provides further guidance on infant PEP, drug dosing and safety. There is a clear urgent need for neonatal preparations for a wider variety of antiretroviral drugs because the current options, particularly in the case of maternal viral resistance, are limited.

In key areas, the National Study of HIV in Pregnancy and Childhood (NSHPC) informs the management of HIV in pregnancy through comprehensive data collection, collation and analysis, and the need to interrogate the data continues as practice changes.

3.1 UK prevalence and epidemiology of HIV in pregnancy, antenatal screening and risk of transmission

Information about the management, epidemiology and outcome of HIV in pregnancy in the UK is available from the National Study of HIV in Pregnancy and Childhood (NSHPC: www.ucl.ac.uk/nshpc). Other vital data sources are Public Health England's HIV surveillance systems (www.gov.uk/government/collections/hiv-surveillance-data-and-management) and the NHS infectious diseases in pregnancy screening (IDPS) programme (www.gov.uk/topic/population-screening-programmes/infectious-diseases-in-pregnancy).

Prevalence of HIV among women giving birth in the UK was monitored for over 20 years through an unlinked anonymous survey, based on residual neonatal dried blood spots, which provided an estimate of HIV prevalence in women giving birth regardless of whether they had been diagnosed [1]. By 2011, the last year for which data were published, the survey covered about 400,000 births in England, and prevalence overall was 2.2 per 1000 women giving birth, and highest in London at 3.5 per 1000. When the survey was discontinued in Scotland in 2008, prevalence was about 0.9 per 1000 women. Among women from sub-Saharan Africa giving birth, overall prevalence was relatively stable in the last 10 years of the survey at 2–3%; among UK-born women there was a gradual increase over the decade from 0.3 to 0.5 per 1000 [2].

National data on HIV in the general population show that around 20,000 women were living with diagnosed HIV in England in 2016, and an estimated 1300 with undiagnosed infection [3]. Between 2012 and 2016 the number of women diagnosed each year with HIV in the UK declined from around 1700 to 1200, and this was particularly marked among women from sub-Saharan Africa. The number of diagnosed pregnant women reported to the NSHPC also declined from a peak of over 1450 in 2010 to around 1100 in 2015, and a little lower in 2016; about three-quarters of women are from sub-Saharan Africa and around 15% were born in the UK or Ireland [4].

Major progress has been made in the UK, as elsewhere, in reducing the rate of vertical transmission of HIV. In 1993, when interventions were virtually non-existent, the vertical transmission rate among diagnosed women was 25.6% [5]. In the mid-1990s only about one-third of pregnant women living with HIV were diagnosed, and most of these women were aware of their status before they became pregnant, with very few being diagnosed antenatally. Once interventions to reduce the risk of vertical transmission were available it became clear that antenatal screening and early detection of maternal infection was vital; the universal offer and recommendation of antenatal HIV testing was introduced in England in 2000 and throughout the UK by 2002. National uptake rates improved year on year, and uptake has exceeded 97% since 2011 [6]. Antenatal screening guidance for laboratories and healthcare providers is regularly updated and available at www.gov.uk/government/collections/infectious-diseases-in-pregnancy-screening-clinical-guidance.

Between 2000 and 2006, with high antenatal detection rates and uptake of effective interventions, the overall transmission rate from diagnosed women was 1.2%, and less than 1% among women who had received at least 14 days of ART. Among more than 2000 women delivering on cART with an undetectable viral load, there were only three transmissions (transmission rate 0.1%) [7]. These very low transmission rates persist, reducing to an estimated 0.57% [8] in 2007–2011, and 0.27% in 2012–2014 [9]. In 2012–2014, 85% of deliveries were to women who already knew their HIV status before they became pregnant, and about 50% of women were having a second or subsequent baby since their HIV diagnosis. Almost all women received cART during pregnancy, while the proportion conceiving on cART has increased from 40% in 2007–2011 to 60% in 2012–2014. The proportion of vaginal deliveries also increased, from 37% to 46%, but emergency CS rates remain high, at around 20–25% of deliveries [4,9]. An increasing proportion of pregnancies are in women aged over 40, rising from 2% in 2000–2004 to 9% in 2010–2014 [10], and at the same time a growing cohort of pregnant women with perinatally acquired HIV is emerging [11].

3.2 HIV infection in children

The number of children (aged under 16) diagnosed with vertically acquired HIV infection in the UK increased from around 70 diagnoses a year in the early 1990s to a peak of 164 in 2003, and then declined to 74 in 2011 and 29 in 2015 [3].

During the last decade about two-thirds of children newly diagnosed in the UK were born abroad. However, despite the high uptake of antenatal screening and effective interventions, perinatal infections still occur in the

UK. The number remained stable at about 30–40 a year between 2001 and 2007. However, as the total number of births to women living with HIV stabilised and then declined, and uptake and impact of screening and interventions improved, this number reduced substantially; it is now fewer than five per year [3,9].

An audit of the circumstances surrounding nearly 90 perinatal transmissions in England in 2002–2005 demonstrated that over two-thirds of these infants were born to women who had not been diagnosed prior to delivery [12]. About half of these undiagnosed women had declined antenatal testing. A smaller proportion had tested negative and had presumably seroconverted in pregnancy, or while still breastfeeding. The findings of a subsequent UK audit of perinatal transmissions between 2006 and 2013 were similar, although the number of transmissions (108 identified by the end of March 2014) had substantially reduced [13]. Both audits also revealed that a high proportion of these women faced multiple issues such as comorbidities, insecure accommodation, immigration concerns, intimate partner violence and other challenging social circumstances during and after pregnancy, and required multidisciplinary support.

Among children living with HIV with follow-up care in the UK and Ireland, the rate of AIDS and mortality combined declined from 13.3 cases per 100 person-years before 1997 to 2.5 per 100 person-years in 2003–2006 [14]. With improving survival, the median age of children in follow-up increased from 5 years in 1996 to 12 years in 2010, and over 800 young people had transferred to adult care by the end of 2015 [4].

3.3 Reporting and long-term follow-up

Aggregated data tables from the UK and Ireland of antiretroviral exposure and congenital malformations are regularly sent to the Antiretroviral Pregnancy Registry (APR).

Individual prospective reports should also be sent to the APR antenatally with postnatal follow-up (Antiretroviral Pregnancy Registry Research Park, 1011 Ashes Drive, Wilmington, NC 28405, USA; UK Tel: 0800 5913 1359; Fax: 0800 5812 1658; for forms visit: www.apregistry.com).

3.4 National Study of HIV in Pregnancy and Childhood (NSHPC)

NSHPC is the surveillance system for obstetric and paediatric HIV for the UK and Ireland, based at the UCL Great Ormond Street Institute of Child Health, London. Children living with HIV and children born to women living with HIV are reported through the British Paediatric Surveillance Unit of the Royal College of Paediatrics and Child Health, or in the case of some units with large caseloads direct to the NSHPC. Diagnosed pregnant women are reported prospectively through a parallel reporting scheme originally established under the auspices of the Royal College of Obstetricians and Gynaecologists. Longer-term data on infected children are subsequently collected through the Collaborative HIV Paediatric Study (CHIPS). It is the responsibility of clinicians caring for women living with HIV and their children to report cases prospectively to the NSHPC. For further information see the NSHPC website (see section 3.1) or the CHIPS website (www.chipscohort.ac.uk/), or email the NSHPC (nshpc@ucl.ac.uk).

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4. The psychosocial care of women living with HIV during and after pregnancy

4.1 Psychosocial issues around HIV and pregnancy

4.1.1	Antenatal HIV care should be delivered by a multidisciplinary team (MDT).	1D
4.1.2	We recommend that pregnant women living with HIV are offered peer support where available.	1B

First, it is important to acknowledge that the majority of women living with HIV engage well in care during pregnancy, resulting in the low rates of vertical transmission outlined in section 3. This is to be celebrated. Furthermore, for many women pregnancy and early motherhood is a joyful time. However, some women may experience psychosocial challenges during and/or after pregnancy. Trans women and non-binary individuals may experience challenges as a result of stigma and discrimination (including within healthcare services), and the lack of trans-inclusive antenatal and obstetric services [1]. Therefore they may require particular support.

HIV is associated with a higher risk of poor mental health [2]. Data from the UK-based ASTRA study reveal that the prevalence of depressive symptoms among women living with HIV is nearly 30% [3]. Furthermore, women may experience significant psychosocial barriers to accessing HIV care such as HIV-related stigma, unemployment and lack of financial resources. It is therefore important to be aware that pregnancy and the postpartum period may precipitate new psychosocial issues, or indeed exacerbate existing issues, among women living with HIV [4]. A recent national review of vertical transmissions has identified psychosocial issues such as immigration and HIV-related stigma as key contributing factors [5].

According to a systematic review of HIV and perinatal mental health, the prevalence of postnatal depression (PND) among women living with HIV in high-income settings is reported to be between 30% and 53% [6]. In the studies that include an HIV-negative comparison group, there was no evidence of an association between HIV status and PND [6]. Factors associated with PND in women living with HIV include past history of mental health issues, financial, immigration and housing concerns, lack of social support, HIV-related stigma, intimate partner violence, substance misuse and lack of support from a partner [6-8]. However there remains an absence of data on perinatal mental health among women living with HIV within a UK setting. Trial data on interventions targeting psychiatric and psychosocial outcomes in pregnant women living with HIV are also currently lacking [6].

The link between gender-based violence and HIV is well established [9]. As in the general population, women living with HIV may be at risk of intimate partner violence during pregnancy, with a lifetime prevalence rate of intimate partner violence in pregnancy estimated to be 14% in women living with HIV in the UK [10]. We therefore fully endorse NICE antenatal guidelines recommending that *all* pregnant women be asked about domestic violence [11].

4.1.1 Social issues

Many women living with HIV will have issues relating to social support and/or immigration. In both situations, it is important to identify the issues as early as possible so that women can be referred for appropriate specialist advice and support. We therefore suggest that all pregnant women living with HIV are routinely asked about their social situation as early as possible during their pregnancy.

Dispersal is an issue that may arise and is generally felt to be inappropriate in pregnant women, especially in late pregnancy or soon after delivery [12-14]. Some short-term visitors to the UK and undocumented migrants are not eligible for free secondary care on the NHS; however, since 1 October 2012, individuals living with HIV have not had to meet any residency requirement in order to access treatment. Treatment for HIV is freely available to anyone regardless of immigration status, and no hospital should refuse HIV treatment to anyone living with HIV.

Since October 2017, all antenatal, intrapartum and postnatal services are required by law to be considered 'immediately necessary'. Any service deemed 'immediately necessary' or 'urgent' cannot be denied to an individual regardless of ability to pay. However, people who are not eligible for free care on the NHS can be billed afterwards for these services.

Advice should be sought from colleagues, the General Medical Council (GMC), British Medical Association and Medical Defence Organisations in difficult cases. Advice can also be sought from organisations such as the Terrence Higgins Trust (www.tht.org.uk) or the National AIDS Trust (www.nat.org.uk). You can also contact the Doctors of the World advice line (0207 515 7534) for advice on access to healthcare in the UK.

4.1.2 Psychosocial care

A critical component in the prevention of vertical transmission of HIV is to facilitate a woman's engagement in care from an MDT that can employ medical interventions and provide appropriate holistic support. Clinicians should be mindful that clinical experience indicates that the management of issues such as adjusting to an HIV diagnosis and uncertainty during pregnancy, and robust confidentiality processes, have an impact on adherence to ART and acceptance of recommended interventions. Adherence to medication is of vital importance for the success of ART. Pregnant women may require extra support and planning in this area, especially if there are practical or psychosocial issues that may impact adversely on adherence. Referral to peer support workers, psychology support and telephone contact may all be considered [15]. Adherence can sometimes be suboptimal postpartum, resulting in viral load rebound [16]; early engagement in HIV care in the postpartum period has been shown to improve adherence [8].

Reassurance about confidentiality is extremely important, especially regarding family members and friends, who may not know the woman is living with HIV, but who are intimately involved with the pregnancy. Women from communities in which HIV is more common may be concerned about HIV 'disclosure-by-association' when discussing certain interventions, including taking medication during pregnancy, having a CS, and avoiding breastfeeding. Possible reasons such as the need to 'take vitamins', or having 'obstetric complications' and 'mastitis' may help the women feel more confident in explaining the need for certain procedures to persistent enquirers [17]. For couples where a male partner is HIV negative, advice should be provided on condom use and PEP following sexual exposure if a woman does not have an undetectable viral load [18].

The importance of informing appropriate healthcare workers about HIV status should be emphasised to women as well as the need for HIV status to be included in the birth plan wherever possible. This includes midwives, GPs, health visitors and paediatricians. The process of inpatient care should be explained clearly so that women can be supported in informing ward staff explicitly about maintaining confidentiality about HIV status, especially around visitors.

4.1.3 The antenatal HIV MDT

The minimum team should comprise an HIV specialist, obstetrician, specialist midwife and paediatrician, with the recommendation of peer and voluntary-sector support. All efforts should be made to involve the woman's GP and health visitor, with her permission. It may be necessary to involve some of the following: patient advocates, social workers, legal advocates, clinical psychologists, psychiatrists, counsellors, health advisors, Citizens Advice Bureau workers, interpreters, community midwives, pharmacists, adult and paediatric clinical nurse specialists and health visitors [19].

In settings with relatively few women living with HIV, it is still important to develop robust pathways of care with identified members of an MDT. Regular links, formal or informal, can also be established with a larger unit to provide advice and support as necessary. Good communication is vital in view of the complexity of the issues involved. An early assessment of the social circumstances of a woman given a new diagnosis of HIV is important. Patients who initially decline interventions or disengage from follow-up need to be identified and actively followed up.

Support by trained peer support workers is a valuable component of the care of a woman living with HIV and should continue into the postpartum period. Peer Mentor Mother programmes to support women living with HIV during pregnancy are well established in the UK and internationally, with positive multidimensional impacts on vulnerable women and improvements in clinical outcomes (such as adherence, prevention of vertical transmission

interventions and lower rates of depression) in randomised controlled trials [20,21]. Many newly diagnosed pregnant women are initially reluctant to engage with peer support because of fears around confidentiality; however, the great majority of women who do engage find that it becomes one of the most highly valued interventions [22,23]. We therefore strongly recommend that pregnant women are offered peer support. More information on Mentor Mothers is available at positivelyuk.org and salamandertrust.net.

4.1.4 The psychosocial care of women newly diagnosed with HIV during pregnancy

Women diagnosed with HIV for the first time during pregnancy may experience significant psychosocial stress and trauma as a result of the diagnosis in the context of pregnancy, and will therefore require the support of an MDT of experienced carers. A new HIV diagnosis may precipitate a complex mix of emotional, psychosocial, relationship, economic and, sometimes, legal issues. The newly diagnosed pregnant woman also has a relatively brief time in which to develop trust in her medical carers and attain sufficient medical knowledge of her situation to be able to make informed decisions that will affect her long-term health, as well as that of her baby and her partner. In the case of newly diagnosed HIV in pregnancy, prompt linkage to HIV care is beneficial [24], as is the offer of psychological support soon after an antenatal HIV diagnosis [25].

Confidence in telling others about an HIV diagnosis will vary from woman to woman, and there may be cultural factors that influence the patterns of telling partners and other social network members [19,26]. Talking about HIV should be encouraged in all women but should be viewed as a process that may take some time [27,28]. Talking about HIV to a family member, other than a sexual partner, should be encouraged as this has been demonstrated to reduce levels of postnatal depression [29]. There are situations in which a woman given a new diagnosis of HIV may be reluctant to share this with a current sexual partner, or appears to want to delay telling indefinitely. This can give rise to complex professional, ethical, moral and, potentially, legal situations. There is a conflict between the duty of confidentiality to the index patient and a duty to prevent harm to others. Breaking confidentiality in order to inform a sexual partner of the index patient's positive HIV status is sanctioned as a 'last resort' by the World Health Organization (WHO) [30] and GMC [31]. However, it is not to be taken lightly as it could have the negative impact of deterring others from testing because of the fear of forced imparting of HIV status and loss of trust by patients in the confidential doctor–patient relationship. Cases with challenging issues around sharing of HIV status should be managed by the MDT. It is important to accurately record discussions and management strategy in these cases. Timely partner testing during the pregnancy should be encouraged where possible and support given.

HIV testing of existing children should be raised with all women. In practice, if the children are asymptomatic the testing is often most easily done when the newborn is attending paediatric follow-up for HIV diagnostic tests [32].

4.2 Perinatal mental health assessment

4.2	Assessment of antenatal and postnatal depression should be undertaken at booking, and 4–6 weeks postpartum and 3–4 months postpartum in accordance with National Institute for Care and Health Excellence (NICE) guidelines.	1D

We advise that HIV MDTs follow existing NICE guidance on the detection of antenatal and postnatal depression [33]. This includes identifying women with past or present severe mental health illness including previous history of postnatal psychosis. These women should be managed in conjunction with a perinatal mental health team. Assessment of mental health should occur at antenatal booking, postnatally at 4–6 weeks, and then again at 3–4 months. This should include asking the following questions:

1. During the past month, have you often been bothered by feeling down, depressed, or hopeless?
2. During the past month, have you often been bothered by having little interest or pleasure in doing things?

If a woman answers 'yes' to either of the initial questions, consider asking a third question:

3. Is this something you feel you need or want help with?

As per the general antenatal population, if a mental health problem is suspected as a result of answers to these questions, we advise further assessment in accordance with NICE guidance, and prompt liaison with perinatal mental health services, or the patient's GP, and/or voluntary groups as appropriate.

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5. Screening and monitoring of pregnant women living with HIV

5.1 Sexual health screening

5.1.1	Sexual health screening is recommended for pregnant women newly diagnosed with HIV.	1B
5.1.2	For women living with HIV and already engaged in HIV care who become pregnant, sexual health screening is suggested.	2C
5.1.3	Genital tract infections should be treated according to British Association for Sexual Health and HIV (BASHH) guidelines.	1B

There are limited data regarding the prevalence of genital infections in pregnant women living with HIV in the UK. Studies of pregnant women living with HIV in London and Slough found a prevalence of bacterial sexually transmitted infection (STIs) of 0–4% and of bacterial vaginosis (BV) of 1–4% [1-3]. A London cohort study found that STI diagnosis was associated with an antenatal HIV diagnosis, disclosing additional sexual partners during pregnancy, nulliparity, a shorter relationship duration and a partner of unknown HIV status [1].

The diagnosis and treatment of genital infections in any individual have clear benefits in terms of both individual-level morbidity and possible onward transmission to sexual partners. In pregnancy, the welfare of the baby is an additional issue. However, apart from the recommendation that all pregnant women should be screened for HIV, HBV and syphilis, asymptomatic HIV-negative pregnant women in the UK are not routinely screened for genital infections [4]. In pregnant women who are living with HIV, an additional consideration is the potential effects of the presence of a genital infection on vertical transmission of HIV. This could occur through an increase in the HIV viral load in the genital tract and/or the presence of chorioamnionitis. In addition, certain infections may be linked to premature birth, an event that occurs more frequently in women living with HIV when compared to HIV-negative women. An American study demonstrated that despite 96.9% of pregnant women living with HIV taking ART, a concomitant STI doubled the risk of spontaneous preterm birth [5].

It has long been recognised that genital infections, in particular ulcerative diseases, are associated with an increased risk of sexual transmission of HIV [6-8]. This may be a consequence of an increase in local HIV replication resulting in a higher viral load in genital secretions, secondary to the presence of specific microorganisms, and/or ulceration and inflammation [9,10]. Organisms associated with BV have been shown to stimulate HIV expression *in vitro* [11,12]. Studies from Kenya have demonstrated a reduction in cervical mucosal shedding of HIV RNA following treatment of gonococcal, chlamydial and non-specific cervicitis [13,14]. In the setting of full virological suppression on cART it is unclear to what extent, if any, the presence of any genital infection will contribute to the vertical transmission of HIV.

Viral load in cervicovaginal specimens has been shown to correlate with vertical transmission of HIV [15]. Genital tract HIV viral load will usually mirror the plasma HIV viral load [16], but there is increasing evidence of compartmentalisation of HIV between the plasma and genital tract. Genital tract HIV has been detected in women with an undetectable plasma viral load [17,18] and genetic diversity of virus from the two compartments has been reported [19]. A number of factors may be responsible for this, including differential drug penetration into body compartments and the presence of genital tract infections. With increasing numbers of women in the UK aiming for and achieving a vaginal delivery, an increasing number of babies are exposed to the cervicovaginal secretions of women living with HIV. The clinical significance of this is not clear. Data from the UK and Ireland [20] and France [21] show no difference in vertical transmission associated with mode of delivery in women with an undetectable viral load, providing some reassurance that the potential discordance may not be clinically relevant.

5.1.1 Herpes simplex virus

A systematic review has demonstrated a correlation between a herpes simplex virus type 2 (HSV-2) diagnosis and HIV vertical transmission (odds ratio [OR] 1.57). However, studies did not always adjust for key confounders such as ART use and mode of delivery [22].

Regarding the relationship between genital HSV-2 shedding and vertical transmission, a Thai study found an association between vertical transmission and HSV-2 shedding in cervicovaginal lavage fluid at 38 weeks' gestation (OR 3.0), but this was no longer statistically significant after adjustment for ART use, maternal CD4 cell count, plasma viral load at delivery and cervicovaginal HIV viral load at 38 weeks (OR 2.3) [23]. Two other studies assessed shedding either at 10–32 weeks' gestation or at delivery, but neither found an association with intrapartum or *in utero* transmission in univariate analyses [21,24].

For pregnant women receiving ART, data regarding the relationship between vertical transmission and HSV-2 are inconclusive. A Ukrainian study, in which 96% of women received antenatal ART (half receiving cART), found no evidence that HSV-2 seropositivity was associated with risk of vertical transmission of HIV in unadjusted analyses. In multivariable analyses, the only factor associated with vertical transmission of HIV was lack of antenatal ART, which was associated with a three-fold increased risk. However, due to the relatively low HIV transmission risk (in comparison with earlier studies examining HSV and vertical transmission of HIV), the study was only powered to rule out a 2.25-fold increased risk of vertical transmission of HIV with HSV-2 antibodies [25]. A Thai study of women living with HIV who were HSV-2 seropositive found that vertical transmission of HIV was not reduced by zidovudine treatment [23].

That there may still be an increased risk associated with HSV shedding with patients on cART is suggested by a randomised, double-blind, placebo-controlled trial of herpes-suppressive therapy in women living with HIV and HSV-2 taking cART in Burkina Faso, which demonstrated that valaciclovir 500 mg bd further reduced genital HIV replication in those women with residual HIV shedding despite cART. However, vertical transmission of HIV was not reviewed [26]. A study from the USA reported greater rates of HSV-2 shedding at delivery in HSV-2-seropositive women with HIV compared to HIV-negative women (30.8% *vs* 9.5%). However, it is not clear whether any women were receiving antiviral HSV suppressive therapy, or what proportion of women living with HIV was receiving ART [27].

The incremental benefit of providing HSV suppression in late pregnancy to women living with HIV with a previous diagnosis of genital HSV and who are taking cART needs further investigation. These women should be treated in line with the BASHH/RCOG guidelines, which recommend that women who are HIV antibody positive and have a history of genital herpes should be offered suppressive aciclovir 400 mg three times daily from 32 weeks of gestation, especially where a vaginal delivery is planned. This aims to reduce the risk of transmission of HIV infection, and to reduce HSV shedding and herpes recurrence at delivery [28].

5.1.2 Chorioamnionitis and BV

Chorioamnionitis may lead to premature rupture of the membranes with the possibility of premature birth [29,30]. Chorioamnionitis, prolonged rupture of membranes and premature birth have all been associated with vertical transmission of HIV and may be interlinked [31-33]. However, a Phase 3 clinical trial of antibiotics to reduce chorioamnionitis-related perinatal HIV transmission showed no benefit in reducing vertical transmission in the context of single-dose nevirapine prophylaxis [34]. Although both *Chlamydia trachomatis* and *Neisseria gonorrhoeae* have been associated with chorioamnionitis, the organisms usually implicated are those associated with BV including *Ureaplasma urealyticum* [35,36]. A strong association between BV and premature delivery has been reported [37,38]. There are data from Malawi that suggest that BV may be associated with an increased risk of maternal HIV acquisition in pregnancy as well as premature delivery and vertical transmission of HIV [36]. A study in which women received zidovudine from 34 weeks of pregnancy reported that maternal fever >38°C and BV were associated with *in utero* transmission of HIV with 2.6-fold and 3.0-fold increased risks, respectively [39]. It is not known how applicable this is in settings in which women receive cART from earlier in pregnancy.

In HIV-negative women, data regarding the effect of screening for and treating BV on premature delivery are conflicting. There are scant pre-cART data on women living with HIV, therefore BV should be treated as per BASHH guidelines (www.bashh.org/guidelines).

5.1.3 STI screening

In the setting of full virological suppression on cART it is unclear to what extent, if any, the presence of any genital infection will contribute to the vertical transmission of HIV. Pregnant women newly diagnosed with HIV should be screened for STIs as per the routine management of newly diagnosed patients [40]. For pregnant women living with HIV and already engaged in HIV care, in the absence of randomised controlled trials but for the reasons

outlined above, the writing group suggests screening for genital tract infections including evidence of BV. This should be done as early as possible in pregnancy and consideration should be given to repeating this at around 28 weeks. Syphilis serology should be performed on both occasions. In addition, any infection detected should be treated according to the BASHH guidelines taking into account recommended treatment regimens in pregnancy, followed by a test of cure. Partner notification should take place where indicated, to avoid re-infection.

5.1.4 Cervical cytology

- With regard to cervical cytology, pregnant women living with HIV should be managed as per the guidelines for the NHS Cervical Screening Programme 2016 [41] and BASHH/BHIVA/FSRH Guidelines on the Sexual and Reproductive Healthcare of People Living with HIV [42]. Routine cytology should be reviewed but deferred until 3 months postpartum.
- A woman referred with abnormal cytology should undergo colposcopy in late first or early second trimester unless there is a clinical contraindication. For low-grade changes triaged to colposcopy on the basis of a positive HPV test, the woman's assessment may be delayed until after delivery.
- If a previous colposcopy was abnormal and in the interim the woman becomes pregnant, the colposcopy should not be delayed.
- If a pregnant woman requires colposcopy or cytology after treatment (or follow-up of untreated cervical intraepithelial neoplasia [CIN] grade 1), her assessment may be delayed until after delivery. However, unless there is an obstetric contraindication, assessment should not be delayed if the first appointment for follow-up cytology or colposcopy is due following treatment for cervical glandular intraepithelial neoplasia.
- The 'test of cure' appointment should not be delayed after treatment for CIN2 or CIN3 with involved or uncertain margin status. In these circumstances if repeat cytology is due, and the woman has missed her appointment prior to pregnancy, cytology or colposcopy during pregnancy can be considered. This should also be reviewed at the postnatal appointment (see section 10).

5.1.5 Contraception

A plan for contraception to be used postnatally should be discussed antenatally with each woman. Antiretrovirals may need to be changed postnatally to align with a woman's choice of contraception. Further guidance on contraception in HIV can be found in the BASHH/BHIVA/FSRH Guidelines on the Sexual and Reproductive Healthcare of People Living with HIV [42].

5.2 Laboratory monitoring of pregnant women living with HIV

5.2.1	Pregnant women who are newly diagnosed with HIV do not require any additional baseline investigations compared with non-pregnant women living with HIV other than those routinely performed in the general antenatal clinic.	1D
5.2.2	HIV resistance testing should be completed and results available prior to initiation of treatment [43], except for late-presenting women (after 28 weeks). Women should be encouraged to continue combination (c)ART post-delivery but, where they choose to stop cART, a further resistance test is recommended to ensure that mutations are not missed with reversion during the off-treatment period.	1D

In the case of late-presenting women, cART, based on epidemiological assessment of resistance, should be initiated without delay and modified once the resistance test is available.

5.2.3	In women conceiving on cART there should be a minimum of one CD4 cell count at baseline and one at delivery.	2D
5.2.4	In women who commence cART in pregnancy, a CD4 cell count should be performed as per routine initiation of cART with the addition of a CD4 count at delivery even if starting at CD4 >350 cells/mm^3.	1C
5.2.5	In women who commence cART in pregnancy, an HIV viral load should be performed 2–4 weeks after commencing cART, at least once every trimester, at 36 weeks and at delivery.	1C

Performing a viral load test at 2 weeks allows for a more rapid assessment of adherence and may be of particular benefit in a late-presenting woman.

5.2.6	In women commencing cART in pregnancy, liver function tests (LFTs) should be performed as per routine initiation of cART and then with each routine blood test.	1C

Hepatotoxicity may occur as a result of the initiation of cART and/or the development of obstetric complications such as obstetric cholestasis, pre-eclampsia, HELLP (haemolysis, elevated liver enzymes, low platelet count) syndrome and acute fatty liver. Close liaison with the obstetric team is recommended.

5.2.1 Failure to suppress

5.2.7	In the event that a woman who has initiated cART during pregnancy has not suppressed plasma viral load to <50 HIV RNA copies/mL, the following interventions are recommended: • Review adherence (including a full exploration of potential impacting factors) and concomitant medication; • Perform resistance test if appropriate; • Consider therapeutic drug monitoring (TDM); • Optimise to best regimen; • Consider intensification.	1C

For a woman who conceives on cART that is not fully suppressive or loses virological control during the pregnancy, these interventions should be undertaken as soon as possible. If treatment failure occurs when the infant is likely to be delivered prematurely and may be unable to take medication enterally, intensification should consist of therapies that readily cross the placenta such as double-dose tenofovir DF, raltegravir and single-dose nevirapine. See also section 6 for further information on ART and pregnancy.

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6. Current issues in the use of ART in pregnancy and pregnancy outcomes

6.1 Conceiving on cART

6.1.1	It is recommended that women conceiving on an effective cART regimen should continue this treatment.	1B
	Exceptions are: Non-standard regimens, for example protease inhibitor (PI) monotherapy; Regimens that have been demonstrated to show lower pharmacokinetics in pregnancy such as darunavir/cobicistat and elvitegravir/cobicistat, or where there is an absence of pharmacokinetic data such as raltegravir 1200 mg once daily (od) (should be administered 400 mg twice daily [bd]). These should be modified to include (depending on tolerability, resistance and prior antiretroviral history) one or more agents that cross the placenta. A woman conceiving on dolutegravir should see her physician as soon as possible to discuss current evidence on neural tube defects.	2D

Despite the lack of a licence for the use of ART in pregnancy, with the exception of zidovudine in the third trimester, there is global consensus that women who conceive on effective cART should continue cART throughout pregnancy and then lifelong. Pregnant women are a unique group within the HIV population as treatment is relevant not only for their own health but also for that of the unborn child and risk of congenital abnormality must be considered when assessing cART in pregnancy. Therefore it may not always be appropriate to use standard adult treatment guidelines as recommended regimens in pregnancy usually consist of triple therapy with less evidence for safety and efficacy of newer antiretrovirals and evolving combinations such as dual therapy and integrase inhibitors.

As pregnancy is a temporary state, concerns about long-term toxicity of cART for a woman may not be relevant during pregnancy. After delivery cART may be switched to a regimen preferable for long-term use in terms of both toxicity and tolerability. Our recommendations are shown in Table 6.1.

Table 6.1. Recommended and alternative agents in pregnancy

	Recommended	Alternative
Nucleoside reverse transcriptase inhibitor (NRTI) backbone	Abacavir/lamivudine Tenofovir DF/emtricitabine	Zidovudine/lamivudine
Third agent	Efavirenz Atazanavir/r	Rilpivirine Darunavir/r Raltegravir 400 mg bd Dolutegravir (after 8 weeks' gestation)

The writing group recommends that choice of therapy should always be discussed in full with every woman and be individualised for the patient, taking into account a woman's concerns and preferences [1], in accordance with the standard treatment guidelines. Nucleoside backbone combinations recommended by BHIVA for HIV in pregnancy include tenofovir DF/emtricitabine and abacavir/lamivudine. Pregnant women may also want to consider zidovudine/lamivudine [1]. Considerations for the backbone include side-effect profile, frequency of

dosing, interactions with the third agent, adverse outcome profiles and prior cART experience including a resistance profile where available. The writing group recommends that women are advised against the combination of tenofovir DF/emtricitabine and lopinavir/r (especially high-dose lopinavir/r), which demonstrated an increased risk of neonatal death and prematurity in the randomised controlled PROMISE trial [2].

Although zidovudine remains the only antiretroviral agent with a licence for use in pregnancy, non-pregnant adults are now rarely prescribed zidovudine as part of cART due to concerns about toxicity. Despite its proven efficacy in preventing vertical transmission of HIV, particularly in the pre-cART era [3], there are no data to support routinely switching to zidovudine, or adding zidovudine to a combination of antiretrovirals that is suppressing HIV viral load to <50 HIV RNA copies/mL in plasma. Analyses of data combined from two observational studies, the European Collaborative Study and the UK and Ireland NSHPC, have shown no difference in pregnancy outcomes between zidovudine-based and zidovudine-sparing cART [4].

Where the risk of treatment failure due to reduced or intermittent drug exposure with hyperemesis gravidarum exceeds the risk of treatment interruption, the writing group recommends that treatment is interrupted for the minimum time required to overcome the issue. If receiving non-nucleoside reverse transcriptase inhibitor (NNRTI)- or raltegravir-based cART, an additional resistance test may be performed. However, there are no data that specifically address this issue in pregnancy.

6.2 Woman is not already on cART: when to start

6.2.1	All pregnant women, including elite controllers, should start ART during pregnancy and be advised to continue lifelong treatment.	1A

Current BHIVA treatment guidelines recommend treatment of all people living with HIV, regardless of CD4 cell count or clinical status [5]. Studies have shown that immediate initiation of cART improves clinical outcomes for patients, regardless of initial CD4 cell count, and reduces transmission of HIV among serodiscordant partners if the partner with HIV has an undetectable HIV viral load on cART [6-8]. All pregnant women living with HIV should be counselled about the importance of continuation of cART postpartum.

6.2.1 Elite controllers

As advice to commence lifelong cART when HIV is diagnosed applies to elite controllers (people with HIV who maintain an undetectable viral load and high CD4 counts without having to take ART), we no longer provide specific recommendations on treatment for elite controllers.

6.2.2 All women not on cART should commence cART

6.2.2	All women not on cART should commence cART • As soon as they are able to do so in the second trimester where the baseline viral load ≤30,000 HIV RNA copies/mL; • At the start of the second trimester, or as soon as possible thereafter, in women with a baseline viral load of 30,000–100,000 HIV RNA copies/mL; • Within the first trimester if viral load >100,000 HIV RNA copies/mL and/or CD4 cell count is less than 200 cells/mm^3. All women should have commenced cART by week 24 of pregnancy.	1C

When determining the optimal time to start cART, the following must be considered:

- The theoretical issues for avoiding medication during pregnancy, in particular the first trimester;
- Evidence of risk of congenital abnormality following exposure to cART (see section 6.5);
- Maternal health;
- Risk of vertical transmission to the infant as determined by maternal viral load, whether cART is taken in pregnancy, and the time on cART prior to delivery.

Major determinants of a woman suppressing to a viral load <50 HIV RNA copies/mL by the time of delivery are the baseline untreated viral load and the time available to achieve this target. In both the UK and Ireland, and also the ANRS French Perinatal Cohort, vertical transmission was significantly associated with starting treatment later in

pregnancy. In the French cohort, the median duration of treatment was 9.5 weeks among women where vertical transmission occurred, compared with 16 weeks for non-transmission (*P*<0.001) [9]. NSHPC data also show an increased risk of transmission in those initiating treatment beyond 30 weeks, compared to those starting earlier [10].

In the Mma Bana study, plasma HIV viral load at delivery <400 HIV RNA copies/mL was observed in 96% (lopinavir/r-based therapy) and 100% (abacavir/lamivudine/zidovudine) of women with baseline plasma viral load <1000 HIV RNA copies/mL, and in 86% (lopinavir/r-based therapy) and 90% (abacavir/lamivudine/zidovudine) with a baseline viral load >100,000 HIV RNA copies/mL. When therapy was initiated at 31–34 weeks, viral suppression was seen in only 78% of women on PI-based therapy [11].

Data from a UK multicentre study retrospectively analysing outcomes in pregnant women initiating cART at a median gestation of 23 weeks demonstrated very low rates of virological suppression in women with a baseline viral load in the upper quartile (>32,641 HIV RNA copies/mL) with only 46% achieving <50 HIV RNA copies/mL by 36 weeks' gestation (the time point used to make most delivery management decisions); this fell to 37% for baseline viral loads >100,000 HIV RNA copies/mL [12]. For all viral loads >10,000 HIV RNA copies/mL, treatment initiation later than 20.3 weeks' gestation was associated with significantly reduced likelihood of successful viral load suppression.

Therefore, the writing group recommends that cART should be commenced as soon as possible in women with baseline viral load >100,000 HIV RNA copies/mL, and at the start of the second trimester, or as soon as possible thereafter, in women with a baseline viral load between 30,000 and 100,000 HIV RNA copies/mL.

Deferring treatment to the start of the second trimester may be necessary if the woman is experiencing nausea and/or vomiting of pregnancy. However, where she is at risk of or has presented with an opportunistic infection, initiation of cART should not be delayed because of pregnancy, to protect both maternal and fetal health.

All women should have commenced cART by week 24 of pregnancy.

In women with a history of preterm delivery (PTD) it may be prudent to start cART as soon as possible after the first trimester to maximise time on cART prior to delivery although there are no supporting data and avoidance of PIs associated with PTD may be considered (see section 6.6).

6.3 Woman is not already on cART: what to start

6.3.1	Women are recommended to start tenofovir DF or abacavir with emtricitabine or lamivudine as a nucleoside backbone.	2C
6.3.2	It is recommended that the third agent in cART should be efavirenz or atazanavir/r, as these are agents with the most safety data in pregnancy.	1C
	Rilpivirine (25 mg od), raltegravir (400 mg bd) or darunavir/r (600/100 mg bd) may be used as alternatives.	1C
	Darunavir/r should be prescribed at the twice daily dose (600/100 mg bd) if known resistance, and consideration should be given to using this higher dose if darunavir is initiated in pregnancy.	2C
	Dolutegravir (50 mg od) may be considered after 8 weeks' gestation which must be confirmed.	1C
	Zidovudine monotherapy is not recommended and should only be used in women declining cART with a viral load of <10,000 HIV RNA copies/mL and willing to have a caesarean section (CS).	1A
	PI monotherapy, tenofovir alafenamide, darunavir/cobicistat and elvitegravir/cobicistat are not recommended in pregnancy.	1C

There is good evidence for the use of efavirenz in pregnancy; however, it is no longer a preferred regimen for ART-naïve patients in BHIVA and international guidelines for treatment of HIV in adults. It may be prescribed to a pregnant woman for the duration of her pregnancy with a subsequent switch postpartum. Rilpivirine may be considered as an alternative.

Ritonavir-boosted PIs are robust and may be employed where there are concerns about adherence. Atazanavir/r is recommended over darunavir/r and lopinavir/r which have an increased risk of preterm delivery.

Raltegravir may also be used but must be dosed at 400 mg bd as there are no pharmacokinetic data to support the use of 1200 mg od in pregnancy.

Dolutegravir is discussed in detail in section 6.5 and can be used only after 8 weeks' gestation (which must be confirmed) until further data on the use of dolutegravir in pregnancy become available.

The efficacy of zidovudine monotherapy for prevention of vertical transmission is well known; transmission rate for women treated with zidovudine monotherapy and assigned to PLCS was 0.8% in the Mode of Delivery study [13]. It is not a recommended option for pregnant women with HIV as it cannot be continued postpartum.

Our recommendations for ART initiation in pregnancy are the same as for when a woman conceives on ART (see Table 6.1).

6.3.3	It is recommended that an integrase inhibitor-based regimen be considered as the third agent of choice in patients: • With high baseline viral load (>100,000 HIV RNA copies/mL) • Where cART is failing to suppress the virus.	 2C 1C

Raltegravir and dolutegravir (after 8 weeks' gestation) may be used in this context. A retrospective cohort analysis of 92 pregnant women with HIV showed more rapid viral suppression in those patients on an integrase inhibitor-containing regimen versus women on ART without an integrase inhibitor [14]. Median time to viral load reduction by greater than 1 $\log_{10}$ unit was 7 days in the integrase inhibitor-containing ART arm and 35 days in the non-integrase inhibitor ART arm (P<0.01). In a second retrospective study of 14 women, raltegravir was either initiated as part of a cART regimen in nine antiretroviral-naïve women or added to an existing antiretroviral regimen in five women who had conceived on cART but had persistent viraemia [15]. Raltegravir was initiated at a gestational age of 34 weeks or later. The median exposure time to raltegravir was 17 days and the mean viral load decline was 2.6 $\log_{10}$ units. Raltegravir was well tolerated but elevated liver enzymes were reported.

6.4 Late-presenting woman not on treatment

6.4.1	A woman who presents after 28 weeks should commence cART without delay.	1B
6.4.2	If the viral load is unknown or >100,000 HIV RNA copies/mL a three- or four-drug regimen that includes raltegravir 400 mg bd is suggested.	2D

Late presentation after 28 weeks and before the onset of labour occurs less frequently since the introduction of the routine offer and recommendation of antenatal HIV screening. With improved turnaround times for viral load testing, a woman presenting beyond 28 weeks may still be managed with a view to a possible vaginal delivery if she commences cART and achieves a viral load of <50 HIV RNA copies/mL by 36 weeks.

As discussed in section 6.7.3, an integrase inhibitor-based cART regimen is recommended because of a more rapid viral load decline compared to other drug combinations. A recent Thai study [16] of 57 pregnant women has shown that intensification of a standard three-drug cART regimen in women with detectable viral load after 28 weeks resulted in a significant reduction in viral load at delivery.

A pilot study in 40 women demonstrated that initiation of raltegravir-based therapy, compared to lopinavir/r-based therapy, resulted in significantly more women with undetectable viral load <50 HIV RNA copies/mL at delivery and a faster median time to viral load reduction to <50 HIV RNA copies/mL of 44 days in the raltegravir arm and 69 days in the lopinavir/r arm [17]. Adverse event incidence rates were also lower in the raltegravir arm.

Based on these emerging data, the writing group recommends initiation with a raltegravir-containing regimen in this group of patients. Thus, where the viral load is unknown or >100,000 HIV RNA copies/mL, a fourth drug, most commonly raltegravir, may be added to the cART regimen.

6.4.3	Management of an untreated woman presenting in labour at term. All women should be given a stat dose of nevirapine 200 mg;	1B
	and commence oral zidovudine 300 mg and lamivudine 150 mg bd;	1B
	and raltegravir 400 mg bd;	2D
	and receive intravenous zidovudine for the duration of labour.	2D
	Please also see section 9.1.3 for HIGH-RISK neonatal management.	

A single dose of nevirapine, regardless of CD4 cell count (even if available) or hepatitis status, should be given immediately as this rapidly crosses the placenta and within 2 hours achieves, and then maintains, effective concentrations in the neonate for up to 10 days [18,19]. cART should be commenced immediately with oral zidovudine and lamivudine and with raltegravir as the preferred additional agent because it also rapidly crosses the placenta [20]. Intravenous zidovudine should be administered for the duration of labour and delivery. Following a loading dose of 2 mg/kg for 1 hour the maintenance dose of 1mg/kg per hour is infused until the cord is clamped [21]. Data from the French cohort indicate that peripartum zidovudine infusion further reduces transmission in women on cART from 7.5% to 2.9% (*P*=0.01) where the delivery viral load is >1000 HIV RNA copies/mL. However, this benefit is not seen if neonatal therapy is intensified [22]. If delivery is not imminent, a CS should be considered.

6.4.4	In preterm labour, if the infant is unlikely to be able to absorb oral medications consider the addition of double-dose tenofovir DF to the treatment described in recommendation 6.4.3 to further load the infant.	2C

Nevirapine and raltegravir should be included in the regimen as they cross the placenta rapidly (see above). In addition, double-dose tenofovir DF (490 mg) has been shown to cross the placenta rapidly to preload the infant, and should be considered where the prematurity is such that the infant is likely to have difficulty taking oral PEP in the first few days of life [23].

6.4.5	Women presenting in labour/with spontaneous rupture of the membranes (SROM)/requiring delivery without a documented HIV result must be advised to have an urgent HIV test. A reactive/positive result must be acted upon immediately, with initiation of interventions to prevent vertical transmission of HIV without waiting for further/formal serological confirmation.	1D

If the woman's HIV status is unknown due to lack of testing, a point-of-care test (POCT) should be performed. Women who have previously tested negative in pregnancy but who have an on-going risk of HIV should ideally also have a repeat fourth-generation laboratory test or, if unavailable, a POCT if presenting in labour. If the test is positive (reactive) a confirmatory test should be performed, but treatment to prevent vertical transmission should commence immediately. Where a POCT is not available, laboratory-based serology must be performed urgently including out of hours, and the result acted upon as above. Baseline samples for CD4 cell count, viral load and resistance should be collected. Treatment should be commenced immediately as per recommendation 6.4.3 above. Three-drug PEP should be given to the neonate (see section 9).

6.5 Evidence on teratogenicity, neonatal outcomes and ART

Pregnant women with HIV remain a special group with specific guidelines for HIV treatment based on teratogenicity and toxicity data on cART use in pregnancy from published reports, national HIV in pregnancy databases and international antiretroviral databases such as the APR.

The APR provides the best data on teratogenicity and first trimester ART exposure although it should be noted that births from the UK contribute to only 4.6% of collected data [24]. This voluntary prospective database records rates of congenital birth defects in babies born to women with first-trimester exposure to ART in comparison to background rates of congenital birth defects and second- or third-trimester only exposures to the same compounds. The congenital malformation rate observed in babies exposed to a specified drug is reported once a minimum of 200 prospective first-trimester exposures to an individual antiretroviral have been reported.

As of January 2018, the APR report for infants exposed to antiretrovirals includes the following.

- Abacavir, atazanavir, lamivudine, emtricitabine, lopinavir, nevirapine, ritonavir, tenofovir DF and zidovudine: there are now more than 200 prospective reports of first-trimester exposure with no signal of increased risk, and a greater than two-fold higher rate than in the general population has been excluded [24].
- Darunavir, efavirenz, indinavir, raltegravir and rilpivirine have been shown to have congenital malformation rates within the expected range, and a congenital malformation rate greater than 1.5-fold higher than in the general population has been excluded.
- For newer agents (cobicistat, dolutegravir, elvitegravir and tenofovir alafenamide) and a number of less commonly prescribed older compounds (saquinavir, fosamprenavir, enfuvirtide, tipranavir, maraviroc and etravirine) there have been insufficient reported outcomes of first-trimester exposure to exclude such risk.

Data from the APR have shown no difference in risk of birth defects for abacavir/lamivudine and non-abacavir/lamivudine backbones [25].

The PROMISE study [2] compared the efficacy of zidovudine/single-dose nevirapine with two combination therapy arms to prevent vertical transmission. The first combination consisted of zidovudine/lamivudine/lopinavir/r and the second comprised tenofovir DF/emtricitabine/lopinavir/r. An unexpected higher rate of early neonatal death, predominantly attributed to preterm birth, was reported in the tenofovir DF/emtricitabine/lopinavir/r combination therapy arm. On review of this large randomised controlled trial, the BMJ Clinical Guidelines group recommended the zidovudine/lamivudine-based antiretroviral regimen over tenofovir DF/emtricitabine with lopinavir/r, because of the reduced risk of infant death [26]. Other reviews have reported no increase in birth adverse events or safety events (and no increased risk of congenital abnormalities) in infants exposed to tenofovir DF compared to non-tenofovir DF-containing regimens, which did not have lopinavir/r as a backbone [27-29]. In addition to these systemic reviews, prospective observational cohorts in pregnancy have shown no differences in adverse outcomes between tenofovir DF/emtricitabine and non-tenofovir DF/emtricitabine backbones [30,31]. Zash *et al.* [31] found that the risk of adverse birth outcome was lowest among infants exposed to a combined regimen of tenofovir DF/emtricitabine and safer than with zidovudine/lamivudine as a backbone. The writing group notes that the dose of lopinavir/r was increased by 50% for the duration of the third trimester in the PROMISE study. This is not standard practice and the writing group recommends against using lopinavir/r at this dose. On review of all the data the writing group does not consider the increase in adverse outcomes in the PROMISE study to be related to the tenofovir DF/emtricitabine backbone alone, but to the combination used (www.bhiva.org/BHIVA-response-to-BMJ-article). The writing group therefore recommends against using the combination tenofovir DF/emtricitabine/lopinavir/r in pregnancy. See also section 6.7.1 and Appendix 3.

An initial meta-analysis on the use of dolutegravir in six studies and from four control databases suggested it appeared safe to use in pregnancy [32]. However, a preliminary unscheduled analysis of an ongoing birth surveillance study in Botswana has reported an increased risk of neural tube defects among infants of women who become pregnant while taking dolutegravir-based regimens [33]. The study reported four cases of neural tube defects out of 426 infants born to women who were on dolutegravir-based regimens at the time of conception. This rate of 0.94% compares to a rate of neural tube defects of 0.12% among infants born to women taking non-dolutegravir-based regimens at the time of conception. Further prospective data are awaited on

women who were on dolutegravir-based regimens at conception and pregnancy is ongoing. Of note there have been no reported neural tube defects in infants born to a further 2812 women in the Botswana study who started dolutegravir during pregnancy, including in the first trimester [34].

Based on these findings the writing group makes the following recommendations:

1. **For a woman on dolutegravir wishing to conceive:**
    - **a.** We advise switching to an alternative effective cART regimen.
    - **b.** The best safety data in pregnancy is for efavirenz or atazanavir/r and these should be considered first line in pregnancy.
    - **c.** All women on dolutegravir wishing to conceive, in whom a switch off dolutegravir is declined or is likely to result in treatment failure, should be started on folic acid 5 mg od based on the original Medical Research Council data on prevention of neural tube defects in the general population [35].
2. **For a woman on dolutegravir who becomes or is pregnant:**
    - **a.** We acknowledge the neural tube has closed within 4 weeks of conception but the mechanism of some of the reported abnormalities remains uncertain. We therefore recommend that women on dolutegravir in the first trimester discontinue dolutegravir until after 8 weeks' gestation (which must be confirmed), and switch to a regimen for which there are more safety data in pregnancy, such as efavirenz or atazanavir/r.
    - **b.** We do not recommend switching from dolutegravir if the pregnancy is confirmed to be already past 8 weeks' gestation.
    - **c.** If the physician/woman choose(s) to switch, use a regimen for which there are the most safety data in pregnancy, such as efavirenz or atazanavir/r.
    - **d.** Detailed anomaly scans should be performed as per national pregnancy guidelines with no additional scans required.

Historical recommendations that efavirenz be avoided in women who may conceive [36] were based on preclinical animal studies that had not been conducted on any other ART, the US Food and Drug Administration (FDA) reclassification of efavirenz to category D, and the paucity of human data. Based on current evidence, the writing group recommends that efavirenz can be used (i.e. both continued and commenced) in pregnancy without additional precautions and considerations above those of other antiretroviral agents [37].

For further information on toxicity and pharmacokinetics and discussion regarding choice of ART, see section 6.7.

6.6 Preterm delivery (PTD)

Rates of PTD in women with HIV are high. This was the case prior to cART and remains so in the current era. However, data on the association between PTD and different antiretroviral agents are complex. Some studies, but not all, implicate boosted PIs. Particularly in observational studies, differences between populations and timing of cART initiation undoubtedly contribute to the discrepant findings, while data on other risks associated with PTD including previous PTD are rarely collected. However, while the early studies investigated women initiating cART in pregnancy it is also becoming apparent that women conceiving on cART, with an undetectable HIV load, still have a higher than expected PTD rate.

Studies showing no association between boosted PIs and PTD

Several large observational studies from the USA have not found an association between cART and PTD [38,39]. A US meta-analysis in 2007 did not find an association between PI-containing cART and PTD [40], and analysis of the NSHPC UK and Ireland data, although demonstrating the increased risk of PTD in women on cART, similarly did not find a difference when comparing PI- and NNRTI-based regimens [41]. In addition, an analysis of data on over 10,000 women reported to the APR from 1989 to 2010 did not find a significant increase in PTD in women with PI exposure with lower pre-existing risk [42]. Over 85% of these reports to the APR came from the USA.

Most studies that have examined the relationship between the timing of cART initiation and PTD have found that the risk was increased in those either conceiving on cART or taking it early in pregnancy (in the first trimester) [40,43-45]. However, an NSHPC UK and Ireland study did not find an association between timing of cART initiation and PTD [41]. A 2010 US study attempted to overcome the potential confounding factors associated with timing of cART initiation by including only women starting cART in pregnancy and comparing PI-containing with non-PI-containing regimens and did not find an association between PI-containing regimens and PTD [46]. In this study, 72% of the 777 women received a PI-based regimen, and in 47% of those the PI was nelfinavir with 22% on lopinavir/r. Further comparison between nelfinavir and lopinavir/r was unfortunately not possible. A small Canadian study retrospectively reviewed 384 women living with HIV compared to a matched HIV-negative cohort [47]. A two-fold increase in preterm birth, low birth weight and small for gestational age parameters was found, however no statistical difference between the two cohorts remained when odds ratio was adjusted for race and history of PTD.

Studies suggesting an association between boosted PIs and PTD

The association between cART and PTD was first reported by the Swiss Cohort study group in 1998 [48], and subsequently from a number of other European studies including three analyses from the European Cohort Study [43,45,49,50]. Analysis of the NSHPC UK and Ireland data in 2007 found that there was a 1.5-fold increased risk of PTD when comparing women on cART with those on monotherapy or dual therapy [41]. One single-centre UK study found the risk was increased in women initiating cART in pregnancy compared to those conceiving on treatment [51].

In two US studies, one multicentre study from the Pediatric Spectrum of HIV Disease cohort and one single-centre study, an association between cART and PTD was found only if cART included a PI [52,53]. Two of the earlier European Cohort Study reports had also noted that the increased risk of PTD in patients on cART was particularly marked in patients on PI-containing cART [43,45].

A 2011 study from the ANRS reported an association between cART and PTD and in the 1253 patients initiating a PI-based regimen, those on ritonavir-based PI regimens were significantly more likely to deliver prematurely compared to those on a non-boosted PI regimen (hazard ratio 2.03; 95% confidence interval [CI] 1.06–3.89) [54]. One additional analysis from the APR of 955 live births exposed to lopinavir/r reported a PTD rate of 13.4% [55]. A retrospective study from the UK reported a PTD rate of 10% in 100 women taking atazanavir/r in pregnancy, of whom 67% had conceived on their regimen [56]. The same group found no difference in PTD rates in a retrospective study comparing lopinavir/r and atazanavir/r as the third agent in cART [57]. The latest publication from the NSHPC suggests that atazanavir/r has a lower PTD rate than lopinavir/r, particularly in women with a CD4 count <350 cells/mm^3 and compared to darunavir/r in women initiating cART in pregnancy [58].

Several randomised studies investigating the use of different antiretroviral regimens in different settings have now been published, although none was designed specifically to address whether ART affects the rate of PTD. The Mma Bana study from Botswana randomly allocated 560 women at 26–34 weeks' gestation, with CD4 cell counts >200 cells/mm^3, to receive either lopinavir/r plus zidovudine/lamivudine (PI group) or abacavir/zidovudine/lamivudine (NRTI group). The PTD rates were significantly higher in the PI group (21.4% *vs* 11.8%; *P*=0.003) [59]. A second study, the Kesho Bora Study, randomly allocated 824 women at 28–36 weeks' gestation, again with CD4 cell counts >200 cells/mm^3, to receive either lopinavir/r with zidovudine/lamivudine or zidovudine monotherapy twice daily plus a single dose of nevirapine at the onset of labour. There was no difference in the PTD rate between the two groups (13% with PI *vs* 11% with zidovudine monotherapy/single-dose nevirapine) [60]. An analysis of placental malaria data from PROMOTE of 391 Ugandan women randomly assigned to lopinavir/r or efavirenz initiated during pregnancy showed no significant difference in PTD: 15.9% and 13.6%, respectively [61]. Finally, in the PROMISE study lopinavir/r prescribed with tenofovir DF/emtricitabine was associated with a high neonatal mortality rate due to severe PTD, which was not seen with lopinavir/r when prescribed with zidovudine/lamivudine, nor with zidovudine monotherapy. However, in both PI arms the doses of lopinavir and ritonavir were increased by 50% for the duration of the third trimester. A role for ritonavir has been proposed – PTD is not associated with nelfinavir (no ritonavir) or with atazanavir/r (100 mg ritonavir), and is most strongly associated with lopinavir (usually 200 mg daily; 300 mg daily in PROMISE).

Summary

The data regarding cART, including individual components of cART, and PTD remain complex and it is likely that there are several drivers. The most consistent findings suggest lopinavir/r should be avoided, while the latest UK data favour atazanavir/r if a PI is indicated. Randomised controlled trial data on the current most commonly prescribed boosted PIs in the UK are not available thus the NSHPC data provide the best guide. Additional data on once daily darunavir/r would be helpful. A patient friendly, approach to assessing the data has been developed by the BMJ guidelines group [62].

Of note, recent reports on the pharmacokinetic profiles of cobicistat and the safety concerns over dolutegravir exposure during the first few weeks of gestation demonstrate that the newest therapies may not be the safest in pregnancy and that older 'tried and tested' regimens may still be preferred, considering that a woman with fully suppressed HIV on therapy has a very low risk of vertical transmission regardless of the combination. Therefore safety in pregnancy becomes the most pressing concern. The importance and long-term impact of PTD, even with access to excellent neonatal care, should not be underestimated.

6.7 Pharmacokinetics of antiretrovirals in pregnancy

6.7	No routine dose alterations are recommended for antiretrovirals during pregnancy if used at standard adult licensed doses, apart from raltegravir, which should be given as 400 mg bd.	1C
	Consider TDM particularly if combining tenofovir DF and atazanavir/r.	2C
	If dosing off licence, consider switching to standard dosing throughout pregnancy or regular TDM.	2C

Physiological changes that occur even during the first trimester of pregnancy may affect the kinetics of drug absorption, distribution, metabolism and elimination, thereby affecting drug dosing [63]. In pregnancy, gastrointestinal pH is increased, transit time becomes prolonged, body water and fat increase, and there are accompanying increases in cardiac output, ventilation and liver and renal blood flow. Plasma protein concentrations decrease, notably albumin and α1 acid glycoprotein; renal sodium reabsorption increases and changes occur in the metabolic enzyme pathway in the liver, including changes in cytochrome P450.

6.7.1 NRTIs

The pharmacokinetics of most NRTIs (zidovudine [64], lamivudine [65] and abacavir [66]) are not significantly altered by pregnancy and dose adjustment is not required.

Tenofovir DF concentrations in the third trimester were reported to be reduced by about 15–25% compared with postpartum, but trough levels were adequate [67,68]; however in a population-based study of tenofovir DF use, clearance in pregnant women appeared to be 39% higher than in non-pregnant women [69]. Higher rates of treatment failure during pregnancy with tenofovir DF-containing combinations have not been reported. Another study reported lower tenofovir DF area under the curve (AUC) and trough levels throughout pregnancy and found that this was linked to higher maternal weight. One double dose of tenofovir DF administered shortly before delivery resulted in plasma concentrations similar to those observed in non-pregnant adults following a standard 245-mg dose and adequate levels in the neonate [23,70] (see section 9). A review of antenatal patients with HIV attending a London hospital showed no decline in renal function during pregnancy in women taking tenofovir DF.

Tenofovir alafenamide is a newer version of tenofovir DF and although data on the safety and pharmacokinetics of tenofovir alafenamide are limited, no signals for concern with regard to birth defect have been reported [71]. However, the writing group does not recommend its routine use in pregnancy until further data are available. This should be discussed with all women who conceive on tenofovir alafenamide, and consideration should be given to switching to an alternative NRTI regimen.

Data on emtricitabine show that while third-trimester concentrations are lower than postpartum the absolute concentrations achieved during pregnancy are adequate and dose adjustment is not required [68,72].

6.7.2 NNRTIs

Rilpivirine is recommended in the current BHIVA Adult Treatment Guidelines [5] as a first-line antiretroviral agent with tenofovir DF and emtricitabine in patients with viral load <100,000 HIV RNA copies/mL. A pharmacokinetic study by the PANNA consortium [73] carried out intensive 24-hour pharmacokinetic profiles in women living with HIV receiving rilpivirine 25 mg od in the third trimester and postpartum. Fifteen women were included in the study and rilpivirine levels were approximately 50% lower during the third trimester than postpartum. However, all women had <50 HIV RNA copies/mL at delivery and there were no vertical transmissions. Based on this, it is recommended that women may be commenced or continued on rilpivirine-containing regimens (with no routine dose adjustment) if they are able to take their medication with a meal to optimise pharmacokinetics, and that they are closely monitored with additional viral load monitoring and TDM if clinically indicated.

Efavirenz 600 mg od was reported in one study of 25 pregnant women to result in third-trimester plasma concentrations that were similar to 6- to 12-week postpartum concentrations. Cord blood to maternal blood ratio was 0.49 resulting in transplacental concentrations in the therapeutic range [74].

A study of the pharmacokinetics of etravirine 200 mg bd in 15 women found an increase in etravirine exposure during pregnancy but still within the range observed in previous studies of non-pregnant individuals with HIV treated with this dose [75]. Fourteen of 15 women had an undetectable viral load during pregnancy and no vertical transmissions were reported. A second study from the PANNA group has shown similar findings [76].

Nevirapine has been extensively investigated in pregnancy and plasma concentrations are similar to those in non-pregnant adults [18,77]. No dose adjustment is required when using licensed doses. There are no data on the prolonged release formulation of nevirapine in pregnant women and therefore consideration should be given to switching patients on 400 mg prolonged release formulation to the 200 mg bd formulation during pregnancy. It should be noted that nevirapine is no longer a preferred treatment option for naïve patients in the current BHIVA Adult Treatment Guidelines [5].

6.7.3 Integrase inhibitors

Raltegravir 1200 mg od should not be used in pregnancy. Instead a woman should be switched to or started on 400 mg bd.

A study of pregnant women taking raltegravir 400 mg bd found adequate trough levels in all 10 women in the study, although levels were very variable and lower than postpartum [76]. In another study of five women, third-trimester concentrations were no lower than postpartum and in the two cord blood samples studied, the cord blood to maternal blood ratio was >1.0 [78]. A third study of 23 women receiving raltegravir 400 mg bd, mostly as intensification of PI-based regimens during pregnancy, showed no statistically significant change in raltegravir concentrations during pregnancy and postpartum [79]. The PANNA study has also shown similar results [80]. In an ongoing prospective study of 31 women who took raltegravir during pregnancy, mostly (74%) starting in the third trimester, no evidence of adverse events has been observed in infants who are being followed up to 6 years [81].

The IMPAACT P1026s study is an ongoing prospective study of antiretroviral pharmacokinetics in pregnant women living with HIV [82]. Results from intensive 24-hour pharmacokinetic profiling for elvitegravir and cobicistat in women during the second and third trimesters and postpartum have been reported. Twenty-nine subjects were included and elvitegravir and cobicistat exposures were lower and clearance higher during pregnancy, compared to postpartum. Viral load at delivery was <50 HIV RNA copies/mL for 14/19 women (74%). Congenital abnormalities were reported in two infants. Analysis of elvitegravir and cobicistat levels in infant blood showed undetectable levels of cobicistat and a similar elvitegravir elimination half-life for infants in comparison to adults. In view of recent data on darunavir/cobicistat in pregnancy, cobicistat-boosted regimens are not recommended in pregnancy.

The IMPACT 1026 trial has also assessed maternal dolutegravir pharmacokinetics and showed that the calculated dolutegravir AUC was 25–30% lower in the second and third trimesters but not statistically significantly different to the AUC during the postpartum period. The AUC was also numerically similar to the value in non-pregnant adults. Therefore no dose adjustment is required [83].

6.7.4 PIs

While ritonavir-boosted PI therapy can maintain suppression of viral load, vertical transmission of HIV would be almost entirely dependent on antiviral activity within the woman. With minimal transplacental transfer, the low to undetectable drug concentrations in the fetus provide no peri-exposure protection. The writing group therefore recommends that, where possible, patients who conceive on PI monotherapy should have their regimen intensified with agents that cross the placenta.

Pharmacokinetic and safety data in pregnancy for cobicistat-boosted PIs show low darunavir exposure during the second and third trimesters of pregnancy which may be associated with virological failure based on a pharmacokinetic study of six pregnant women [84]. Compared with levels 6–12 weeks postpartum, where mean exposure of darunavir boosted with cobicistat was 90%, darunavir levels were lower in the second (56%) and third trimesters (50%). Cobicistat exposure was 63% and 49% in the second and third trimesters respectively. Therefore darunavir/cobicistat should not be initiated in pregnancy and women receiving this combination as part of cART and who become pregnant should be switched to an alternative such as darunavir/r. When given with elvitegravir, cobicistat has been shown to have lower levels during pregnancy and it does not cross the placenta [82]. For this reason, the writing group recommends that the boosting agent is switched from cobicistat to ritonavir for women who conceive on a cobicistat-boosted PI regimen. When initiating PIs during pregnancy, it is recommended that ritonavir is the boosting agent of choice.

PIs are highly protein bound and placental transfer in humans appears to be limited. During the third trimester of pregnancy, small reductions in protein binding can significantly increase free drug levels. For example, the protein binding of lopinavir reduces marginally to 99%, which results in 17% more unbound lopinavir [85]. It is therefore difficult to interpret the significance of studies that show reduced total plasma levels, with an increased likelihood of trough levels below the target during pregnancy. Compared with concentrations postpartum, concentrations of lopinavir/r 400/100 mg during the third trimester are reduced by 28%. The protein-free fraction is moderately increased (17%) and, at the standard dose, lopinavir appears to be clinically effective with a wide variation in individual plasma trough concentrations. A study using the tablet formulation showed that women taking three tablets bd (lopinavir/r 600/150 mg) achieved similar AUC levels to non-pregnant adults taking the standard dose of two tablets bd [86]. The improved bioavailability of the tablet formulation is also found in pregnant women and this, together with the impact of pregnancy on changes in protein binding, increases the protein-free fraction in the third trimester [87]. The writing group recommends that no dose adjustment is required in pregnancy for patients on lopinavir/r but notes that this treatment is no longer preferred for the reasons given above.

A study from Italy demonstrated similar atazanavir concentrations at standard 300 mg dose with ritonavir 100 mg od during the third trimester and postpartum [88]. However, recently third-trimester 24-hour AUC concentrations 28% lower than postpartum concentrations were reported from North America. Third-trimester concentrations of atazanavir in women taking tenofovir DF were lower still (i.e. approximately 50% of the postpartum values of women on atazanavir without tenofovir DF), and 55% of women in the study taking tenofovir DF had lower than target atazanavir concentrations. The study authors therefore recommended that it may be necessary to increase the dose of atazanavir to 400 mg (when given with ritonavir 100 mg od) during the third trimester [89]. A systematic review has demonstrated that grade 3–4 maternal hyperbilirubinaemia rates are doubled with atazanavir/r 400/100 mg [90]. Data from the Europe-based PANNA study also revealed a 33% reduction in third-trimester AUC and last measurable plasma atazanavir concentrations compared with postpartum. However, all drug concentrations measured, including with co-administered tenofovir DF, were above the recommended minimum plasma concentration for wild-type virus and therefore the writing group recommends consideration of an increased dose in experienced patients on an individual basis only if required [91].

Atazanavir/r 400/100 mg is also recommended in women who require an H2 antagonist during pregnancy, however the combination of atazanavir/r, tenofovir DF and an H2 antagonist is not recommended [90].

When prescribed with zidovudine/lamivudine, plasma concentrations achieved with atazanavir/r 300/100 mg od are only 21% less (by AUC) than historic controls whereas trough concentrations were reported to be comparable to these controls. Increasing the dose of atazanavir to 400 mg od during the third trimester increased trough concentrations by 39% and doubled the risk of hyperbilirubinaemia [92]. A case note review of 122 women in London receiving atazanavir/r did not show virological failure during pregnancy despite 83% receiving standard dosing of 300 mg with ritonavir 100 mg, and the authors concluded that the data did not support routine atazanavir dose escalation in pregnancy [56].

For darunavir, a study from the USA showed reduced troughs and 24-hour AUC values with daily dosing in pregnancy, whereas twice daily dosing produced levels more comparable to those in non-pregnant individuals [93]. The authors concluded that twice daily dosing should be used in pregnancy and higher doses may be required. For women receiving darunavir/r 800/100 mg, the AUC was reduced by 38% in the second trimester and by 39% in the third trimester compared to postpartum levels. With twice daily dosing the AUC was reduced by 26% in both trimesters. Similar findings have been reported from the PANNA network with subtherapeutic trough concentrations with 800/100 mg od dosing and no detectable darunavir in any of the cord blood samples collected [94]. Zorrilla *et al.* reported that, although total darunavir exposure decreases during pregnancy, there were no significant changes in unbound darunavir concentration compared with postpartum and concluded that no dose adjustment is required when darunavir/r is prescribed at 600/100 mg bd [95]. Others have also reported that although there is a reduction in darunavir levels during pregnancy, this is less pronounced when unbound darunavir levels are measured [94,96].

A pharmacokinetic study by the IMPAACT P1026s study group showed no impact on third-trimester darunavir levels by further increasing the dose from 600/100 mg bd to 800/100 mg bd, therefore this is not recommended [97]. The clinical relevance of these pharmacokinetic studies has yet to be fully determined.

It is the view of the writing group that if a patient conceives on darunavir-based cART and has a fully suppressed viral load on a daily regimen, this regimen may be continued. A more cautious approach using twice daily darunavir may be considered if initiating ART in pregnancy with darunavir or where there is known protease resistance. Although the pharmacokinetic data are consistent across studies, the virological impact during pregnancy and postpartum are unknown. Such outcome data are needed. Where the 600/100 mg bd dose is used, women should be reviewed postpartum for appropriateness to switch to the 800/100 mg od dose.

In general, there are still limited data on the currently available PI formulations. Given this lack of data and the considerable degree of interpatient variability, TDM for PIs during pregnancy can be considered, but is not routinely recommended in the absence of studies that show improved outcomes. If performed, TDM should be conducted at steady state (2 weeks or more into therapy) and repeated in the third trimester.

6.7.5 Other agents

The pharmacokinetic profiles of enfuvirtide in pregnancy, as well as of tipranavir and maraviroc, have not been described. It is noteworthy that enfuvirtide does not cross the placenta [98].

6.8 Stopping ART postpartum

6.8.1	Stopping ART after delivery is not recommended; women who wish to stop ART should be counselled on the risks and managed as per the BHIVA guidelines for the treatment of HIV-positive adults with antiretroviral therapy [5].	1B

6.9 HIV-2

6.9.1	Case discussion with experts with experience of managing HIV-2 is recommended for all women.	1D
6.9.2	A boosted PI-based regimen such as twice daily darunavir/r is recommended in women with HIV-2.	1C

Vertical transmission of HIV-2 is considerably less common than of HIV-1, varying between 0% and 4% in the absence of any intervention to reduce transmission [99-101]. It is likely that this can be explained by the lower viral loads seen in HIV-2 infection [101]. Nevertheless, vertical transmission can occur; of note, dual infection with HIV-1 and -2 as well as mono-infection can occur. There is no systematic evidence to guide choice of treatment for pregnant women with HIV-2 or PEP for the infant. Case discussion with experts with experience of managing HIV-2 is recommended for all women. A ritonavir-boosted PI-based regimen is recommended and tenofovir DF/emtricitabine with twice daily darunavir/r would be likely to have the greatest anti-viral efficacy. It is suggested that such treatment is used, even in the presence of an undetectable HIV-2 viral load; this would help to avoid management difficulties if the viral load becomes detectable late in pregnancy. Agents used as PEP for

the infant are a matter for expert opinion and discussion. Zidovudine monotherapy would be the minimum recommendation, but clinicians may wish to use triple therapy with raltegravir as a cautious approach and certainly if the viral load is detectable at delivery. Raltegravir is suggested because HIV-2 is sensitive to integrase inhibitors [102] and there is greater experience and availability of suitable formulations in paediatric dosing (see Appendix 3).

6.10 References

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7. HIV and hepatitis virus co-infections

7.1 Hepatitis B virus (HBV)

The combination of HIV, chronic HBV infection and pregnancy presents unique management considerations. Referral to the local designated specialist should be undertaken to ensure that all aspects of care are addressed, including the effects of HBV/HIV on pregnancy, effects of pregnancy on the course of co-infection, antiretroviral management for both HBV and HIV, and prevention of vertical transmission for both viruses. Pregnant women with advanced cirrhosis should be managed in a tertiary centre with a hepatologist.

The prevalence of HBV co-infection in pregnant women tends to reflect that of the adult population (Europe/Africa 4–10%) [1-4] and is 40% higher than that found in the general population (HIV positive *vs* HIV negative: relative risk [RR] 1.40; 95% CI 1.16–1.69) [1]. Up to one-third of hepatitis B surface antigen (HBsAg) is wild-type (hepatitis B envelope antigen [HBeAg] positive) and, depending on region, up to 6% of individuals may be co-infected with hepatitis delta virus. Rates of HBV/HIV co-infection vary with race and ethnicity so that changing immigration patterns in Western countries with traditionally low prevalence may significantly influence rates at a regional level (e.g. 6% among Asian women in the USA *vs* 0.6% in white women) [5]. The same is true for injecting drug use (prevalence <0.1% in Northwestern Europe compared to 1–4% in Southern Europe) and sexual transmission (prevalence is higher in men who have sex with men).

Although plausible because of higher levels of HBV DNA in women living with both HBV and HIV, there is no evidence of increased vertical transmission of HBV in co-infection compared with mono-infection. The impact of pregnancy on women with HBV mono-infection is small. There appears to be no worsening of liver disease in the majority of women, although case reports of hepatic exacerbations/fulminant hepatic failure have been reported; alanine transaminase (ALT) levels tend to fall, HBeAg seroconversion occurs in a small minority and may be associated with liver dysfunction, and HBV DNA levels may rise by as much as 1 $\log_{10}$ unit. The impact of HBV infection on pregnancy appears negligible.

By contrast, the effect of HIV on HBV disease progression includes higher levels of HBV replication (HBV DNA levels and proportion HBeAg positive), higher mortality when compared to HIV or HBV mono-infection, a higher rate of chronicity (20–80% compared to 3–5% in HIV-negative individuals with risk increasing with lower CD4 cell counts at the time of HBV acquisition), lower ALT levels, higher rate of hepatoma, lower rate of spontaneous loss of HBeAg or HBsAg and seroconversion to anti-HBe and anti-HBs, faster progression to cirrhosis, and a higher incidence of lamivudine resistance [6].

7.1.1	On diagnosis of new HBV infection, confirmation of viraemia with quantitative HBV DNA, ‘e’ antigen status as well as hepatitis A virus (HAV), HCV and hepatitis D virus (HDV) screening and tests to assess hepatic inflammation/fibrosis and liver function are recommended.	1C
7.1.2	LFTs should be repeated at 2 and 4 weeks after commencing ART to detect evidence of hepatotoxicity or immune reconstitution inflammatory syndrome (IRIS) and then monitored regularly throughout pregnancy and postpartum.	1C

In a pregnant woman living with HIV and newly diagnosed with HBV (HBsAg positive on antenatal screening or diagnosed preconception), baseline hepatitis B markers (anti-HBc/HBeAg/anti-HBe status) and level of the virus (HBV DNA), the degree of inflammation and synthetic function (ALT, aspartate transaminase [AST], albumin and international normalised ratio [INR]), an assessment of fibrosis and the exclusion of additional causes of liver disease (e.g. haemochromatosis and autoimmune hepatitis) are indicated. Additionally, patients should be assessed for the need for HAV immunisation, by testing for HAV immunoglobulin (Ig)G antibody, as well as for HDV co-infection (HDV serology and HDV RNA if positive).

Liver biopsy and hepatic elastometry (FibroScan) are relatively contraindicated during pregnancy [7], therefore clinical assessment, use of blood panel-based fibrosis markers (e.g. aspartate aminotransferase-to-platelet ratio 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] however it is not recommended for use in pregnancy. 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 [13,14] and international guidelines [15].

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.	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 lamivudine/emtricitabine-resistant HBV or HIV.	1C
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 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 [16]. 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 [17,18], but as stated previously there are no safety data in pregnant women therefore it should be avoided unless tenofovir DF is contraindicated. 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 [19] 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 [13], 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 [20]. It also selects for resistance for both HBV and HIV less rapidly and less often than lamivudine [20]. 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) [21]. Further studies comparing emtricitabine/lamivudine with lamivudine alone produced similar results [22].

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) [23].

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 [24]. 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 [25]. 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 [26] 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 [27].

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 [28].

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) [29]. 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 [30].

Another meta-analysis suggested that oral antiviral therapies in pregnancy, including lamivudine, telbivudine and tenofovir DF, reduce the rates of vertical HBV transmission [31].

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 [32].

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* [33].

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 [34]. 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 [32] 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 [35,36]. 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 [37,38]. Conversely, the higher risk of HCV transmission seems to be ameliorated in co-infected mothers who have suppressed HIV on ART [39,40]. 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) [37,38]. 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 [41].

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 [42-44]. 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 [39,40]. Indeed some studies have shown a lower risk of HCV transmission in infants born by CS [45,46]. However, a meta-analysis in HCV mono-infected women concluded that there was no effect of mode of delivery on risk of vertical transmission [47]. Effective cART significantly reduces the rate of HCV transmission, possibly by reducing HCV viraemia [39,48]. Lack of immune regulation during pregnancy may also facilitate HCV transmission via peripheral blood monocytes [49]. No correlation between HCV genotype or interleukin-28 polymorphisms and transmission has been identified [44,50,51]. 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* [52].

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 [53]. 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 [54]. 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@increscarch.com).

There are limited data on the possible teratogenicity of DAA-based IFN-free therapy without ribavirin. The currently licensed DAA therapies sofosbuvir, sofosbuvir/ledipasvir fixed-dose combination (FDC), daclatasvir, dasabuvir, grazoprevir/elbasvir FDC and sofosbuvir/velpatasvir FDC have not shown teratogenicity in small-animal studies, but have variable ability to cross the placenta and into breast milk [55-57]. Paritaprevir/ribavirin/ombitasvir FDC and daclatasvir have both shown risk of malformations in small animals at supranormal dose exposures [58,59].

There is no evidence that HCV can be transmitted vertically in the absence of HCV viraemia, therefore only viraemic patients would be considered for therapy. The current standard of care in HCV therapy is DAA-based IFN-free therapy with or without ribavirin [60]. There are no definitive studies on the safety of HCV antiviral therapy during pregnancy.

Finally, it is recognised that a small number of individuals with both HCV and HIV are HCV antibody negative but HCV viraemic. Where there is evidence of liver inflammation or fibrosis, profound immune deficiency or risk factors, an HCV viral load assay should be performed.

7.2.3	Pregnant women with both HCV and HIV should not be treated for HCV with ribavirin-based directly acting antiviral (DAA) therapies, and all women who discover they are pregnant while receiving treatment should discontinue HCV therapy immediately.	1B
7.2.4	Women with both HCV and HIV of child-bearing age wishing to become pregnant should be prioritised for DAA-based HCV therapy.	2D

Given the issues with treatment during pregnancy and the postnatal period, it is the writing group's view that HCV-infected women of child-bearing age wishing to become pregnant should be prioritised for DAA-based anti-HCV therapy regardless of fibrosis stage, and should delay pregnancy until after treatment is completed or longer if ribavirin based as noted above. See section 9 for guidance on subsequent screening of the infant.

7.2.5	Vaccination against HBV is recommended for all women with both HCV and HIV after the first trimester, unless already immune.	1C

Immunisation for HBV uses an inactivated vaccine. Limited data are available on the use of HBV vaccination in pregnancy and none in pregnant women living with HIV. Moreover, no randomised trial has been performed to determine the optimum dosing schedule for use in pregnancy [61]. Nevertheless, several guidelines indicate that pregnancy is not a contraindication for HBV immunisation, including in pregnant women with both HCV and HIV [24].

In single-arm open studies in HIV-negative persons, seroconversion rates for HBV are no different in the pregnant and non-pregnant woman and no fetal risks have been reported. In a prospective clinical trial in pregnant women, an accelerated schedule at 0, 1 and 4 months was found to be effective and well tolerated, and had the advantage of potential completion prior to delivery [62]. Patients with higher CD4 cell counts and on cART generally show improved responses to vaccination. Regardless of CD4 cell count, anti-HBs level should be measured 6–8 weeks after completion of vaccination. In a systematic review and meta-analysis of five studies, an increased-dose HBV vaccination schedule improved anti-HBs response rates compared to standard-dose HBV vaccination (OR 1.96; 95% CI 1.47–2.61) with separate randomised trial data demonstrating improved serological response with four-dose regimens [63].

7.2.6	In all HAV non-immune women with both HCV and HIV, HAV vaccination 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 also uses an inactivated vaccine and data for HAV vaccination in this setting are similarly limited. Individuals living with HIV with CD4 cell counts <300 cells/mm^3 should receive three instead of the standard two doses of HAV vaccine over 6–12 months [24].

7.2.7	In the absence of obstetric complications, normal vaginal delivery can be recommended if the woman is receiving effective cART for HIV, irrespective of HCV viral load.	2C

As HCV antiviral therapy is contraindicated in pregnant women due to possible teratogenicity, mode of delivery remains the only possible risk factor amenable to intervention. No randomised studies of CS compared to normal vaginal delivery to prevent vertical transmission of HCV have been performed. In HCV mono-infection, two meta-analyses failed to show a significant decrease in HCV vertical transmission among women who underwent CS compared with women who gave birth vaginally (OR 1.10–1.19) [47]. In the first European Paediatric Hepatitis Network (EPHN) cohort, a subgroup analysis of women with both HCV and HIV (*n*=503; 35.4%) demonstrated a reduced risk of vertical transmission of HCV with CS (OR 0.43; 95% CI 0.23–0.80) [64]. However, in a later analysis also from the EPHN (*n*=208; 15.0%) no such association was found (OR 0.76; 95% CI 0.23–2.53) [39]. In this later analysis, the rate of vertical transmission of HCV was reduced (8.7% *vs* 13.9%) and more women probably received cART (41%), which was associated with a significant HCV viral load reduction compared to those who received HIV monotherapy or no therapy (OR 0.26; 95% CI 0.07–1.01). There was also a trend towards lower HCV viral load in this group, which may in part explain the findings. In addition, in a small French cohort of women with both HCV and HIV (29% on cART), rates of vertical transmission did not differ significantly between infants born by

vaginal delivery or CS [65]. A recent systematic review concluded that no intervention, in terms of mode of delivery, obstetric intervention or avoidance of breastfeeding, reduces the risk of HCV transmission [66]. cART should be given to all pregnant women with both HCV and HIV, regardless of CD4 cell count or HIV viral load because of the evidence of increased HIV vertical transmission in this group.

7.2.8	cART should be continued postpartum in all women with both HIV and HCV regardless of HCV viraemia, fibrosis stage or CD4 cell count.	1A

Recommendations for lifelong ART are in line with current BHIVA guidelines [67] and section 6 in these guidelines. Furthermore, effective HIV suppression improves liver histology even in the absence of effective HCV treatment [68,69].

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8. Obstetric management

8.1 Antenatal management

8.1.1	Fetal ultrasound imaging should be performed as per national guidelines regardless of maternal HIV status.	1D

The National Screening Committee [1] and the NICE antenatal guidelines [2] recommend that ultrasound screening for fetal anomaly should be offered to all pregnant women between 18+0 and 20+6 weeks' gestation. There is no evidence to alter this for women living with HIV.

In the past, because of a theoretical increased risk of anomaly due to first-trimester ART exposure, more detailed ultrasound scanning (i.e. in a fetal medicine unit) has been considered. The evidence from prospective reports of first-trimester ART exposure to the APR [3] does not support the need for increased surveillance with the most commonly prescribed therapies (listed in Appendix 3), although with newer medication the knowledge base is inevitably limited (see also section 6). APR reports on the frequency and nature of birth defects and ART are updated every 6 months (www.apregistry.com).

8.1.2	The combined screening test for fetal aneuploidies and non-invasive prenatal testing (NIPT) for those who screen as high risk is recommended as this has the best sensitivity and specificity and will minimise the number of women who may need invasive testing.	1A

NICE antenatal guidelines [2] also recommend that all women should be offered screening for trisomies 13, 18 and 21. The most effective screening is with the combined test at 11+0 to 13+6 weeks' gestation. This includes maternal age, nuchal translucency, β-human chorionic gonadotrophin (βHCG) and pregnancy-associated plasma protein A (PAPP-A). In the general population this has a detection rate of 92.6% with a false-positive rate of 5.2% [4].

For women who present too late for the combined test, the most clinically effective and cost-effective serum screening test for Down's syndrome (triple or quadruple test) should be offered between 15 weeks 0 days and 20 weeks 0 days [2]. However, significantly increased levels of βHCG and α-fetoprotein and lower levels of unconjugated oestriol (the elements of the 'triple test') have been observed in women with HIV [5-7] while a reduction in βHCG in patients treated with PI-based [8] or NNRTI-based cART has been reported. Down's syndrome is associated with increased βHCG, therefore HIV infection *per se* may increase the false-positive rate in women and thus increase the number of invasive tests offered compared with the general population [9]. PAPP-A and nuchal translucency are unaltered by HIV infection or ART [10] and thus are the preferred screening modality for women presenting between 15 and 20 weeks' gestation.

In 2016 the National Screening Committee recommended that NIPT of free fetal DNA in maternal serum should be offered to all pregnant women in the UK who are stratified as high risk after the combined test or serum screening tests [11]; at the time of writing, widespread implementation of this has yet to be adopted. NIPT has been shown to be highly effective at screening for fetal aneuploidy, with a lower false-positive rate and higher positive predictive values than standard screening [12]. The adoption of NIPT for women stratified as high risk following screening will further reduce the number of women to whom invasive prenatal diagnostic tests are offered.

8.1.3	Invasive prenatal diagnostic testing should not be performed until after the HIV status of the woman is known, and should ideally be deferred until HIV viral load has been adequately suppressed to <50 HIV RNA copies/mL.	1C

Limited data suggest that amniocentesis is safe in women on cART [13-15]. There are minimal data on other forms of prenatal invasive testing. It is now possible to use NIPT to screen for Down's syndrome and other common aneuploidies. All clinicians performing a prenatal invasive test should know the woman's HIV status, and if necessary delay the invasive test until the HIV result is available. Where possible, amniocentesis should be

deferred until the viral load is <50 HIV RNA copies/mL. The fetal medicine team should discuss management with an HIV physician in cases where a woman has a detectable HIV viral load.

8.1.4	If not on cART and the invasive diagnostic test procedure cannot be delayed until viral suppression is achieved, it is recommended that women should commence cART to include raltegravir and be given a single dose of nevirapine 2–4 hours prior to the procedure.	1D

The French Paediatric HIV Infection Study Group observed an increased risk of HIV transmission (RR 1.9; 95% CI 1.3–2.7; *P*=0.003) with 'antenatal procedures' that included amniocentesis, cerclage, laser therapy and amnioscopy [16]. This study was conducted between 1985 and 1993 and, of the 1632 mother–infant pairs (overall transmission 19%), only 100 women had received zidovudine, mostly for advanced HIV infection.

There are few studies on the safety of invasive testing in the cART era. A study of 9302 pregnancies in France in 2009 (including 166 during which an amniocentesis was performed) showed that the risk of vertical transmission of HIV in the untreated group increased from 16% to 25% in women who had an amniocentesis; in those on zidovudine alone the risk increased from 3% to 6% and in those on cART there were no transmissions in 81 women who underwent amniocentesis [17]. Viral load data were not reported, but in other settings suppression of viral load reduces transmission.

A further study of nine women on cART in France (in 2008) [15] and 17 women on cART in Portugal (1996–2009) showed no transmissions, whereas transmission occurred in one of six women either not diagnosed with HIV prior to amniocentesis, or not treated prior to the procedure. There are no studies and few case reports in the cART era examining chorionic villus sampling or cordocentesis [18]. For evidence relating to choice of ART to reduce transmission risk associated with amniocentesis, see section 6.4.

8.1.5	External cephalic version (ECV) can be offered to women with plasma viral load <50 HIV RNA copies/mL.	2D

ECV for breech presentation can be performed at term from 37+0 weeks of gestation in women with an undetectable plasma viral load. In nulliparous women, ECV may be offered from 36+0 weeks of gestation, in line with current guidance.

There is less obstetric risk to the baby and woman when the fetus is head-down at the time of birth. ECV is a procedure by which the fetus, which is lying bottom first, is manipulated through the woman's abdominal wall to the head-down position. If the fetus is not head down by about 36 weeks of pregnancy, ECV reduces the chance that the fetus will present as breech at the time of birth, and thus reduces the chance of caesarean section. There is no published evidence that helps decision making regarding ECV in the pregnant woman living with HIV. For the general maternity population, ECV is recommended [2]. There is a low rate of complications, with an estimated 0.5% incidence of immediate caesarean section [2].

The question of whether ECV might increase the risk of vertical transmission of infections such as HIV is important; however, there is currently no direct evidence to support this. The incidence of fetomaternal haemorrhage after ECV has been estimated at 2.4%, this represents the new presence of fetal blood cells in the maternal circulation after the procedure [19]. It has been postulated that, due to the structure and function of the placenta, the risk of maternal blood entering the fetal circulation due to ECV is much lower [19]. It is also reassuring that in a randomised trial of fundal pressure to expel the baby during caesarean section, no evidence of maternal–fetal transfusion was found [20]. It is the writing group's opinion, therefore, that ECV can be offered to women with a breech presentation who have a plasma viral load <50 HIV RNA copies/mL.

8.2 Mode of delivery

For women taking cART, a decision regarding recommended mode of delivery should be made after review of plasma viral load results at 36 weeks.

8.2.1	For women with a plasma viral load of <50 HIV RNA copies/mL at 36 weeks, and in the absence of obstetric contraindications, planned vaginal delivery should be supported.	1C
8.2.2	For women with a plasma viral load of 50–399 HIV RNA copies/mL at 36 weeks, pre-labour CS (PLCS) should be considered, taking into account the actual viral load, the trajectory of the	1C

	viral load, length of time on treatment, adherence issues, obstetric factors and the woman's views.	
8.2.3	Where the viral load is ≥400 HIV RNA copies/mL at 36 weeks, PLCS is recommended.	1C

Published cohort data from the UK and other European countries have shown vertical transmission rates of <0.5% in women with plasma HIV RNA <50 HIV RNA copies/mL taking cART, irrespective of mode of delivery [21-25]. These studies support the practice of recommending planned vaginal delivery for women on cART with plasma viral load <50 HIV RNA copies/mL.

The most recent analysis from the NSHPC UK and Ireland surveillance study investigated vertical transmission of HIV in women delivering between 2000 and 2011 (*n*=2000) [26] and found that the overall transmission rate in women with undetectable viral load (<50 HIV RNA copies/mL) was 0.09%, and 0.06% (4/6345) when two *in utero* transmissions were excluded; there was no significant difference between CS and planned vaginal delivery (0.11% *vs* 0.15%; *P*=0.53). For all modes of delivery, risk of transmission was significantly higher when viral load was 50–399 HIV RNA copies/mL than when fully suppressed (<50 HIV RNA copies/mL). Among 1033 women with viral load of 50–399 HIV RNA copies/mL, vertical transmission rates were 0.8% following CS and 1.6% following planned vaginal delivery (*P*=0.39). Women delivering by CS had a slightly shorter duration of cART than those who had planned vaginal deliveries in this group (median 12.4 *vs* 13.9 weeks; *P*=0.007). Excluding five *in utero* transmissions, the vertical transmission rate among women with viral load of 50–399 HIV RNA copies/mL was 0.26% (2/777) following CS and 1.1% (2/188) following planned vaginal delivery (*P*=0.17).

A recent analysis from the ANRS French Perinatal cohort examined CS in 8977 women delivering on cART between 2000 and 2010, and found no difference in unadjusted vertical transmission rates by mode of delivery in 3075 women delivering at term (>37 weeks) with a viral load <50 HIV RNA copies/mL (0.3% for vaginal delivery, 0.3% for CS and 0.3% for non-CS; *P*=1.00). For 707 women who delivered at term with viral load of 50–399 HIV RNA copies/mL, there was also no difference in transmission by mode of delivery (1.0%, 1.0% and 2.5% respectively; *P*=0.24). The authors did not comment on the timing of transmission in the infants diagnosed with HIV [27].

Older data were reported from the ANRS French Perinatal cohort of 5271 women delivering between 1997 and 2004, of whom 48% were on cART. In women on cART with a delivery viral load <400 HIV RNA copies/mL there was no significant difference in vertical transmission rates according to mode of delivery, with 0.4% (3/747) transmission in the CS group compared with 0.5% (3/574) transmission in the vaginal delivery group (*P*=0.35). The effect of mode of delivery was also analysed for women delivering with a viral load >10,000 HIV RNA copies/mL and no significant protective effect of CS was seen (OR 1.46; 95% CI 0.37–5.80). Vertical transmission of HIV was low at 0.4% in women delivering with a viral load <50 HIV RNA copies/mL but mode of delivery data for this subset were not provided [25].

By contrast, data from the European Collaborative Study of 5238 women delivering between 1985 and 2007 showed that in 960 women delivering with a viral load <400 HIV RNA copies/mL, PLCS was associated with an 80% decreased risk of vertical transmission after adjusting for cART and prematurity (adjusted OR 0.2; 95% CI 0.05–0.65). There were only two transmissions among 599 women delivering with viral load <50 HIV RNA copies/mL (transmission rate 0.4%) with one delivering vaginally at <34 weeks and one by emergency CS at 37 weeks, but further analysis was not possible [21].

A potential explanation for the differing conclusions of the effect of mode of delivery on vertical transmission in women with delivery plasma viral load <400 HIV RNA copies/mL in these two studies is that there may be a significant difference in the viral load distribution <400 HIV RNA copies/mL between studies. This highlights the fact that it is not possible to infer that vertical transmission rates from studies using a viral load assay with a cut-off value <400 HIV RNA copies/mL can necessarily be applied to patients with plasma viral loads of 50–399 HIV RNA copies/mL using current assays with lower limits of detection of 50 HIV RNA copies/mL or less.

Although neither of the most recent UK and French analyses showed a statistically significant difference in vertical transmission by mode of delivery for women with plasma viral loads between 50 and 399 HIV RNA copies/mL, in the UK/Ireland dataset the risk of vertical transmission for women delivering vaginally is about twice that of those delivering by CS, and this rises to four-fold when *in utero* transmissions are excluded. The writing group therefore recommends that CS should be considered in this group taking into account the actual viral load, the trajectory of the viral load, length of time on treatment, adherence issues, obstetric factors and the woman's views.

Multiple observational studies and a randomised controlled trial established the benefit of CS in women not on effective ART, reducing the risk of vertical transmission by two-thirds in the pre-cART era. More recent observational studies only included very small numbers of women delivering vaginally with a viral load >400 HIV RNA copies/mL, due to the evolution of recommended clinical practice. Studies to date do not provide data to determine the viral threshold above which CS should definitely be recommended. However, given the conflicting data regarding the effect of mode of delivery on vertical transmission in women with a viral load <400 HIV RNA copies/mL, together with the data from the UK study showing a 2.4-fold increased risk of transmission for every 1 $\log_{10}$ unit increase in viral load associated with mode of delivery, the writing group continues to recommend CS for all women with a viral load ≥400 HIV RNA copies/mL.

8.2.4	In women for whom a vaginal delivery has been planned and labour has commenced, obstetric management should follow the same guidelines as for the HIV-negative population, apart from duration of ruptured membranes (see section 8.3).	1C

Traditionally amniotomy, fetal scalp electrodes and blood sampling, instrumental delivery and episiotomy have been avoided in HIV infection because of theoretical transmission risks. Data from the pre-cART era have been reviewed, and show little or no risk for many of these procedures. Scant data are available from the cART era.

The French cohort (1985–1993) provides data on the risk of various obstetric factors in a predominantly untreated, non-breastfeeding population. Procedures, classified as amniocentesis and other needling procedures, cerclage, laser therapy and amnioscopy, were associated with an increased risk of transmission (RR 1.9; 95% CI 1.3–2.7).

Fetal skin lesions (RR 1.2; 95% CI 0.7–1.8) and episiotomy/tear (RR 1.0; 95% CI 0.7–1.3) were not associated with transmission [16]. In a retrospective study from Spain, predominantly in the pre-cART era, HIV transmission occurred in 26.3% of infants exposed to fetal scalp monitoring (electrodes or pH sampling or both) compared with 13.6% exposed to neither type of monitoring (RR 1.94; 95% CI 1.12–3.37) [28]. However, prolonged rupture of membranes was a significant contributor to the risk of transmission associated with this invasive monitoring. In the Swiss cohort neither fetal scalp electrodes (RR 2.0; 95% CI 0.58–6.91) nor pH blood sampling (RR 1.73; 95% CI 0.58–5.15) were confirmed as independent risk factors [29]. In the Women and Infants Transmission Study (WITS) cohort (1989–1994) artificial rupture of membranes (RR 1.06; 95% CI 0.74–1.53) and exposure to blood during labour (RR 0.7; 95% CI 0.4–1.27) or delivery (RR 1.06; 95% CI 0.74–1.52) were not associated with transmission [30].

Induction has previously been avoided as there were concerns about the duration of ruptured membranes and risk of vertical transmission but recent evidence (see section 8.3) appears to be reassuring with regard to these concerns.

Data from the predominantly untreated French cohort (1985–1993) showed no risk with instrumental vaginal delivery (RR 0.8; 95% CI 0.6–1.2) [16]. Data from the smaller Swiss cohort (*n*=494; 1986–1996; transmission rate 16.2%) also failed to identify instrumental delivery as a risk factor for transmission (RR 1.82; 95% CI 0.81–4.08) despite less than 20% of the cohort taking any ART for prophylaxis [29].

The NSHPC recently reported data on operative vaginal deliveries in women in the cART era between 2008 and 2016; of 3023 vaginal deliveries, 251 infants were delivered with forceps or vacuum [13]. Infection status was available for 222/233 infants who had reached 18 months of age: one infant was diagnosed with HIV, but timing of infection is unclear and there were other risk factors present. This is consistent with previously reported transmission rates in this population, and numbers are too small to draw further conclusions.

In the absence of trial data for women with HIV infection who undergo an operative vaginal delivery, evidence to support a benefit of any type of operative vaginal delivery compared to CS for women or their infants is limited to expert judgement and extrapolation from other datasets, and is subject to inherent biases. There are theoretical reasons why low cavity traction forceps may be preferred to a vacuum-assisted delivery (i.e. as it is generally accepted that they are associated with lower rates of fetal trauma than vacuum-assisted delivery). In women with a viral load <50 HIV RNA copies/mL it is unlikely that the type of instrument used will affect transmission risk and thus the one the operator feels is most appropriate should be used as in the non-HIV population (and following national guidance [31]).

The importance of the use of ART in the prevention of vertical transmission of HIV is clear and undisputed. High-quality studies to determine the remaining contribution of obstetric events and interventions to prevent transmission in the setting of a fully suppressed HIV viral load have not been performed and are unlikely to be performed in the near future.

HIV DNA [32] and HIV RNA [33] in cervicovaginal lavage have been identified as independent transmission risk factors. Large cohort studies from the UK and Ireland as well as from France have concluded that there is no significant difference in vertical transmission in women with an undetectable HIV viral load when comparing those who have a planned vaginal delivery and those who have a CS. These studies provide some reassurance with regard to concerns raised about possible discordance between plasma and genital tract viral load that have been reported in patients with an undetectable viral load on cART [34-37]. The clinical significance of this phenomenon is not clear and further research is warranted.

Furthermore, there are reassuring results from the limited studies that have examined the effect on vertical transmission of amniocentesis and length of time of rupture of membranes in women on cART and in those with a viral load <50 HIV RNA copies/mL. An association between vertical transmission and the use of instrumental delivery, amniotomy and episiotomy is not supported by data from the pre-cART era and there is a lack of data from the cART era. Therefore, while acknowledging the potential for discordance between the plasma and genital tract viral load, the writing group considers that there is no compelling evidence to support the continued avoidance of these procedures as well as induction of labour in women on cART for whom a vaginal delivery had been recommended on the basis of viral load.

The data regarding fetal blood sampling and the use of scalp electrodes also originate from the pre-cART era and have yielded conflicting results. The writing group acknowledges a lack of data from the cART era, but concludes that it is unlikely that the use of fetal scalp electrodes or fetal blood sampling confers increased risk of transmission in a woman with an undetectable viral load although this cannot be proven from the current evidence. Electronic fetal monitoring should be performed according to national guidelines [31]. HIV infection *per se* is not an indication for continuous fetal monitoring as there is no increased risk of intrapartum hypoxia or sepsis. If the woman has no other risk factors, she can be managed by midwives either in a midwifery-led unit or at home. She will need to continue with cART through labour and adequate provision needs to be made for examination and testing of the newborn and dispensing of medication to the newborn in a timely fashion (see section 9).

8.2.5	Vaginal birth after CS (VBAC) can be offered to women with a viral load <50 HIV RNA copies/mL.	1D

In the absence of randomised trial data for women with HIV infection who undertake VBAC, evidence to support a benefit of VBAC and vaginal birth over CS is limited to expert judgement that is subject to inherent biases.

The probability of a successful vaginal delivery remains dependent on current and past obstetric factors. In general, provided that the woman is being cared for in a consultant-led maternity unit and the labour properly monitored with rapid recourse to CS in the face of any difficulty, the outcome of trial of labour for both the woman and neonate is good, even if scar dehiscence occurs [38]. In the general maternity population, 70% of women who attempt VBAC manage a vaginal delivery with a uterine rupture rate of around 0.3%. Therefore, where a vaginal birth has been recommended on the basis of cART and viral load, maternal management of the delivery, including a decision regarding VBAC, should be as for a woman without HIV.

8.2.6	Where the indication for CS is the prevention of vertical transmission, CS should be undertaken at between 38 and 39 weeks' gestation.	1C
	Where PLCS is undertaken only for obstetric indications and plasma viral load is <50 HIV RNA copies/mL, the usual obstetric considerations apply and the CS will usually be performed after 39 weeks' gestation.	1C

The timing of CS is a balance between the risks of transient tachypnoea of the newborn (TTN) and the likelihood of labour supervening before the scheduled CS [39]. Where the indication for CS is prevention of vertical

transmission, the earlier timing reflects the importance of avoiding the onset of labour. In these cases, the risk of transmission associated with labour and SROM is considered to outweigh the risk of TTN. Where CS is undertaken only for obstetric indications, the optimal timing of PLCS is after 39 weeks of gestation [38]. The risk of TTN at this gestation is approximately 1 in 300 and this risk doubles for every week earlier that delivery occurs. The administration of steroids to the woman to reduce the risk of TTN should be considered prior to 38 completed weeks. The NICE guidelines committee on preterm labour and birth found no reliable evidence of benefit of antenatal corticosteroids in terms of fetal or neonatal death, intraventricular haemorrhage, chronic lung disease or reducing requirement for ventilation or pressure support after 36 weeks' gestation [40]. However, a subsequent meta-analysis showed that maternal corticosteroids reduced the risk of respiratory distress syndrome in infants born at ≥37 weeks' gestation (RR 0.40; 95% CI 0.27–0.59) [41]. Therefore, maternal corticosteroid administration should be considered where PLCS is carried out before 39 weeks.

8.3 Management of SROM

8.3.1	In all cases of term pre-labour SROM, delivery within 24 hours should be the aim.	1C
8.3.2	If maternal HIV viral load is <50 HIV RNA copies/mL, immediate induction or augmentation of labour is recommended in women who have pre-labour SROM, with a low threshold for treatment of intrapartum pyrexia. For all women with viral load <50 HIV RNA copies/mL, obstetric management should aim for delivery within 24 hours of SROM.	1C
8.3.3	For women with SROM and a last measured plasma viral load of 50–399 HIV RNA copies/mL, immediate CS is recommended, but should take into account the actual viral load, the trajectory of the viral load, length of time on treatment, adherence issues, obstetric factors and the woman's views.	1C
8.3.4	For women with SROM and maternal HIV viral load ≥400 HIV RNA copies/mL, immediate CS is recommended.	1C

In the pre-cART era, several studies [30,42,43] suggested that prolonged duration of ruptured membranes, usually defined as more than 4 hours, in women who were either untreated or if treated were largely receiving zidovudine monotherapy, resulted in a significantly increased risk of vertical transmission. A widely quoted meta-analysis (not reporting viral load data) subsequently showed a 2% increase in relative risk of transmission per hour of membrane rupture (adjusted OR 1.02; 95% CI, 1.01–1.04; for each 1-h increment). Transmission increased from 12% with <1 hour of membrane rupture to 19% with >12 hours of membrane rupture [44].

There are few published studies on SROM from the cART era. A study from Spain of 500 women living with HIV examined the effect of various obstetric risk factors on vertical transmission rates in women on no treatment, monotherapy or dual therapy, and in those on cART. Ruptured membranes >6 hours compared to <6 hours was only significantly associated with transmission in the group of women receiving no treatment (26.6% *vs* 11.9%; *P*<0.01). Corresponding transmission rates were 14.3% versus 7.1% (*P*=NS) for the monotherapy or dual therapy group and 0.8% versus 0.0% (*P*=NS) for the women on cART [45].

The NSHPC has reported data on 1464 women with undetectable viral load with duration of SROM for births at term between 2007 and 2012. In these 1464 women delivering with a viral load <50 HIV RNA copies/mL, the vertical transmission rate was 0.12% (1/809) in women with SROM <4 hours and 0.15% (1/655) in women with SROM ≥4 hours and <24 hours (OR 1.14; 95% CI 0.07–18.27). There were no transmissions in the 55 women with viral load <50 RNA copies/mL and duration of SROM >24 hours, but this represents very few cases [46]. Data from North America in 2012 showed similar results. In over 700 women with HIV (89% received cART, 10% monotherapy and 1% no treatment), the perinatal transmission rate was 1% in those with SROM <4 hours and 1.9% in those with SROM for >4 hours. In those with a viral load <1000 HIV RNA copies/mL there were no cases of perinatal transmission (493 cases with SROM up to 25 hours). Only viral load >10,000 HIV RNA copies/mL was shown to be an independent risk factor [47]. Therefore, for women on

cART with SROM at term with a viral load <50 HIV RNA copies/mL and who do not have an obstetric contraindication to vaginal delivery, a CS is not recommended for the prevention of vertical transmission. When planning the birth, it should be discussed that women are recommended to contact their maternity unit for in-person assessment as soon as any SROM is suspected. Women with HIV with a history of SROM should be prioritised for induction/augmentation when they present. Obstetricians should be aware that although there is no evidence of increased transmission risk in women with undetectable viral load with SROM <4 hours and 4 to <24 hours, there are few data for transmission risk beyond this time, and therefore they should aim for delivery within 24 hours, weighing up the risks of intervention as appropriate.

As both acute and chronic chorioamnionitis have been associated with perinatal transmission [43,48-50], albeit from studies largely performed in the pre-cART era, it is recommended that labour should be expedited for all women with SROM at term. Hence women with SROM at term with a viral load <50 HIV RNA copies/mL should have immediate induction with a low threshold for the treatment of intrapartum pyrexia. The NICE induction of labour guidelines [51] and the NICE intrapartum guidelines [31] should be followed with regard to use of antibiotics and mode of induction.

NSHPC data for the effect of SROM more than or less than 4 hours for women with a viral load >50 HIV RNA copies/mL are more difficult to interpret as the numbers are currently small. In the published analysis, there was no significant difference in vertical transmission rates between SROM <4 hours and SROM 4 to <24 hours in women at all viral load levels (vertical transmission rates were 0.34% and 0.64% respectively; OR 1.90; 95% CI 0.45–7.97). However, transmission rates were 0.13% in women with viral load <50 HIV RNA copies/mL (2/1519), 2.05% in women with viral load of 50–999 HIV RNA copies/mL (3/146) and 23.08% in women with viral load >10,000 HIV RNA copies/mL (3/13). There were too few women for a subgroup analysis comparing vertical transmission rates with SROM <4 hours and >4 hours in women with viral load >50 HIV RNA copies/mL.

A single-centre study from Miami of 707 women on ART showed that SROM >4 hours was associated with an increased risk of vertical transmission if the viral load was >1000 HIV RNA copies/mL. There was no association at <1000 HIV RNA copies/mL, but it is not possible to determine the number of women with a viral load greater than 50 and less than 1000 HIV RNA copies/mL in this group.

It is the recommendation of the writing group that CS should be considered for women with a viral load of 50–399 HIV RNA copies/mL at term. Again, if CS is not carried out, delivery should be expedited to occur within 24 hours, as above.

Until further data are available, an urgent (category 2) CS is recommended where the viral load is >400 HIV RNA copies/mL regardless of treatment [52].

In women who have a detectable viral load it may be possible to optimise their cART regimen to reduce the risk of vertical transmission (see recommendation 6.3.3).

8.3.5	The management of preterm SROM at ≥34 weeks is the same as that of term SROM, except that women at 34–37 weeks' gestation will require group B streptococcus prophylaxis in line with national guidelines.	1C
8.3.6	When preterm SROM occurs at <34 weeks: • Intramuscular steroids should be administered in accordance with national guidelines; • Where HIV viral load is not controlled, this should be optimised; • There should be multidisciplinary discussion about the timing and mode of delivery.	1C

There are no data to inform the optimum management of preterm labour in women living with HIV. Decisions regarding the optimum management of early preterm SROM require the assessment of a number of factors including the exact gestation, the facilities available, maternal viral load and the presence of other comorbidities such as infection and pre-eclampsia. Corticosteroids to improve fetal lung maturation and oral erythromycin should be given as per the NICE guidelines on preterm labour [40]. Decisions regarding timing of delivery should be made in consultation with the full MDT including the neonatal unit. Induction is recommended from 34 weeks' gestation in women with SROM who are not in labour to minimise the risk of developing chorioamnionitis.

If maternal HIV viral load is not fully suppressed, consideration should be given to the options available to optimise therapy. An additional concern is that the early preterm infant may be unable to tolerate oral therapy and therefore loading the infant through the transplacental route with maternal ART is recommended (see section 6 for further information on cART in pregnancy). There is most experience with maternal oral nevirapine 200 mg stat >2 hours prior to delivery, but double-dose tenofovir DF and standard-dose raltegravir 400 mg bd should also be considered.

8.4 Use of intrapartum intravenous infusion of zidovudine

8.4.1	Intrapartum intravenous zidovudine infusion is recommended in the following circumstances:	
	For women with a viral load >1000 HIV RNA copies/mL plasma who present in labour or with SROM or who are admitted for PLCS.	1C
	For untreated women presenting in labour or with SROM in whom the current viral load is not known.	1C
	The use of intrapartum intravenous zidovudine infusion can be considered in women on cART with a plasma HIV viral load <1000 HIV RNA copies/mL.	1C

The use of intravenous zidovudine for women on cART with a viral load between 50 and 1000 HIV RNA copies/mL can be considered regardless of mode of delivery. However, continued oral dosing of their current regimen is a reasonable alternative.

Intravenous zidovudine (as part of an intervention package; see section 6.4) has also been recommended for women who present in labour having not received ART.

From the updated French data, there is no evidence that intrapartum intravenous zidovudine further reduces the risk of vertical transmission in women on cART unless maternal HIV viral load is >1000 HIV RNA copies/mL and this benefit is no longer seen if intensive neonatal therapy is given [53]. However, individual circumstances vary, and intravenous zidovudine may be considered as one of a number of maternal intrapartum antiretroviral options for women with viral load >50 HIV RNA copies/mL who present in labour or with SROM or who are admitted for CS provided this does not delay other interventions.

8.5 Multiple pregnancies

There are no published studies comparing multiple versus singleton pregnancies in HIV. Based on the available evidence, comprising expert opinion, there is no increased risk of vertical transmission in multiple pregnancies. Multiple pregnancies are more common in older pregnant women with HIV than in the HIV-negative population [54]. The number of pregnant women with HIV over 40 years of age has increased from 2% of all pregnant women over 40 in 2000–2004, to 9% in 2010–2014 [54], therefore further data are likely to emerge. Multiple pregnancies should be managed according to obstetric need of the woman and as per HIV-negative protocols.

8.6 Place of birth

8.6.1	All women living with HIV are recommended to give birth in a facility that has direct access to paediatric care (i.e. a co-located birth centre or obstetric unit).	1D

Given that infants born to women living with HIV will require PEP as soon as possible after birth and within 4 hours (see section 9) and a blood test, the writing group recommends that all women living with HIV give birth in a facility that has direct access to paediatric care (i.e. a co-located birth centre or obstetric unit).

8.7 Water birth

8.7.1	There is scant safety evidence to support water births in women living with HIV; however, women who choose a water birth should be supported to achieve this where the viral load is <50 HIV RNA copies/mL.	1D

A Cochrane review published in 2018 examined obstetric outcomes following immersion during the first and second stages of labour (15 trials included). Outcomes related to HIV were not specifically reviewed. Overall, there was little or no difference in spontaneous vaginal birth, instrumental birth or CS with water immersion in the first stage (moderate- to low-quality evidence), but immersion in the first stage may reduce the use of regional anaesthesia (moderate-quality evidence). For women immersed in the second stage, there was little or no difference between groups for spontaneous vaginal birth. The quality of evidence was very low for the outcomes instrumental birth, CS or neonatal intensive care unit admissions therefore it remains uncertain whether water birth makes any difference. There was no evidence on the incidence of third- or fourth-degree tears, blood loss or neonatal infection. When immersion in water during the second stage of labour and birth was compared to no immersion, there was one reported death in the immersion group in one trial. The infant was born alive to a woman with HIV who was treated 2 weeks prior to birth for vaginal infection. The infant died at 2.5 hours after birth. After investigation the cause of death was determined to be intrauterine infection [55]. The writing group recommends that the lack of safety evidence should be discussed with women living with HIV who are considering a water birth. Women who choose to give birth in water should be supported to do so where the viral load is <50 HIV RNA copies/mL.

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9. Neonatal management

9.1 Infant PEP

Infant PEP should be started within 4 hours of delivery (see Figure 9.1 and Appendix 3).

9.1.1	VERY LOW RISK	1C
	Two weeks of zidovudine monotherapy is recommended if all the following criteria are met: • The woman has been on cART for longer than 10 weeks; AND • Two documented maternal HIV viral loads <50 HIV RNA copies/mL during pregnancy at least 4 weeks apart; AND • Maternal HIV viral load <50 HIV RNA copies/mL at or after 36 weeks.	
9.1.2	LOW RISK	1C
	Extend to 4 weeks of zidovudine monotherapy: • If the criteria in 9.1.1 are not all fulfilled but maternal HIV viral load is <50 HIV RNA copies/mL at or after 36 weeks; • If the infant is born prematurely (<34 weeks) but most recent maternal HIV viral load is <50 HIV RNA copies/mL.	
9.1.3	HIGH RISK	1C
	Use combination PEP if maternal birth HIV viral load is known to be or likely to be >50 HIV RNA copies/mL on day of birth, if uncertainty about recent maternal adherence or if viral load is not known.	
9.1.4	Neonatal PEP should be commenced as soon as possible after birth, and at least within 4 hours	1D
9.1.5	In the context of known maternal resistance to zidovudine with VERY LOW or LOW RISK, zidovudine monotherapy is still recommended for infant PEP.	1D
9.1.6	If HIGH RISK (combination PEP indicated) and there is a history of documented maternal zidovudine and/or nevirapine resistance, seek expert advice. If advice is not immediately available, commence standard three-drug PEP (zidovudine, lamivudine and nevirapine) until guidance is provided.	1D

As critical decisions relating to categorisation of risk relate directly to the maternal viral load at the time of delivery, the writing group recommends that this result should be available as early as possible and certainly within 72 hours of delivery.

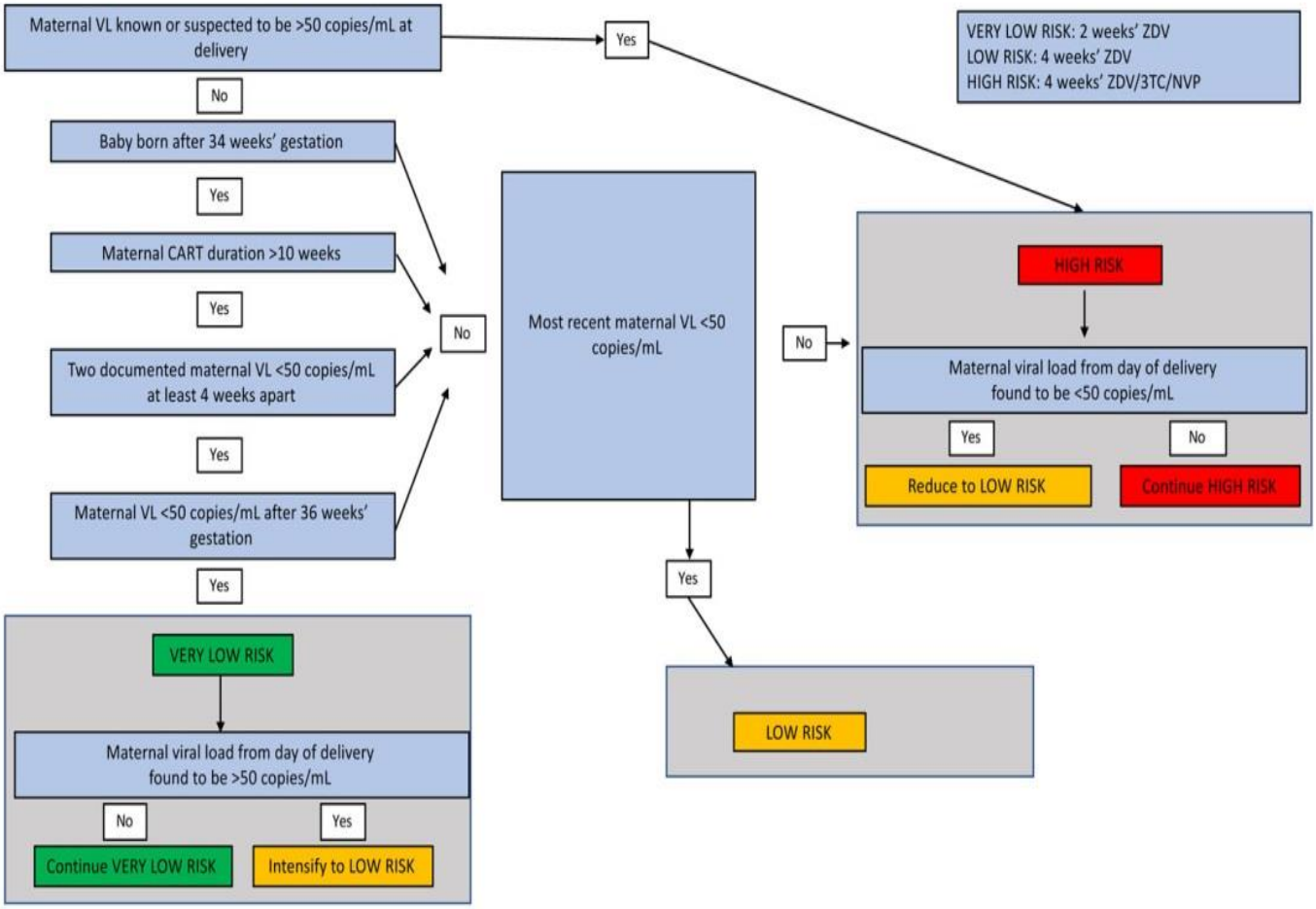

Figure 9.1. Algorithm for infant treatment

9.1.1 VERY LOW RISK

Zidovudine monotherapy for the infant has been part of the prevention of vertical transmission of HIV strategy since the publication of the results of the ACTG 076 trial in 1994 [1]. The relative contributions of the antenatal, peripartum and infant components have been difficult to quantify. In the ACTG 076 study, neonatal zidovudine 2 mg/kg every 6 hours was given for 6 weeks.

In the last version of the BHIVA pregnancy guidelines, 4 weeks of oral zidovudine was recommended for all infants except in specific HIGH-RISK circumstances relating to detectable or unknown maternal viral load at time of delivery [2]. This has been part of a hugely successful strategy to reduce the vertical transmission rate in the UK and Ireland with transmission now occurring only under exceptional circumstances [3].

In Germany, in an attempt to reduce neonatal exposure to zidovudine further, a strategy of using 2 weeks of neonatal zidovudine in the lowest-risk situations has been recommended for over 10 years with no signal that this has resulted in increased transmission [4].

French cohort data have provided further evidence that reducing neonatal PEP duration would be safe. No transmissions occurred among 2651 infants born to women receiving ART before conception, continuing ART throughout pregnancy and delivery with an HIV viral load <50 HIV RNA copies/mL (upper 95% CI 0.1%) [5]. Although this report does not specify the nature of neonatal PEP received, the absence of any transmission in this 'real world' setting gives support to the recommendation of reducing the duration of infant PEP as long as specific criteria are fulfilled.

In the pre-cART era, a randomised placebo-controlled trial of zidovudine monotherapy in Thailand compared four strategies for the prevention of vertical transmission of HIV:

- Maternal zidovudine monotherapy from 28 weeks' gestation through to delivery and neonatal zidovudine for 6 weeks (long-long);
- Maternal zidovudine from 35 weeks' gestation and neonatal zidovudine for 3 days (short-short);
- Maternal zidovudine from 28 weeks' gestation and neonatal zidovudine for 3 days (long-short);
- Maternal zidovudine from 35 weeks' gestation and neonatal zidovudine for 6 weeks (short-long).

Analysis demonstrated the efficacy of the 'long-short' regimen to be equivalent to that of the 'long-long' regimen. This led the authors to conclude that a regimen of 3 days of PEP would be sufficient when the woman had commenced zidovudine at 28 weeks' gestation [6].

Adult PEP guidelines for sexual exposure to HIV now recommend against PEP in the context of known viral load <50 HIV RNA copies/mL, based on strong evidence provided by large randomised trials investigating treatment as prevention of transmission [7]. In Switzerland, this evidence has now been extrapolated to the context of the prevention of vertical transmission of HIV, supporting the national guidelines recommending no PEP to infants born to women on cART with documented viral load <50 HIV RNA copies/mL on the two most recent measurements prior to delivery. For all other situations three-drug combination PEP is recommended [8].

It is the writing group's opinion that adult 'treatment as prevention' studies should be extrapolated to the prevention of vertical transmission with caution. The HIV transmission risk for peripartum exposure is much higher than for sexual or occupational exposure (10–20% *vs* 0.1–1.5%) [7,9]. The nature of exposure is also different. The fetus may be exposed at any time from conception to delivery; exposure at the time of delivery carries a particularly HIGH RISK.

Mother-to-infant trafficking of maternal cells (including CD4 cells) occurs and these cells can persist in the infant circulation after birth [10]. Although the relevance of this process in HIV transmission is not known, it has recently been suggested to have implications for vertical transmission of HBV [11]. Of note, this was the justification for 6 weeks of neonatal PEP in the original ACTG 076 study [1].

For these reasons, a 'no PEP' strategy is not included in this current BHIVA guideline. However, in the context of extremely low transmission rates in the UK, the writing group now recommends a shortened, 2-week course of zidovudine in VERY LOW RISK situations.

European cohort data indicate that risk of transmission remains LOW and stable if maternal cART is initiated more than 10 weeks prior to delivery [12]. Two weeks of infant zidovudine is therefore recommended if a woman has been on cART for more than 10 weeks, with a viral load <50 HIV RNA copies/mL on the most recent two occasions during pregnancy prior to delivery (at least 4 weeks apart) and a viral load <50 HIV RNA copies/mL at or after 36 weeks' gestation.

9.1.2 LOW RISK

Two weeks of zidovudine is only recommended if all criteria in section 9.1.1 are met. If these criteria are not met but the maternal viral load is <50 HIV RNA copies/mL at time of delivery, zidovudine therapy should be extended to 4 weeks as in the 2014 BHIVA guidelines [2]. Cohort data indicate that prematurity is still possibly a risk factor for transmission [13]. Although it is difficult to determine the contribution of reduced duration of ART to this increased risk, the writing group recommends the use of 4 weeks of infant zidovudine if the woman commenced ART in pregnancy and delivers prematurely (<34 weeks) with a viral load <50 HIV RNA copies/mL.

If the criteria in section 9.1.1 are fulfilled and the infant commences zidovudine monotherapy but the maternal delivery HIV viral load is subsequently discovered to be greater than 50 HIV RNA copies/mL the duration of infant PEP should be extended to 4 weeks.

9.1.3 HIGH RISK

There is one large randomised controlled trial of combination therapy in neonates born to women who did not receive ART prior to delivery [14]. Infants were randomly allocated at less than 48 hours of age to: 6 weeks of zidovudine monotherapy; 6 weeks of zidovudine with three doses of nevirapine in the first week of life; or 6 weeks of zidovudine, with nelfinavir and lamivudine for 2 weeks. The HIV vertical transmission rate was 8.5%,

and in multivariate analysis only ART arm and maternal HIV viral load were significantly associated with transmission. Perinatal transmission was two-fold higher in the zidovudine alone arm compared to the multiple ART arms (*P*=0.034). There was no significant difference in transmission rates between the two multiple ART arms. Neonatal neutropenia was significantly higher in the three-drug arm.

In a randomised African study, babies born to women presenting at delivery received single-dose nevirapine or single-dose nevirapine and 1 week of zidovudine. Of those HIV negative at birth, 34 (7.7%) who received nevirapine plus zidovudine and 51 (12.1%) who received nevirapine alone were infected (*P*=0.03); protective efficacy was 36% for the dual combination [15].

However, in two other randomised African studies where the women received short-course ART, for infants who did not acquire HIV at birth there was no significant difference in transmission rate at 6 weeks for dual versus monotherapy short-course regimens for the infant: zidovudine plus lamivudine versus nevirapine [16]; or zidovudine plus nevirapine versus nevirapine [17].

NSHPC data from the UK and Ireland (2001–2008) demonstrate how the use of combination PEP in neonates has increased over time [18]. In total, 99% of 8205 infants received any PEP; for the 86% with data on type of PEP, 3% received dual and 11% triple regimens. The use of triple PEP increased significantly over this period, from 43% to 71% for infants born to untreated women, and from 13% to 32% where women were viraemic despite cART. HIV infection status was known for 89% of infants with information on PEP; 14.7% of infants who received no PEP were infected (5 of 34, all born vaginally to untreated women compared to 1.0% of those who received any PEP [72 of 7286]). Among infants born vaginally to untreated women, those who received PEP were significantly less likely to be infected than those who did not (8.5% [4/47] *vs* 45.5% [5/11]; *P*=0.002). However, in this cohort study, because of the overall low rate of transmission and selective use of triple PEP for infants at higher risk of HIV, it was not possible to explore the association between type of PEP and infection status.

Data from the European Pregnancy and Paediatric Cohort Collaboration (EPPICC) has shown increasing use of combination PEP across Europe. In 5285 HIGH-RISK mother–infant pairs (27.7% no antenatal or intrapartum antiretroviral prophylaxis, 17.3% only intrapartum prophylaxis, 55.0% detectable viral load at delivery despite antenatal ART), 23.9% of infants received combination PEP. Study results did not indicate an advantage of combination PEP compared to single-drug neonatal prophylaxis; however, the authors concluded that this observation may result from confounding or combination PEP only being effective in a subgroup of HIGH-RISK infants [19].

There are no randomised trials of combination PEP for infants where women are receiving cART. In a French study, transmission rates with dual therapy (zidovudine and lamivudine) given to both the neonate and woman (1.6%) were lower than zidovudine monotherapy reported in historical controls (6.8%; OR 0.22; 95% CI 0.2–0.5) [20].

9.1.4 Choice of triple combination PEP for neonates

Most neonates born in the UK to women known to have HIV will be exposed to ART *in utero*, during delivery and in the first month of life. The range of combinations of ART to which neonates are being exposed *in utero* continues to increase. Neonatal drug metabolism is generally slower than that of older infants or children and is even less efficient in premature neonates. Due to a lack of neonatal pharmacokinetic and efficacy studies and suitable formulations, ART dosing regimens remain restricted to a small proportion of antiretrovirals (Appendix 3).

For infants born to ART-naïve women, or where drug resistance is unlikely, zidovudine, lamivudine and nevirapine is a well-tolerated combination regimen with the most clinical experience [18,19,21-24] (see Appendix 3 for dosing).

Neonatal pharmacokinetic studies have been performed for zidovudine [25], lamivudine [26,27], tenofovir DF [28] and emtricitabine [29] and dosing regimens are available for most of the nucleoside analogues from age 1 month [30].

The pharmacokinetic profiles of nevirapine in neonates have been described in detail [31-35].

In contrast to the PIs, nevirapine efficiently crosses the placenta (see below) and is well absorbed by the neonate [36]. Neonatal metabolism of nevirapine is induced where there has been antenatal *in utero* exposure [31,32]; if this drug is given to the neonate when the women has taken it for 3 or more days, the full dose of 4 mg/kg/day

should be started at birth, rather than the induction dose of 2 mg/kg/day (Appendix 3). In combination PEP, owing to its long half-life, nevirapine should be stopped 2 weeks before co-prescribed antiretroviral drugs to reduce the risk of nevirapine monotherapy exposure and the development of NNRTI resistance should transmission have occurred.

The recommended regimen for standard three-drug PEP is therefore a total of 2 weeks of nevirapine (at full or incremental dosing) with 4 weeks of zidovudine and lamivudine as shown in detail in Appendix 3.

Dosing for raltegravir for neonates has recently been described (IMPAACT P1110). This requires increasing doses after the first and fourth weeks of life [37] (see Appendix 3). As raltegravir may affect bilirubin metabolism, total and split bilirubin should be checked during the first week of life, although the risk of discontinuation due to hyperbilirubinaemia in the study was low [37]. Appropriate raltegravir dosing for premature neonates is not yet available, and they are more vulnerable to hyperbilirubinaemia.

The writing group therefore recommends that raltegravir should only be prescribed to preterm neonates in exceptional circumstances. Its use should only be considered after seeking expert advice and where there is multidrug resistance.

Pharmacokinetics-supported dosing is available for lopinavir/r based on infants who have acquired HIV initiating therapy in the first 6 weeks of life [38-40] and a study that included infants treated from birth [41]. However, evidence of adrenal suppression has been documented in some neonates treated with lopinavir/r, particularly preterm infants [42]. This is in addition to case reports of cardiac, renal and neurological toxicity, especially in, but not restricted to, premature infants, and including one death during PEP with lopinavir/r [43]. No effects have been observed with maternal lopinavir/r in the absence of neonatal dosing. It remains unclear whether these effects are related to lopinavir/r specifically or could be seen with other ritonavir-boosted PIs.

The writing group therefore recommends that lopinavir/r should be avoided in routine infant PEP and should only be prescribed to preterm neonates in exceptional circumstances. Its use should only be considered after seeking expert advice and where there is multidrug resistance. Close metabolic monitoring in hospital should be undertaken for the first 5 days of life.

9.1.5 Intravenous ART in the neonate

The only licensed ART available for intravenous use in sick and/or premature neonates who are unable to take oral medication is zidovudine [25,44]. Reduced oral and intravenous dosing schedules for premature infants are available (Appendix 3).

The very premature neonate is at risk of necrotising enterocolitis (NEC) if enteral feeding is commenced too soon or increased too rapidly. It is not known whether very early enteral administration of ART can exacerbate this risk. In a large French case-controlled study of NEC, being an infant of a woman with HIV was associated with an increased risk of NEC (OR 6.63; 95% CI 1.26–34.8; *P*=0.025), although the numbers were too small to ascertain the effect of maternal and/or infant ART [45]. Premature infants should be commenced on intravenous zidovudine until enteral feeding is established, when zidovudine may be given enterally. The premature dosing regimen should be used (Appendix 3).

The fusion inhibitor enfuvirtide is the only other antiretroviral that is administered parenterally, usually subcutaneously, in adults and children. Enfuvirtide does not cross the placenta. Although intravenous enfuvirtide has been given to a small number of infants born to women with multidrug-resistant HIV, no formal neonatal pharmacokinetic studies have been conducted to date. An unlicensed intravenous dosing regimen for infants at risk of multidrug-resistant HIV has been adapted from the paediatric subcutaneous treatment study [46] and an adult intravenous dosing study [47] (see Appendix 3 and seek expert advice).

When an infant has been started on combination PEP because the maternal viral load was considered likely to be >50 HIV RNA copies/mL at delivery and subsequently the delivery maternal viral load is shown to be <50 HIV RNA copies/mL, it is reasonable to simplify the infant PEP to zidovudine monotherapy as in section 9.1.2.

9.1.6 Timing of neonatal PEP

All infant PEP should be started within 4 hours of delivery.

There are no clear data on how late infant PEP can be initiated and still have an effect, but all effective studies of infant PEP have started treatment early and animal data show a clear relationship between time of initiation and effectiveness, with no benefit demonstrated if commenced after >72 hours [48-50]. Immediate administration of PEP is especially important where the woman has not received any ART.

9.1.7 Maternal genotypic resistance

For infants born to women on fully suppressive cART, zidovudine monotherapy PEP remains reasonable, even where the woman has a previous history of zidovudine exposure with resistance (thymidine-associated mutations). On cART, the risk of transmission from a woman with fully suppressed viral replication is extremely low (~0.1%) and, although history of zidovudine resistance in maternal virus and infant PEP regimen has not been dissected, the frequency of transmission of zidovudine-resistant virus is concomitantly very low.

Despite minimal supporting evidence, this has been standard practice in the UK for several years without a signal from cohort data that transmissions are occurring in this context. Theoretical support for this approach comes from evidence that wild-type virus may be preferentially transmitted in the context of a maternal mixed population including zidovudine-resistant virions [51]. Furthermore, Swiss cohort data demonstrated no transmission among six infants born to women with zidovudine-resistant virus [52]. A substudy of the ACTG 076 trial showed that low-level zidovudine resistance was not associated with an increased risk of transmission [53]. Retrospective data from the US found no significant association between maternal zidovudine resistance and risk of transmission [54].

Historical French cohort data demonstrated possible transmission of zidovudine-resistant virus following failed zidovudine prophylaxis in a very small number of woman–infant pairs, although in all these cases (where data were available) the woman had detectable viral load at the time of delivery [55]. In the WITS cohort, presence of zidovudine-resistance mutations was shown in multivariate analysis to be associated with increased risk of transmission, although a significant proportion of women in this study had detectable HIV at the time of delivery [56].

There is therefore very little data on the risk of transmission of zidovudine-resistant HIV in the context of fully suppressed maternal viral load at time of delivery and infant zidovudine monotherapy. However, observational data from the UK have not shown this to be a practice associated with increased transmission risk.

Some clinicians prefer to choose another antiretroviral, with no history of maternal resistance, for infant post-exposure monotherapy. The established alternatives, nevirapine and lamivudine, have potent antiretroviral effect but a low (single-point mutation) barrier to resistance. In the event of transmission, the likelihood of an infant developing new resistance on zidovudine monotherapy is probably less than with nevirapine or lamivudine. The dosing and safety issues with lopinavir/r and raltegravir are outlined above. With infant feeding patterns, it is difficult to separate drug dosing from feeds, so drugs without food restrictions are preferred; this is another advantage of zidovudine.

Neonatal zidovudine monotherapy therefore remains a reasonable approach for infants born to women with a plasma viral load <50 HIV RNA copies/mL, even if there is a previous history of zidovudine resistance.

There are no data available on the efficacy of modified combination PEP when maternal zidovudine and/or nevirapine resistance has been demonstrated. Expert advice should be sought and use of alternative drug combinations should be considered following careful risk assessment.

9.1.8 HIV-2

9.1.8	If a woman is known to have HIV-2 infection, follow the same advice as for HIV infant PEP but if HIGH RISK (combination PEP indicated), nevirapine will not be effective. Seek expert advice. If advice is not immediately available, commence zidovudine, lamivudine and raltegravir until guidance is available (see Appendix 3).	2C

There are no data available to suggest that babies born to women living with HIV-2 who are at VERY LOW or LOW RISK of vertical transmission should be managed any differently from those born to women with HIV. If the maternal viral load is undetectable at or after 36 weeks' gestation, the same guidance should therefore be followed as described above for HIV-exposed infants.

HIV-2 is intrinsically resistant to NNRTIs. There are no data to guide practice in the event of a HIGH-RISK delivery in the context of HIV-2 infection. The same guidance for the use of three-drug PEP should be followed as in section 9.1.3, replacing nevirapine with raltegravir. If raltegravir is not available, lopinavir/r could be used but with caution, as discussed in the previous section. Infants receiving raltegravir or lopinavir/r PEP should be monitored for toxicity in the first few days of life as per Appendix 3. Blood samples for infant testing should be sent to a UK laboratory that routinely provides HIV-2 testing.

9.1.9 PEP beyond 4 weeks

9.1.9	Infant PEP should not be given beyond 4 weeks.	1C
	PEP should not be restarted unless significant subsequent exposure (e.g. maternal viral load detectable during breastfeeding). Seek expert advice regarding need for PEP following breast milk exposure during an episode of maternal viraemia.	1D

Indications for PEP outside the neonatal period (e.g. following breast milk exposure to HIV) involves a complex risk assessment in relation to timing of HIV exposure, which may be staggered. Expert advice should be sought. See section 9.4 for further information on monitoring during breastfeeding.

9.2 Pneumocystis pneumonia (PCP) prophylaxis

9.2.1	Co-trimoxazole prophylaxis is recommended from 1 month of age if HIV PCR screening is positive at any stage or if the infant is confirmed to be diagnosed with HIV. This should only be stopped if HIV infection is subsequently excluded.	1C

Pneumocystis pneumonia (PCP) in infants with HIV is associated with high mortality and morbidity. However, as the risk of neonatal HIV infection has fallen to <1% where interventions for the prevention of vertical transmission are in place, the necessity for PCP prophylaxis has declined and in most European countries it is no longer prescribed routinely for HIV-exposed infants, even when a baby is born to a woman with a viral load >50 HIV RNA copies/mL.

Co-trimoxazole should be prescribed from 4 weeks of age for infants with a positive PCR screening test for HIV before 4 weeks of age. This should be continued if infection is confirmed and stopped if infection is excluded. Infants with a first positive HIV molecular diagnostic test result at any age between 4 weeks and 1 year should be started on co-trimoxazole prophylaxis immediately until HIV infection is confirmed or excluded (see Appendix 3 for dose).

9.3 Immunisation

9.3.1	Immunisations should be given as per the national schedule outlined in the Green Book [57].	1C
9.3.2	Rotavirus vaccine is not contraindicated (unless HIV diagnosis has been confirmed and infant is severely immunosuppressed).	1C
9.3.3	If there is VERY LOW or LOW RISK of HIV transmission and BCG at birth is indicated, this should not be delayed.	1D

Rotavirus vaccine should be given to all HIV-exposed infants unless confirmed infected and shown to be severely immunosuppressed. If uncertain about administration of live vaccines, expert advice should be sought. Infants considered at VERY LOW or LOW RISK of HIV transmission (i.e. maternal viral load <50 HIV RNA copies/mL at or after 36 weeks' gestation) may be given BCG at birth if indicated according to UK guidelines for HIV-unexposed infants.

9.4. Infant feeding

There are no data on the risk of HIV transmission via breast milk in high-income countries. In low- to middle-income settings, the overall postnatal risk of HIV transmission via breast milk when women are treated with cART has been reported as 1.08% (95% CI 0.32–1.85) at 6 months and 2.93% (95% CI 0.68–5.18) at 12 months, however in these studies women only received cART for 6 months and often breastfed for longer [58]. In the more recent PROMISE trial, women received cART throughout the breastfeeding period, and the transmission rate was 0.3% (95% CI 0.1–0.6) at 6 months and 0.6% (95% CI 0.4–1.1) at 12 months [59].

Factors that increase the risk of HIV transmission via breast milk when women are not on cART include:

- Detectable HIV viral load;
- Advanced maternal HIV disease;
- Longer duration of breastfeeding;
- Breast and nipple infection/inflammation;
- Infant mouth or gut infection/inflammation;
- Mixed feeding, in particular solid food given to infants less than 2 months of age [60].

Where a woman is on cART and breastfeeding, it is presumed that the same factors are relevant, albeit less so, depending on adherence and viral load suppression.

Historically the risk of HIV transmission in women not on cART was affected by feeding other solid foods to young infants. The transmission risk for exclusive breastfeeding is 9.0/100 child-years; for predominantly feeding breast milk with other liquids is 9.5/100 child years; and for giving early solid foods rises to 41.2/100 child-years [60]. Whether this risk persists with feeding of solid foods when women breastfeed on cART with full viral suppression is not yet known.

An analysis of data from four African studies published before 2012, where women were on cART from before conception, estimated that the postnatal HIV transmission probability was around 0.16% per month of breastfeeding [61]. However, this estimated transmission risk is at least twice that seen in infants enrolled in the PROMISE trial at 12 months of age [59].

9.4.1 Breastfeeding advice for women with HIV living in the UK

9.4.1	In the UK and other high-income settings, the safest way to feed infants born to women with HIV is with formula milk, as there is on-going risk of HIV exposure after birth. We therefore continue to recommend that women living with HIV feed their babies with formula milk.	1D

Current WHO advice on breastfeeding for women with HIV is aimed at low- and middle-income countries where there is a high risk of infant morbidity and mortality from diarrhoea, pneumonia and other infections, and where formula feeding is not safe or affordable for many families. All women with HIV are advised to start cART as soon as possible after HIV diagnosis and continue lifelong treatment. They are advised to breastfeed their infants exclusively for the first 6 months, while adhering to cART, then to add complimentary foods as appropriate after this time. They are advised not to stop breastfeeding until other safe and adequate foods are available, and to continue up to 12–24 months of age [62].

Suppressive maternal cART significantly reduces, but does not eliminate, the risk of vertical transmission of HIV through breastfeeding. The undetectable=untransmissable (U=U) statement applies only to sexual transmission, and we currently lack data to apply this to breastfeeding. Other considerations are the lack of lactation studies for most antiretroviral agents, meaning that the pharmacokinetic properties of ART in breastmilk are poorly understood, and the potential effects of exposure to ART in the breastmilk on infants who do not acquire HIV [63].

The writing group therefore continues to recommend formula feeding by women living with HIV to eliminate the risk of postnatal transmission.

9.4.2 Supporting women living with HIV to formula feed

9.4.2	Abstaining from breastfeeding can have financial and psychological repercussions for women, requiring support from the HIV MDT.	1C
	Women advised not to breastfeed for their baby's health should be provided with free formula feed to minimise vertical transmission of HIV.	1D

It is important to be aware that not breastfeeding can come at an emotional, financial and social cost to women living with HIV [64,65], and we advise that women receive appropriate support from their HIV MDT (which may include peer support, psychological and practical support, and financial support for formula feeding) [64-66].

We advise discussing infant feeding intentions early in pregnancy so that appropriate information and support can be provided. When women living with HIV are advised not to breastfeed, this can have a significant financial impact. There is a risk that some women with insufficient finances will forgo their own nutritional needs in order to afford formula for their infant, thus compromising their own health and potentially compromising the effectiveness of their HIV treatment [65]. Women with irregular immigration status and no recourse to public funds and women with a low income are particularly vulnerable to these barriers [65]. The provision of free formula milk, and the appropriate equipment to use it, alleviates any financial burden attached to this key prevention tool [64]. This ensures that women can make decisions on how to feed their infant without being influenced by cost. Free provision of formula milk also has the potential to improve women's retention in HIV care postpartum [67,68].

We acknowledge that provision of free formula for women living with HIV remains inconsistent across the UK. We advise clinics and voluntary sector organisations to map local services. There are different ways in which formula milk may be provided (see Box 1). Other examples of formula milk schemes can be found in the National AIDS Trust Policy Briefing on access to formula milk for women living with HIV [65].

> Jonathan Mann Clinic runs a scheme that provides vouchers for pregnant women and new mothers living with HIV, enabling the purchase of sterilisers, bottles and formula milk. The scheme is available to women who deliver at Homerton Hospital or who are residents of Hackney and attending HIV care at other clinics. At 30 weeks, pregnant women receive an entitlement letter from their midwife that they take to their HIV department, helping with compliance with care and treatment. They are given an initial voucher for £120 in the form of a Tesco payment card, which is then followed up with a further £80 at their 6-week postnatal appointment, and another £80 after 3 months. The scheme has been well received by women who report that it has removed much of the fear they had about not being able to breastfeed. The scheme is funded by the local authority and supports approximately 50 women per year.

Box 1. Formula milk scheme at Jonathan Mann Clinic, Homerton Hospital, London, UK

9.4.3 Suppression of lactation

9.4.3	Women not breastfeeding their infant by choice, or because of viral load >50 HIV RNA copies/mL, should be offered cabergoline to suppress lactation.	1C

Cabergoline is an ergot derivative introduced in the mid-1990s to inhibit puerperal lactation. It can also be used in the treatment of Parkinson's disease, prolactinomas, acromegaly and amenorrhea and galactorrhea secondary to neuroleptic use [69,70]. Cabergoline is a dopamine agonist with a higher affinity and specificity for the dopamine D_2 receptor than bromocriptine [71]. The suppression of prolactin release is more prolonged with cabergoline than with bromocriptine [72], such that a single dose of 1 mg cabergoline may be used to inhibit lactation on day 1 postpartum giving the equivalent effect of 2 weeks of bromocriptine. Adverse effects are similar to those reported with other ergot derivatives, but cabergoline appears to be better tolerated [73].

A small prospective study in Canada included 22 women who received cabergoline postpartum [74]. Taken on days 2 and 15 postpartum, cabergoline successfully suppressed lactation with an absence of pain, swelling or nipple discharge in over 86% of women. However, side effects were common and seen in nine women on day 2

and in 10 women on day 15. Most frequently reported side effects were dizziness and hand or foot numbness, hand or foot pain and nausea, but overall women were satisfied with the treatment and would recommend its use to a friend.

The option of using cabergoline should be discussed in advance with each woman and included in her birth plan. It should be made clear that it will reduce the discomfort of lactation if not breastfeeding but will prevent her from breastfeeding once taken.

9.4.4 Choosing to breastfeed in the UK

9.4.4	Women who are virologically suppressed on cART with good adherence and who choose to breastfeed should be supported to do so, but should be informed about the low risk of transmission of HIV through breastfeeding in this situation and the requirement for extra maternal and infant clinical monitoring.	1D
	When a woman decides to breastfeed, she and her infant should be reviewed monthly in clinic for HIV RNA viral load testing during and for 2 months after stopping breastfeeding.	1D
	Maternal cART (rather than infant pre-exposure prophylaxis [PrEP]) is advised to minimise HIV transmission through breastfeeding and safeguard the woman's health.	1D

Women who choose to breastfeed should be advised of the small on-going risk of HIV transmission. They should be supported in their decision, if they fulfil the following criteria:

- A fully suppressed HIV viral load (for as long a period as possible, but certainly during the last trimester of pregnancy);
- A good adherence history;
- Strong engagement with the perinatal MDT;
- Prepared to attend for monthly clinic review and blood HIV viral load tests for themselves and their infant during and for 2 months after stopping breastfeeding (see section 9.5.1.2).

Information for women considering breastfeeding should also be provided in written form and can be adapted locally from patient information leaflets developed by the writing group (see the BHIVA website: www.bhiva.org/pregnancy-guidelines). Women who do not fulfil the above criteria should be advised against breastfeeding. Women who breastfeed with a known detectable HIV viral load should be referred to social care as this places their infant at significant risk of HIV infection. A supportive and harm reduction approach of working openly together should be taken, to maintain trust and reduce the risk of women being pressurised to breastfeed in secret [64,75].

The risk of transmission in women on cART does still increase according to the duration of breastfeeding [76]. Women who wish to breastfeed (and meet the criteria specified above) should be advised to breastfeed for as short a time as possible, to exclusively breastfeed for the first 6 months, and to cease breastfeeding if they have breast infection/mastitis or if they or their infant has gastrointestinal symptoms. They should be given clear information, including how to manage common complications of breastfeeding, and have ready access to clinical advice and peer support. When weaning to solids, women should follow standard UK guidance, introducing complementary foods after 6 months of age, if still breastfeeding. Abrupt weaning from breast to formula and/or solids can be avoided, as long as the maternal HIV viral load remains fully suppressed.

In resource-poor settings, neonatal PrEP is equally effective as maternal cART in preventing HIV transmission via breast milk. In the PROMISE-PEP trial (ANRS 12174), infant regimens of daily lamivudine or lopinavir/r were equally effective up to 50 weeks (transmission rate on lopinavir/r: 1.4%, 95% CI 0.4–2.5; on lamivudine: 1.5%, 95% CI 0.7–2.5), with similar rates of grade 3–4 side effects of approximately 50% in both arms [76]. In the PROMISE trial, daily nevirapine as infant PrEP was comparable to maternal cART up to 12 months of breastfeeding, with a reported transmission rate of 0.3% (95% CI 0.1–0.6) at 6 months and 0.6% (95% CI 0.4–1.1) at 12 months [59].

As lifelong maternal cART is now the WHO recommendation, these infant PrEP regimens are less likely to be used on a large scale. There are no clinical trials of maternal cART plus infant PrEP in the context of breastfeeding, although it has been suggested that this could be a feasible approach in resource-poor settings where women may not have fully suppressed viral load and may be more likely to give medication to the infant than take it themselves [77].

Given the health benefits of cART for the woman herself, and the equivalent efficacy of maternal cART and infant PrEP in reducing risk of vertical transmission of HIV through breastfeeding, we recommend that maternal cART (rather than infant PrEP) be used in cases where a woman chooses to breastfeed. Healthcare providers requiring advice on use of medicines during the breastfeeding period can contact the UK Drugs in Lactation Advisory Service (www.sps.nhs.uk/ukdilas).

When a woman decides to breastfeed, she and her infant should be reviewed monthly in clinic for HIV RNA viral load testing during and for 2 months after stopping breastfeeding (see section 9.5.1.2).

The NSHPC is now collecting enhanced surveillance data on women with HIV who breastfeed and their infants. This will contribute to epidemiological data for the future (www.ucl.ac.uk/nshpc).

9.4.5 Communication with health professionals

With sensitivity to concerns about confidentiality, women should be strongly encouraged to inform partners/families and healthcare providers (including midwives, health visitors and GPs) and anyone else involved in their care (such as lactation consultants) about their HIV status. This will enable the family and local team to give appropriate support and advice, especially regarding feeding, vaccinations and medical assessment of the infant.

9.5 Diagnosis of infant HIV status

9.5.1	Molecular diagnostics for HIV infection should be performed on the following occasions.	
9.5.1.1	Non-breastfed infants:	1C
	• During the first 48 hours and prior to hospital discharge; • If HIGH RISK, at 2 weeks of age; • At 6 weeks (or at least 2 weeks after cessation of infant prophylaxis*); • At 12 weeks (or at least 8 weeks after cessation of infant prophylaxis*); • On other occasions if additional risk; • HIV antibody testing for seroreversion should be checked at age 18–24 months. *BHIVA guidelines on duration of PEP have changed for VERY LOW-RISK infants, see section 8.1.	
9.5.1.2	Breastfed infants:	
	• During the first 48 hours and prior to hospital discharge;	1C
	• At 2 weeks of age;	1D
	• Monthly for the duration of breastfeeding;	1D
	• At 4 and 8 weeks after cessation of breastfeeding;	1D
	• HIV antibody testing for seroreversion should be checked at age 18–24 months.	1C

9.5.1 Assays for the diagnosis of HIV infection status in infants

The gold standard test for HIV infection in infancy was HIV DNA PCR on peripheral blood lymphocytes. In a number of studies, including the large French perinatal cohort, equal or increased early sensitivity with amplification of viral RNA with no false-positive results has been reported [78,79].

Infants acquiring HIV intrapartum may have low peripheral blood HIV levels, so HIV DNA/RNA may not be amplified from all infected infants at birth. Indeed, a positive HIV DNA/RNA result within 72 hours of birth is taken as presumptive evidence of intrauterine transmission. Within the first few weeks of life the sensitivity of the viral diagnostic tests increases dramatically and by 3 months of age 100% of non-breastfed infants with HIV are likely to be detected [78].

Although HIV RNA and DNA assays have similar sensitivity, RNA assays commonly require 1 mL plasma, whereas DNA can be performed on smaller samples. If the sample requires dilution due to a low volume, which is often the case with paediatric samples, the lower limit of detection will be increased (with a corresponding decrease in assay sensitivity). In addition, where transmission may have occurred *in utero*, subsequent maternal ART with agents that cross the placenta could lead to a false-negative RNA result in an infected infant. In this situation, the infant should be tested using DNA PCR. As HIV DNA PCR is not widely available, a faster result may be obtained with a local RNA test. However, if HIV RNA is detected, HIV DNA PCR is recommended as a confirmatory test.

The same considerations regarding using primers known to amplify maternal virus apply to both RNA and DNA assays. In view of the genomic diversity of HIV, a maternal sample should always be obtained for HIV DNA or RNA amplification with, or prior to, the first infant sample to confirm that the primers used detect the maternal virus. If the maternal virus cannot be detected, a different primer set and/or test should be used. There has been an increase in the number of cases, usually in women established on ART with undetectable HIV viral load, where it has not been possible to amplify maternal DNA using four different primer sets. An HIV antibody test at 18 months is of particular importance in this scenario.

Evidence from the French perinatal cohort demonstrated that neonatal ART, especially if more than one drug, can delay the detection of both HIV DNA and RNA in the infant [79]. For this reason, the second and third HIV molecular tests are performed at 2 weeks and 2 months after stopping PEP, i.e. usually at 4–6 weeks and 10–12 weeks of age depending on PEP duration. If all tests are negative and the baby is not being/has not been breastfed, parents can be informed that the child does not have HIV. For infants at HIGH RISK of infection, an additional early HIV test may be undertaken at 2–3 weeks of age. For infants breastfeeding from women on cART (see section 9.4), HIV viral diagnostic tests should be undertaken at least monthly for the woman and infant while breastfeeding, and then additionally for the infant, at 4 and 8 weeks after complete cessation of breastfeeding.

Loss of maternal HIV antibodies should be confirmed at 18–24 months of age. Ideally an HIV antibody test should be used to confirm loss of maternal antibodies rather than a combined HIV antibody–antigen test. Combined tests (fourth generation and above) are highly sensitive and may still give a positive HIV result until up to 2 years of age [80]. Testing for loss of maternal HIV antibody remains important as, rarely, late postnatal infection may occur, even when all early HIV viral genome diagnostic tests were negative (French Perinatal cohort: 5/4539 cases) [81]. This may be due to breastfeeding, premastication of infant food or unknown intrafamilial exposure.

If any of the infant HIV tests are found to be positive, an immediate repeat test on a new sample should be requested to confirm infection. When an infant is diagnosed with HIV, PCP prophylaxis should be started immediately, if the baby is not already on it, and an urgent referral to the local specialist HIV clinic should be made to initiate infant cART. Maternal and infant HIV resistance testing should be undertaken to help delineate reasons for PEP failure and guide treatment. HIV services for children in the UK are organised in managed networks; details of the Children's HIV National Network (CHINN) and contacts for local paediatricians can be found on the Children's HIV Association (CHIVA) website (www.chiva.org.uk).

9.6. Neonatal management in maternal hepatitis co-infection

9.6.1	Follow national guidance for management of maternal HBV in pregnancy and for prevention of transmission of HIV to the infant (see also section 7.1).	1D

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 a woman is HBeAg positive;
- Or anti-HBe negative;
- Or anti-HBe is unknown [82].

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 who is both HBsAg and HBeAg positive is 70–90% and for a woman who

is HBsAg positive but HBeAg negative is 10–40%. 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* [83]. Therefore, maternal cART together with prompt post-delivery neonatal immunoprophylaxis is the ideal approach for preventing vertical transmission of HBV.

9.6.2	Follow usual practice for investigation and management of maternal HCV in pregnancy (see also section 7.2).	1D

No postnatal interventions are currently available for reducing risk of transmission of HCV to infants of women with HCV and HIV. Testing and follow-up of these infants should follow usual practice recommended for infants born to women with HCV alone, with consideration of combining HIV and HCV follow-up assessments in the first 18 months to 2 years.

9.7 HIV exposed but uninfected (HEU)

9.7.1	In light of evidence for possible increased infectious morbidity in HIV exposed but uninfected (HEU) children, timely routine vaccination should be ensured and general practitioners (GPs), health visitors and secondary care physicians should be made aware of possible increased risk in order to inform decisions when assessing risk in primary care.	1D

With increasingly successful rollout of prevention of vertical transmission of HIV interventions across the globe, the number of HEU children is increasing in parallel. A growing body of evidence, mainly from observational studies in low- and middle-income countries, suggests that these children may be at increased risk of morbidity (mainly infection related) in early life (reviewed in [84] and [85]). Multiple potential confounding factors make interpretation and conclusions from such studies challenging. *In utero* exposure to an altered maternal immune system and ART have both been proposed as potential factors contributing to an impairment in HEU neonatal immunity [85]. Much less information is available from high-incoming settings and findings are inconsistent [86-89].

In view of these concerns, although it remains to be demonstrated that HEU children in the UK are at increased risk of morbidity, the writing group recommends that all healthcare professionals involved in the care of HEU children in early life are made aware of this potential additional risk factor. The need for timely and complete routine immunisations should also be emphasised.

9.8 References

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10. Postpartum management of women

10.1 Antiretroviral therapy

10.1.1	All women are recommended to continue cART postpartum.	1A

It is recommended that all women remain on ART postpartum [1,2], although ultimately this is a woman's choice. For women who start on ART in pregnancy there may be an opportunity to simplify regimens, for example to once daily co-formulated regimens, or switch to newer regimens. Additionally, women who started darunavir/r bd in pregnancy should be switched to daily dosing unless there is evidence of significant genotypic resistance (see also section 6) [3]. Viral rebound has been demonstrated in women living with HIV postpartum, with the risk greater than in non-pregnant women with HIV [4]. Adherence can decline in the postnatal period as a result of concerns about side effects, the lifelong nature of treatment, fear of HIV status being shared and fear of HIV-related stigma within the community and in clinics [5-7]. It is important to be aware of the potential for compromised adherence, and to provide appropriate support including peer mentoring, which has been shown to improve adherence [6].

10.2 Support services

10.2.1	Women should have their support needs assessed postpartum and be referred to appropriate services in the Trust, community and/or voluntary groups without delay.	1D

The support required by each woman and the support services available at each HIV service will vary considerably and should be individualised for each woman. Support required may include child care, help with housing, access to food, peer mentoring and legal and advocacy services. The HIV MDT should work with local peer-led and voluntary organisations to tailor support to each woman. Referrals to partner organisations should have commenced at first presentation in pregnancy (see section 4) and be continued in the postnatal period. For women with drug or alcohol issues, continued support should be offered on an on-going basis. The minority of women who experience pregnancy loss may require additional support through HIV peer mentoring or support services such as the Miscarriage Association (www.miscarriageassociation.org.uk/) or Sands (www.sands.org.uk/).

10.3 Postnatal follow-up of women

10.3.1	All women should be reviewed in the postnatal period by a named member of the MDT within 4–6 weeks.	1C

It is important to be aware that there may be issues with retention in care after pregnancy, with disengagement of care rates estimated at 12% in both the NSHPC and the Swiss Cohort, and caring responsibilities identified as a barrier to accessing care [8-10]. It is essential to see all women in the postpartum period for follow-up of both medical and social issues, and to promote linkage back to general HIV care. We recommend that all women receive an appointment to see a named member of the HIV MDT and adequate ART until this appointment prior to discharge after delivery. This is particularly important for women newly diagnosed with HIV in pregnancy. The infant's postnatal 6-week check provides a good opportunity to also see the woman. A full assessment of the birth experience is important to provide constructive feedback to the MDT and to ensure pregnancy pathways are working well. This will also allow women to receive support for any difficult experiences they may have had. Should a woman miss her first postnatal appointment, every effort should be made by the HIV MDT to contact her and address any barriers in order to re-establish care.

10.4 Mental health assessment and support

10.4.1	Women should have their mental health needs assessed postpartum and those assessed as having mental health issues should be referred to appropriate services in the Trust, community and/or voluntary groups without delay.	1D

As discussed in section 4, mental health issues are common in the context of HIV and pregnancy. All women should be assessed as recommended in section 4.2. If there are concerns about postnatal depression, women should be linked to Trust community hub perinatal mental health services or referred to HIV liaison/community psychiatry for further assessment. Peer mentoring should be offered as additional support.

10.5 Contraception

10.5.1	Contraceptive needs should be discussed with all women, and ART may be changed to optimise a woman's contraception choice as long as the ART prescribed is fully active against the viral genotype.	1D

Ovulation usually resumes at 6 weeks postpartum but may occur earlier in non-breastfeeding women. A plan for contraception postnatally should have been discussed in advance of delivery (see section 5.1.5) and revisited in the early postpartum period and at the 4- to 6-week follow-up. Women should be advised that it is possible to conceive before the first postnatal menses and therefore to use condoms if necessary until the postnatal review [11]. It is important to try to accommodate both the contraceptive and ART wishes of each woman. There are multiple ART agents available which do not interact with systemic oestrogens and/or progestogens such as all NRTIs, raltegravir, dolutegravir, rilpivirine and maraviroc. ART may be changed to optimise a woman's contraception choice as long as the ART prescribed is fully active against the viral genotype. A full guide to drug–drug interactions between ART and hormonal contraceptives is available at www.hiv-druginteractions.org.

10.6 Cervical cytology

10.6.1	Cytology should be scheduled 3 months post-delivery as per the Guidelines for the NHS Cervical Screening Programme 2016.	1C

As discussed in section 5, cervical screening is not routinely recommended in pregnancy but can be resumed, as per the Guidelines for the NHS Cervical Screening Programme 2016, 3 months postpartum [12,13].

10.7 Testing of partner and/or older children

10.7.1	For the woman newly diagnosed with HIV in pregnancy, testing of her partner and/or other children should be completed.	1D

Postpartum follow-up may be an opportune time to revisit testing of partners and/or older children. A woman newly diagnosed in pregnancy should be counselled and supported regarding testing of her other children and partner, if appropriate and there are no other concerns (such as risk of intimate partner violence, see section 4). She should be informed that as well as significantly reducing her risk of vertical transmission of HIV [14], being on cART will also reduce her risk of sexual transmission. When her viral load is undetectable for 6 months or more she will not transmit HIV sexually; however, she should be advised to use condoms with her untested or HIV-negative partner until that time [15].

10.8 References

1. Lundgren JD, Babiker AG, Gordin F *et al.* Initiation of antiretroviral therapy in early asymptomatic HIV infection. *N Engl J Med* 2015; **373**: 795–807.

2. Danel C, Moh R, Gabillard D *et al.* A trial of early antiretrovirals and isoniazid preventive therapy in Africa. *N Engl J Med* 2015; **373**: 808–822.

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4. Huntington S, Thorne C, Newell ML *et al.* The risk of viral rebound in the year after delivery in women remaining on antiretroviral therapy. *AIDS* 2015; **29**: 2269–2278.

5. Adams JW, Brady KA, Michael YL *et al.* Postpartum engagement in HIV care: an important predictor of long-term retention in care and viral suppression. *Clin Infect Dis* 2015; **61**: 1880–1887.

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8. Aebi-Popp K, Kouyos R, Bertisch B *et al.* Postnatal retention in HIV care: insight from the Swiss HIV Cohort Study over a 15-year observational period. *HIV Med* 2016; **17**: 280–288.

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12. NHS Choices. *Cervical screening*. 2015. Available at: www.nhs.uk/conditions/cervical-screening (accessed October 2018).

13. Fakoya A, Lamba H, Mackie N *et al.* British HIV Association, British Association of Sexual Health and HIV and Faculty of Sexual and Reproductive Health guidelines for the management of the sexual and reproductive health of people living with HIV infection 2008. *HIV Med* 2008; **9**: 681–720.

14. Cohen MS, Chen YQ, McCauley M *et al.* Prevention of HIV-1 infection with early antiretroviral therapy. *N Engl J Med* 2011; **365**: 493–505.

15. Rodger AJ, Cambiano V, Bruun T *et al.* Sexual activity without condoms and risk of HIV transmission in serodifferent couples when the HIV-positive partner is using suppressive antiretroviral therapy. *JAMA* 2016; **316**: 171–181.

11. List of abbreviations

3TC	Lamivudine
ABC	Abacavir
ALT	Alanine transaminase
APR	Antiretroviral Pregnancy Registry
APRI	Aspartate aminotransferase-to-platelet ratio index
ART	Antiretroviral therapy
AST	Aspartate transaminase
AUC	Area under the curve
AZT	Zidovudine
BASHH	British Association for Sexual Health and HIV
BCG	Bacillus Calmette–Guérin
bd	Twice daily
BHIVA	British HIV Association
BV	Bacterial vaginosis
cART	Combination antiretroviral therapy
CHINN	Children's HIV National Network
CHIPS	Collaborative HIV Paediatric Study
CHIVA	Children's HIV Association
CI	Confidence interval
CIN	Cervical intraepithelial neoplasia
CME	Continuing medical education
CS	Caesarean section
DAA	Directly acting antiviral
EPPICC	European Pregnancy and Paediatric Cohort Collaboration
FDA	Food and Drug Administration
FDC	Fixed-dose combination
FIB-4	Fibrosis-4 index
FSRH	Faculty of Sexual and Reproductive Healthcare of the RCOG
GMC	General Medical Council
GP	General practitioner
HAV	Hepatitis A virus
HBeAg	Hepatitis B-e antigen
HBIG	Hepatitis B immunoglobulin
HBsAg	Hepatitis B surface antigen

HBV	Hepatitis B virus
HCG	Human chorionic gonadotrophin
HCV	Hepatitis C virus
HDV	Hepatitis D virus
HSV-2	Herpes simplex virus type 2
IFN	Interferon
Ig	Immunoglobulin
INR	International normalised ratio
INSTI	Integrase strand transfer inhibitor
IRIS	Immune reconstitution inflammatory syndrome
LFT	Liver function test
MDT	Multidisciplinary team
NEC	Necrotising enterocolitis
NICE	National Institute for Care and Health Excellence
NIPT	Non-invasive prenatal testing
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTI	Nucleoside reverse transcriptase inhibitor
NSHPC	National Study of HIV in Pregnancy and Childhood
NVP	Nevirapine
od	Once daily
OR	Odds ratio
PAPP-A	Pregnancy-associated plasma protein A
PCP	Pneumocystis pneumonia
PCR	Polymerase chain reaction
PEP	Post-exposure prophylaxis
PI	Protease inhibitor
PLCS	Pre-labour caesarean section
PND	Postnatal depression
POCT	Point-of-care test
PrEP	Pre-exposure prophylaxis
PTD	Preterm delivery
r	Ritonavir
RAL	Raltegravir
RCOG	Royal College of Obstetricians and Gynaecologists
RCT	Randomised controlled trial
RR	Relative risk
SR	Systematic review

SROM	Spontaneous rupture of the membranes
STI	Sexually transmitted infection
T-20	Enfuvirtide
TD	Tenofovir disoproxil salt
TDF	Tenofovir disoproxil fumarate
TDM	Therapeutic drug monitoring
TTN	Tachypnoea of the newborn
VBAC	Vaginal birth after caesarean section
VL	Viral load
WHO	World Health Organization
ZDV	Zidovudine

Appendix 1: PICO questions

Search 1	Safety and efficacy of antiretrovirals in pregnancy
Study design	Systematic reviews (SRs), randomised controlled trials (RCTs), observational, risk, economic
Population	Women living with HIV
Intervention	Starting antiretroviral therapy during pregnancy
Comparator	None
Outcomes	Death, AIDS, non-AIDS comorbidities, maternal obstetric morbidity, infant mortality and morbidity, mother-to-child HIV transmission, drug resistance

1.1. Conceiving on HAART
Should existing antiretroviral medication be changed?
Is there a difference between maternal and infant outcomes between zidovudine and non-zidovudine containing regimens?
Is there robust evidence in humans of excess birth defects in infants who were conceived on, or exposed in the first trimester to, efavirenz?

1.2. Naïve to HAART: mother needs ART for herself
Which antiretroviral regimen should be recommended?
What gestation should this start?
Should she continue this after delivery?

1.3. Naïve to HAART: mother does not need HAART for herself
Which antiretroviral regimen should be recommended?
At what gestation should this start?
Should she continue this after delivery?

1.4. Late presenting woman not on treatment
Which antiretroviral regimen should be recommended?

1.5. Pharmacokinetics
Should ARV dosages be altered in pregnancy?
Are there any ARVs that should not be used in pregnancy?

Search 2	Hepatitis viruses co-infection
Study design	SRs, RCTs, observational, risk, economic
Population	HIV/HBV/HCV co-infected women
Intervention	Starting antiretroviral therapy during pregnancy
Comparator	None
Outcomes	Death, AIDS, non-AIDS comorbidities, maternal obstetric morbidity, infant mortality and morbidity, mother-to-child HIV transmission, drug resistance

2.1. Hepatitis B (HBV)
Which antiretroviral regimen should be recommended?
Should this be continued after delivery?
What is the preferred mode of delivery for women with HBV co-infection?
Should all infants born to hepatitis B co-infected mothers receive (a) hepatitis B vaccination; (b) hepatitis B immune globulin?
Should pregnant women with HBV be vaccinated against HAV?
When should ARVs be commenced in context of hepatitis co-infection, HBV and HCV and breastfeeding

2.2. Hepatitis C (HCV)
Which antiretroviral regimen should be recommended?
Should this be continued after delivery?
What is the preferred mode of delivery for women with HCV co-infection?
Should pregnant women with HCV be vaccinated against HBV and HAV?
Is there a place for treating hepatitis C in pregnancy to prevent mother-to-child transmission of hepatitis C?
Should these women be monitored in any additional way compared to those not co-infected?
Should the HCV be treated?
Which antiretroviral regimen should be recommended?
Use of DAAs in pregnancy and safety

Search 3	Delivery, fetal monitoring and obstetric issues
Study design	SRs, RCTs, observational, risk, economic
Population	Women living with HIV
Intervention	Obstetric delivery and fetal monitoring
Comparator	None
Outcomes	Death, AIDS, non-AIDS comorbidities, maternal obstetric morbidity, infant mortality and morbidity, mother-to-child HIV transmission, drug resistance

3.1. Mode of delivery
At what level would a HIV viral load be 'safe' for vaginal delivery?
When should a caesarean section be performed?
What antiretroviral therapy should be given during delivery?

3.2. Obstetric procedures
When should a vaginal birth after caesarean (VBAC) be regarded as 'safe'?
Is it safe to perform ECV (external cephalic version)?
Induction of labour, instrumental delivery, episiotomy in HIV-positive pregnant women
What fetal monitoring tests should be performed during delivery?

3. Trisomy/anomaly screening tests, amniocentesis and chorionic villus sampling
Which tests are most appropriate for use in women living with HIV?
What should be the antiretroviral management of a woman requiring amniocentesis or chorionic villus sampling who is not yet on antiretroviral therapy?
Which tests are most appropriate for use in women living with HIV?

3.4. Ruptured membranes
What is the optimum antiretroviral therapy and obstetric management for women presenting with both term and preterm rupture of membranes?

Search 4	Paediatric issues
Study design	SRs, RCTs, observational, risk, economic
Population	HIV-exposed infants
Intervention	Antiretroviral treatment and prophylaxis for neonates
Comparator	None
Outcomes	Death, AIDS, non-AIDS comorbidities, infant mortality and morbidity, mother-to-child HIV transmission, drug resistance

4.1. Infant post-exposure prophylaxis
Which drugs should be used for infant post-exposure prophylaxis and for how long?
Should PCP prophylaxis be administered to the neonate?

4.2. Infant feeding
Is an update required to the BHIVA position statement?
If mother breastfeeds, how frequently should mother and baby be monitored and what tests should be used?
How should infants be fed (breast or bottle)?
Use of cabergoline

4.3. Infant testing
What tests should be undertaken on the neonate and when?

Search 5	Investigations and monitoring in pregnancy
Study design	SRs, RCTs, observational, risk, economic
Population	Women living with HIV
Intervention	Starting antiretroviral therapy during pregnancy
Comparator	None
Outcomes	Death, AIDS, non-AIDS comorbidities, maternal obstetric morbidity, infant mortality and morbidity, mother-to-child HIV transmission, drug resistance

5.1. HIV monitoring
What baseline tests should be recommended for women living with HIV?
How often should they be repeated?
How should we investigate and manage abnormal liver function in pregnancy?

5.2. Sexual health
When should we recommend sexual health screening and how often?
How should we manage genital infections in HIV-positive pregnant women?

Appendix 2: Summary of the modified GRADE system

BHIVA revised and updated the Association's guideline development manual in 2011 [1]. BHIVA has adopted the modified Grading of Recommendations Assessment, Development and Evaluation (GRADE) system for the assessment, evaluation and grading of evidence and the development of recommendations [2,3].

1A Strong recommendation. High-quality evidence. Benefits clearly outweigh risk and burdens, or vice versa. Consistent evidence from well-performed, randomised controlled trials or overwhelming evidence of some other form. Further research is unlikely to change our confidence in the estimate of benefit and risk. Strong recommendations can apply to most individuals in most circumstances without reservation. Clinicians should follow a strong recommendation unless there is a clear rationale for an alternative approach.	**2A** Weak recommendation. High-quality evidence. Benefits closely balanced with risks and burdens. Consistent evidence from well-performed, randomised controlled trials or overwhelming evidence of some other form. Further research is unlikely to change our confidence in the estimate of benefit and risk. Weak recommendation; best action may differ depending on circumstances or individuals or societal values.
1B Strong recommendation. Moderate-quality evidence. Benefits clearly outweigh risk and burdens, or vice versa. Evidence from randomised controlled trials with important limitations (inconsistent results, methods flaws, indirect or imprecise), or very strong evidence of some other research design. Further research may impact on our confidence in the estimate of benefit and risk. Strong recommendation and applies to most patients. Clinicians should follow a strong recommendation unless a clear and compelling rationale for an alternative approach is present.	**2B** Weak recommendation. Moderate-quality evidence. Benefits closely balanced with risks and burdens, some uncertainly in the estimates of benefits, risks and burdens. Evidence from randomised controlled trials with important limitations (inconsistent results, methods flaws, indirect or imprecise). Further research may change the estimate of benefit and risk. Weak recommendation, alternative approaches likely to be better for some individuals under some circumstances.
1C Strong recommendation. Low-quality evidence. Benefits appear to outweigh risk and burdens, or vice versa. Evidence from observational studies, unsystematic clinical experience, or from randomised controlled trials with serious flaws. Any estimate of effect is uncertain. Strong recommendation; applies to most patients. Some of the evidence base supporting the recommendation is, however, of low quality.	**2C** Weak recommendation. Low-quality evidence. Uncertainty in the estimates of benefits, risks and burdens; benefits may be closely balanced with risks and burdens. Evidence from observational studies, unsystematic clinical experience, or from randomised controlled trials with serious flaws. Any estimate of effect is uncertain. Weak recommendation; other alternatives may be reasonable.
1D Strong recommendation. Very low-quality evidence. Benefits appear to outweigh risk and burdens, or vice versa. Evidence limited to case studies. Strong recommendation based only on case studies and expert judgement.	**2D** Weak recommendation. Very low-quality evidence. Uncertainty in the estimates of benefits, risks and burdens; benefits may be closely balanced with risks and burdens. Evidence limited to case studies and expert judgement. Very weak recommendation; other alternatives may be equally reasonable.

References

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Appendix 3: Drug dosing for infants

<table>
<tr><th>DRUG</th><th>DOSE</th><th>COMMENTS/SIDE EFFECTS</th></tr>
<tr><td colspan="3">NRTIs: nucleoside reverse transcriptase inhibitors</td></tr>
<tr><td>Zidovudine
(ZDV) (Retrovir®)
Also known as azidothymidine (AZT)

Liquid – 10 mg/mL</td><td><u>Oral:</u>
<table>
<tr><th>Gestation +/- weight</th><th>Dose</th></tr>
<tr><td><30/40 gestation at birth</td><td>2 mg/kg twice a day</td></tr>
<tr><td>30–34/40 gestation at birth</td><td>2 mg/kg twice a day for 2/52 then 2 mg/kg three times a day</td></tr>
<tr><td>≥34/40 gestation at birth and ≤2 kg</td><td>4 mg/kg twice a day – round dose <u>up</u> to the nearest 0.5 mg to assist administration</td></tr>
<tr><td>≥34/40 gestation at birth and >2 kg</td><td>See dose banding table</td></tr>
</table>
<u>Duration oral dosing:</u>
• Very low risk monotherapy – 2 weeks
• Low risk monotherapy – 4 weeks
• Combination therapy – 4 weeks
<u>Intravenous:</u>
• ≥34/40 gestation – 1.5 mg/kg four times a day
• <34/40 gestation – 1.5 mg/kg twice a day, change to four times a day at 34/40</td><td>Anaemia, neutropenia
<table>
<tr><th>Weight range (kg)</th><th>Oral dose (equivalent to 4 mg/kg)
<u>TWICE A DAY</u></th><th>Volume to be given orally
<u>TWICE A DAY</u></th></tr>
<tr><td>2.01–2.12</td><td>8.5 mg</td><td>0.85 mL</td></tr>
<tr><td>2.13–2.25</td><td>9 mg</td><td>0.9 mL</td></tr>
<tr><td>2.26–2.37</td><td>9.5 mg</td><td>0.95 mL</td></tr>
<tr><td>2.38–2.50</td><td>10 mg</td><td>1 mL</td></tr>
<tr><td>2.51–2.75</td><td>11 mg</td><td>1.1 mL</td></tr>
<tr><td>2.76–3.00</td><td>12 mg</td><td>1.2 mL</td></tr>
<tr><td>3.01–3.25</td><td>13 mg</td><td>1.3 mL</td></tr>
<tr><td>3.26–3.50</td><td>14 mg</td><td>1.4 mL</td></tr>
<tr><td>3.51–3.75</td><td>15 mg</td><td>1.5 mL</td></tr>
<tr><td>3.76–4.00</td><td>16 mg</td><td>1.6 mL</td></tr>
<tr><td>4.01–4.25</td><td>17 mg</td><td>1.7 mL</td></tr>
<tr><td>4.26–4.50</td><td>18 mg</td><td>1.8 mL</td></tr>
<tr><td>4.51–4.75</td><td>19 mg</td><td>1.9 mL</td></tr>
<tr><td>4.76–5.00</td><td>20 mg</td><td>2 mL</td></tr>
</table></td></tr>
<tr><td>Lamivudine (3TC) (Epivir®)
Liquid 10 mg/mL</td><td><u>Oral:</u> usually as part of combination therapy
2 mg/kg twice a day – round dose <u>up</u> to nearest 0.5 mg to assist administration</td><td>Anaemia, neutropenia
(much less common than with ZDV)</td></tr>
<tr><td>Abacavir (ABC) (Ziagen®)
Liquid 20 mg/mL</td><td><u>Oral:</u> usually as part of combination therapy
2 mg/kg twice a day– round dose <u>up</u> to nearest 1 mg to assist administration</td><td>Hypersensitivity reactions have not been noted in neonates</td></tr>
<tr><td>Tenofovir
(TDF) (Viread®)
245 mg tenofovir disoproxil = 300 mg TDF</td><td><u>Oral:</u> usually as part of combination therapy
All doses now based on tenofovir disoproxil salt (TD)
(*245 mg TD tablet dissolved in 24.5 mL water gives 10 mg/mL)
4.9 mg/kg (0.49 mL/kg*) once a day (round dose <u>up</u> to the nearest 0.5 mg (<10 mg) or 1 mg (≥10 mg) to assist administration)</td><td>Renal dysfunction: consider monitoring renal function weekly</td></tr>
<tr><td colspan="3">NNRTI: non-nucleoside reverse transcriptase inhibitor</td></tr>
</table>

<table>
<tr><td>Nevirapine (NVP)
(Viramune®)

Liquid 10 mg/mL</td><td><u>Oral:</u> usually as part of combination therapy
2 mg/kg once a day for 1 week, then 4 mg/kg once a day for 1 week – round doses <u>up</u> to the nearest 0.5 mg to assist administration
If mother has already received >3 days of nevirapine:
4 mg/kg once a day – (round doses <u>up</u> to the nearest 0.5 mg)</td><td>Rash and liver dysfunction – rare in neonates
Stop NVP after 2/52, in view of long half-life, continue other PEP agents for full 4/52</td></tr>
<tr><td colspan="3">INSTI: integrase strand transfer inhibitor</td></tr>
<tr><td>Raltegravir
(RAL) (Isentress®)
100 mg sachets for oral suspension (10 mg/mL)</td><td><u>Oral:</u> usually as part of combination therapy
1.5 mg/kg once a day from birth to day 7, then 3 mg/kg twice a day until 4 weeks of age. See dose banding:
<table><tr><th>Body weight (kg)</th><th>Dose</th></tr><tr><td colspan="2">In full-term neonates >37 weeks</td></tr><tr><td colspan="2">Birth to 1 week – once a day dosing</td></tr><tr><td>2 to <3 kg</td><td>4 mg once a day</td></tr><tr><td>3 to <4 kg</td><td>5 mg once a day</td></tr><tr><td>4 to <5 kg</td><td>7 mg once a day</td></tr><tr><td colspan="2">1 to 4 weeks – twice a day dosing</td></tr><tr><td>2 to <3 kg</td><td>8 mg twice a day</td></tr><tr><td>3 to <4 kg</td><td>10 mg twice a day</td></tr><tr><td>4 to <5 kg</td><td>15 mg twice a day</td></tr></table></td><td>Rash and liver dysfunction: monitor liver function tests at 5–7 days of age</td></tr>
<tr><td colspan="3">PI - protease inhibitor</td></tr>
<tr><td>Lopinavir/ritonavir
(Kaletra®)
Liquid:
5 mL = (Lopinavir 400 mg + ritonavir 100 mg)</td><td><u>Oral:</u> usually as part of combination therapy
300 mg/m^2 (of lopinavir) twice a day – use dose banding table below
<table><tr><th>Weight range (kg)</th><th>SA range (m^2)</th><th>Kaletra volume to be given orally <u>TWICE A DAY</u></th></tr><tr><td>1–1.5</td><td>0.1–0.13</td><td>0.5 mL</td></tr><tr><td>1.51–2</td><td>0.14–0.16</td><td>0.6 mL</td></tr><tr><td>2.01–2.5</td><td>0.17–0.19</td><td>0.75 mL</td></tr><tr><td>2.51–3</td><td>0.20–0.21</td><td>0.8 mL</td></tr><tr><td>3.01–3.5</td><td>0.22–0.24</td><td>0.9 mL</td></tr><tr><td>3.51–4</td><td>0.25–0.26</td><td>1 mL</td></tr><tr><td>4.01–4.5</td><td>0.27–0.28</td><td>1.1 mL</td></tr><tr><td>4.51–5</td><td>0.29–0.30</td><td>1.2 mL</td></tr></table></td><td>Severe adrenal dysfunction, electrolyte imbalance and cardiogenic shock in neonates, especially premature infants
Avoid in premature infants, only use, as per birth plan, when benefit of giving outweighs the potential risks
Monitor for signs of toxicity, check U+E, pH, glucose, lactate, LFT, daily for first 5 days</td></tr>
<tr><td colspan="3">FI: fusion inhibitor</td></tr>
<tr><td>Enfuvirtide
(Fuzeon®)
(T-20)</td><td><u>Intravenous:</u> usually as part of combination therapy
2 mg/kg IV twice a day (as infusion over 30 minutes)
Method: To reconstitute the 108 mg vial slowly add 1.1 mL of water for injections from the vial of diluent provided to the vial of enfuvirtide powder, do not shake or invert the vial. The powder will</td><td>Experimental IV dosing regime
Use only, as per birth plan, when benefit of giving outweighs the potential risks</td></tr>
</table>

	take up to 45 minutes to dissolve. The resulting solution contains 90 mg in 1 mL. Add 1 mL (90 mg) of the solution to 10 mL of water for injections, then further dilute to 45 mL with water for injections, do not shake or invert the syringe. The final solution contains 90 mg in 45 mL (2 mg in 1 mL) from which to administer the required dose	
PCP prophylaxis		
Co-trimoxazole (Septrin®) 240 mg in 5 mL liquid	**BW ≥2 kg** 120 mg = 2.5 mL **BW <2 kg** 60 mg = 1.25 mL ONCE a day on 3 days per week	Only HIV-infected infants, start at 4 weeks of age. May rarely cause rash and bone marrow suppression