British HIV Association guidelines for the management of HIV infection in pregnant women 2018

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Contents

1. Scope and purpose

The overall purpose of these guidelines is to provide guidance on best clinical practice in the treatment and management of pregnant women living with HIV (human immunodeficiency virus) in the UK 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 mother herself, 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 postnatal management of women has been added.

1.1 Guideline development process

The British HIV Association (BHIVA) revised and updated the Association's guideline development manual in 2011 (www.bhiva.org/GuidelineDevelopmentManual.aspx; see also Appendix 1). 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 who 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. In addition, BHIVA members were asked to come forward 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 and strategy (including the definition of populations, interventions and outcomes) are outlined in Appendices 2 and 3. The literature searches for the 2018 guidelines covered the period from July 2013 up until July 2017 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 1), 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 a patient representative who was 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 the journal *HIV Medicine*
- Publication in *HIV Medicine*
- Shortened version detailing concise summary of recommendations
- E-learning module accredited for CME
- Educational slide set to support local and regional educational meetings
- National BHIVA audit programme

1.4 Summary of guideline update and date of next review

There have been some changes in recommendations. The prevalence data from the UK have been updated.

- We have updated infant feeding advice to include new data on breastfeeding and the emotional impact not breastfeeding may have on women. We discuss the use of cabergoline in non-breastfeeding women. Length of infant PEP has been shortened where risk of vertical transmission is VERY LOW.
- We have expanded the section on 'The psychosocial care of women living with HIV during and after pregnancy' and moved its position within the guidelines.
- Safety: new data on raltegravir, rilpivirine, dolutegravir, elvitegravir.
- Prescribing: all women are recommended to start on treatment and remain on it lifelong. As this includes elite controllers this section has been removed.
- Hepatitis: information added on tenofovir alafenamide for hepatitis B and direct acting agents for hepatitis C.
- We have added a section on the postnatal management of women living with HIV.

The guidelines will be next fully updated and revised in 2023. The Writing Group will, however, continue to confer regularly to consider new information from high-quality studies and publish amendments and addendums to the current recommendations prior to the full revision date where this is thought to be clinically important to ensure continued best clinical practice.

2. Recommendations and auditable outcomes

2.1 Recommendations

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

4.1	Antenatal HIV care should be delivered by a multidisciplinary team (MDT), the precise composition of which will vary.	1D
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 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 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. Women should be encouraged to continue cART 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.	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 should be performed as per routine initiation of cART and then at each antenatal visit.	1C
5.2.7	In the event that a woman who has initiated cART during pregnancy has not suppressed plasma viral load <50 HIV RNA copies/mL at 36 weeks the following interventions are recommended: • Review adherence 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 antiretroviral therapy in pregnancy and pregnancy outcomes

6.1 Conceiving on ART

6.1.1	It is recommended that women conceiving on a cART regimen should continue this.	1B
	Exceptions are: Non-standard regimens, for example protease inhibitor (PI) monotherapy, regimens which have been demonstrated to show lower pharmacokinetics in pregnancy and protease inhibitors demonstrated to increase risk of pre-term delivery. These should be modified to include (depending on tolerability, resistance and prior antiretroviral history) one or more agents that cross the placenta.	2D

6.2 Naïve to cART: mother needs ART for herself

6.2.1	All pregnant women, including elite controllers, should start ART during pregnancy and continue lifelong.	1A
6.2.2	Women should commence ART as soon as they are able to do so in the second trimester, but within the first trimester if VL >100,000 HIV RNA copies/mL and/or CD4 cell count is less than 200 cells/mm^3. All women should have commenced ART by week 24 of pregnancy.	1C

6.3 Woman is not already on ART: what to start

6.3.1	Women are recommended to start tenofovir disoproxil fumarate or abacavir with emtricitabine or lamivudine as a nucleoside backbone as recommended in the BHIVA adult antiretroviral treatment guidelines.	2C
6.3.2	In the absence of specific contraindications, it is recommended that the third agent in cART should be in accordance with the BHIVA adult antiretroviral treatment guidelines, where there are sufficient clinical and pharmacokinetic data for use of the third agent in pregnancy.	1C
6.3.3	It is recommended that an integrase inhibitor-based regimen is considered as the third agent of choice in patients with high baseline viral load (>100,000 HIV RNA copies/mL), where cART is being started late in pregnancy or where it is failing to suppress the virus.	2C
6.3.4	No routine dose alterations are recommended for ARVs during pregnancy if used at adult licensed doses	1C
	Consider third trimester TDM particularly if combining tenofovir and atazanavir	2C
	If dosing off licence, consider switching to standard dosing throughout pregnancy or regular TDM	2C
	Darunavir should be prescribed at the twice daily dose if known resistance and consideration should be given to using this higher dose if darunavir is initiated in pregnancy	2C
6.3.5	All women are recommended to commence lifelong cART. Where a woman declines cART despite on-going counselling and support to start therapy, zidovudine monotherapy is a non-preferred option in women refusing cART who have a baseline VL of <10,000 HIV RNA copies/mL and a CD4 cell count of >350 cells/mm^3. and who consent to a Caesarean section	1A

6.5 Late-presenting woman not on treatment

6.5.1	A woman who presents after 28 weeks should commence cART without delay.	1B
6.5.2	If the viral load is unknown or >100,000 copies/mL a three- or four-drug regimen that includes raltegravir is suggested.	2D
6.5.3	For details on how to manage an untreated woman presenting in labour at term, please see section 8.1.6 (high-risk neonatal management). All women should be given a stat dose of nevirapine 200 mg;	1B
	and commence fixed-dose zidovudine with lamivudine;	1B
	and raltegravir and receive IV zidovudine for the duration of labour.	2D

6.5.4	In preterm labour, if the infant is unlikely to be able to absorb oral medications consider the addition of double-dose tenofovir disoproxil fumarate to the treatment described in recommendation 6.5.3 to further load the baby.	2C
6.5.5	Women presenting in labour/ROM/requiring delivery without a documented HIV result must be recommended 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
6.6.1	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 antiretroviral treatment of adults living with HIV.	1B

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 HAV, HCV and HDV screening and tests to assess hepatic inflammation/fibrosis and liver function are recommended.	1C
7.1.2	Liver function tests 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	Since 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 infection and no contraindication to any drug.	1B
7.1.5	If tenofovir is not currently part of ART it should be added.	1B
7.1.6	Lamivudine/emtricitabine may be omitted from the antiretroviral regimen and tenofovir 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 potential antiviral benefits over lamivudine, is co-formulated with tenofovir (TDF and TAF), and appears to be equally safe during pregnancy and hence is the preferred option to be given with tenofovir in co-infection.	2D
7.1.9	In all HAV non-immune HBV co-infected women, 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
7.1.10	cART active against both HBV and HIV should be continued in all HBV co-infected women post-delivery.	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 mother has fully suppressed HIV viral load on cART, irrespective of HBV viral load.	1C
7.1.13	Neonatal immunisation with or without HBIG should commence within 24 hours of delivery.	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	Liver function tests 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	1C

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

Section 8. Obstetric management

8.1 Antenatal care

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 trisomy 21 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 mother 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 performed in women with HIV.	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, a planned vaginal delivery is recommended.	1C
8.2.2	For women with a plasma viral load of 50–399 HIV RNA copies/mL at 36 weeks, 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 recommended and labour has commenced, obstetric management should follow the same guidelines as for the HIV-negative population.	1C
8.2.5	Vaginal birth after Caesarean section (VBAC) should be offered to women with a viral load <50 HIV RNA copies/mL.	1D
8.2.6	Where the indication for PLCS is the prevention of vertical transmission, PLCS should be undertaken at between 38 and 39 weeks' gestation.	1C

8.3 Management of spontaneous rupture of membranes

8.3.1	In all cases of term pre-labour spontaneous rupture of the membranes (ROM) delivery should be expedited.	1C
8.3.2	If maternal HIV viral load is <50 HIV RNA copies/mL immediate induction of labour is recommended, with a low threshold for treatment of intrapartum pyrexia.	1C
8.3.3	For women with a last measured plasma viral load of 50–999 HIV RNA copies/mL, immediate Caesarean section 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
8.3.4	If maternal HIV viral load is ≥1000 RNA copies/mL plasma immediate Caesarean section is recommended.	1C
8.3.5	The management of prolonged premature rupture of membranes (P-PROM) at ≥34 weeks is the same as term ROM (see section 8.3 Management of spontaneous rupture of membranes) except women who are 34–37 weeks' gestation will require group B streptococcus prophylaxis in line with national guidelines.	1C
8.3.6	When P-PROM occurs at <34 weeks: • Intramuscular steroids should be administered in accordance with national guidelines • Virological control 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 of >1000 HIV RNA copies/mL plasma who present in labour, or with ruptured membranes or who are admitted for planned CS.	1C
	For untreated women presenting in labour or with ruptured membranes in whom the current viral load is not known.	1C
	There are no data to support the use of intrapartum intravenous zidovudine infusion in women on cART with a plasma HIV viral load <1000 HIV RNA copies/mL.	1C

Section 9. Neonatal management

9.1 Infant post-exposure prophylaxis (PEP). See Appendix 4 for dosing recommendations

9.1.1	VERY LOW RISK	1C
	Two weeks' zidovudine monotherapy is recommended if all the following criteria are met: • Mother 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' zidovudine monotherapy: • If the criteria in 9.1.1 are not all fulfilled but maternal HIV VL is <50 HIV RNA copies/mL at or after 36 weeks • If baby born prematurely (<34 weeks) but most recent maternal HIV VL is <50 HIV RNA copies/mL	
9.1.3	HIGH RISK	1C
	Use combination PEP if maternal birth HIV VL known to be or likely to be >50 HIV RNA	

	copies/mL on day of birth, if uncertainty about recent maternal adherence or if VL not known.	
9.1.4	Neonatal PEP should be commenced very soon after birth, certainly 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 not immediately available, commence standard 3 drug PEP (zidovudine, lamivudine, nevirapine) until guidance is provided.	1D

9.1.8 HIV-2

9.1.8	If mother known to be HIV-2 infected follow the above advice but if HIGH RISK (combination PEP indicated) NVP will not be effective. Seek expert advice. If advice not immediately available commence AZT, 3TC and RAL until guidance available.	2C

9.1.9 PEP beyond 4 weeks

9.1.9	Infant PEP should be stopped at 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 is positive at any stage or if the infant is 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 national schedule.	1C
9.3.2	Rotavirus vaccine is not contraindicated (unless HIV diagnosis has been confirmed and 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

9.4 Infant feeding

9.4.1	In the UK and other resource rich settings the safest way to feed infants born to mothers with HIV is with formula milk, as this eliminates on-going risk of HIV exposure after birth.	1D
9.4.2	Abstaining from breastfeeding can have financial and psychological repercussions for women, requiring support from the HIV MDT.	1C
9.4.3	Women who are virologically suppressed on cART with good adherence and who choose to breastfeed may be supported to do so, but should be informed about the low risk of transmission of HIV through breastfeeding in this situation.	1D
9.4.4	Maternal cART (rather than neonatal PEP) is advised to minimise HIV transmission through breastfeeding.	1D

9.5 Infant testing

9.5.1	Molecular diagnostics for HIV infection should be performed on the following occasions	
9.5.1.1	Exclusively 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 (at least 2 weeks post cessation of infant prophylaxis*) • at 12 weeks (at least 8 weeks post 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. 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 (HIVEU)

9.7.1	In light of evidence for possible increased infectious morbidity in HIVEU, timely routine vaccination should be ensured and GPs, health visitors and secondary care physicians should be made aware of possible increased risk in order to inform decisions when risk assessing in primary care.	1D

Section 10 Postnatal management of women

10.1.1	All women are recommended to continue cART postpartum.	1A
10.2.1	All women should be reviewed in the postnatal period by a named member of the multidisciplinary team within 4–6 weeks.	1C
10.3.1	Women not breastfeeding their infant by choice, or because of HIV RNA>50 copies/mL, should be offered cabergoline to suppress lactation.	1C
10.4.1	Women advised not to breastfeed for their baby's health should be provided with free formula feed to minimise vertical transmission of HIV.	1D
10.5.1	Women should have support needs assessed postpartum and be referred to appropriate services in the Trust, community and/or voluntary groups without delay.	1D
10.6.1	Women should have 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
10.7.1	Contraceptive needs should be discussed with all women, and ART may be changed to	1D

	optimise a woman's contraception choice as long as the ART prescribed is fully active against the viral genotype.	
10.8.1	Cytology should be scheduled as per the Guidelines for the NHS Cervical Screening Programme 2016, 3 months post-delivery.	1C
10.9.1	For the woman newly diagnosed with HIV in pregnancy, testing of the woman's 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 ROM/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 hepatitis B virus co-infection who have liver function tests performed 2 weeks after commencing cART to detect evidence of antiretroviral hepatotoxicity or IRIS.
7	Proportion of women with hepatitis C virus co-infection who have liver function tests 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 Caesarean sections performed and their indication.
10	Proportion of infants <72 hours old, born to untreated mothers 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 mothers living with HIV who have HIV antibody testing for seroreversion performed at age 15–24 months.
13	Proportion reviewed postpartum by 6 weeks
14	Proportion with documented mental health assessment at booking, and at 4–6 weeks postpartum

3. Introduction

One of the major successes in the management of individuals living with HIV has been the prevention of vertical transmission of HIV-1. With the widespread implementation of routine antenatal screening for HIV-1, vertical transmission is now a rare occurrence in the UK. Despite few recent randomised controlled trials regarding the use of antiretroviral therapy (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 clinical care of pregnant women living with HIV. The guidelines are intended to inform and aid healthcare workers in the management of pregnant women with 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.

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 a multidisciplinary team (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 RISK according to maternal viral load and ART. PEP has been shortened where risk of vertical transmission is VERY LOW to 14 days. We have added a section on the postnatal management of women living with HIV.

An increasing number of women are aiming for and achieving a vaginal delivery but the rate of emergency Caesarean sections 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 Caesarean sections. 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 of <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 hepatitis B virus or hepatitis C virus co-infection. For the first time these guidelines have addressed the issue of continuation of cART post delivery in women. The paediatric section provides further guidance on infant post-exposure prophylaxis (PEP), drug dosing and safety. It is clear that there exists an 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 http://www.ucl.ac.uk/nshpc). Other vital data sources are Public Health England's HIV surveillance systems (https://www.gov.uk/government/collections/hiv-surveillance-data-and-management), and the NHS infectious diseases in pregnancy screening (IDPS) programme (https://www.gov.uk/topic/population-screening-programmes/infectious-diseases-in-pregnancy).

Prevalence of HIV amongst 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 the UK in 2016, and an estimated 1300 with undiagnosed infection [3]. Between 2012 and 2016 the number of women diagnosed each year declined from around 1700 to 1200, and 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 those 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 health care providers is regularly updated and available at https://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, a transmission rate of 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 Caesarean section 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 perinatally infected pregnant women is emerging [11].

3.2 HIV infection in children

The number of children (all ages 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 those undiagnosed women had declined antenatal testing. A smaller proportion had tested negative and had presumably seroconverted in pregnancy, or while still breastfeeding. A subsequent UK audit of perinatal transmissions between 2006 and 2013 showed a similar picture, 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 mothers had multiple issues such as co-morbidities, insecure accommodation, immigration issues, intimate partner violence, and other challenging social circumstances to contend with 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

It is the responsibility of clinicians caring for women with living HIV and their children to report them prospectively to the NSHPC. 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 made to the APR antenatally with postnatal follow-up. Antiretroviral Pregnancy Registry Research Park, 1011 Ashes Drive, Wilmington, NC 28405, USA

In UK call 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)

This is the UK and Ireland's surveillance system for obstetric and paediatric HIV, 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). For further information see the NSHPC website (www.ucl.ac.uk/nshpc), the CHIPS website (www.chipscohort.ac.uk), or email (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	Antenatal HIV care should be delivered by a multidisciplinary team (MDT), the precise composition of which will vary.	1D

First, it is important to acknowledge that the majority of women living with HIV care engage well in care during pregnancy, resulting in the low rates of vertical transmission outlined in section 3. This is to be celebrated. However, some women may experience psychosocial challenges during and/or after pregnancy.

HIV is associated with a higher risk of poor mental health [1]. Data from the UK-based ASTRA study reveal that the prevalence of depression among women living with HIV is nearly 30% [2]. 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 [3]. A recent national review of vertical transmissions has identified psychosocial issues such as immigration and HIV-related stigma as key contributing factors [4].

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% [5]. In the studies that include an HIV-negative comparison group, there was no evidence of an association between HIV status and PND [5]. Factors associated with PND in women living with HIV include past history of mental health issues, financial issues, immigration concerns, housing issues, lack of social support, HIV-related stigma, intimate partner violence, substance misuse, and lack of support from a partner [5-7]. However there remains an absence of data on perinatal mental health among women living with within a UK setting. Trial data on interventions targeting psychiatric and psychosocial outcomes in pregnant women living with HIV are also currently lacking [5].

Women living with HIV may be at risk of intimate partner violence during pregnancy (as are women without HIV), with lifetime prevalence rate of intimate partner violence in pregnancy estimated to be 14% in women living with HIV [8]. We therefore fully endorse NICE antenatal guidelines recommending that *all* pregnant women be asked about domestic violence [9].

4.1.1 Social issues

Many women living with HIV will have issues relating to social support needs and/or immigration issues. 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 if they are late in pregnancy or are recently delivered [10-12]. 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, it has been law that all antenatal, intrapartum and postnatal services are 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.

It is advisable to get advice from colleagues, the GMC, BMA 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 Doctors of the World, who give advice on access to healthcare in the UK, on their advice line (0207 515 7534).

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 a multidisciplinary team who 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 [13]. Adherence can sometimes be sub-optimal postpartum, resulting in viral load rebound [14]; early engagement in HIV care in the postpartum period has been shown to improve adherence [7].

Reassurance about confidentiality is extremely important, especially regarding family members and friends who may not know about HIV, but who are intimately involved with the pregnancy. Women from communities with high levels of HIV awareness may be concerned about HIV 'disclosure-by-association' when discussing certain interventions, including taking medication during pregnancy, having a Caesarean section, 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 [15]. For couples where a male partner is HIV-negative, advice should be provided on condom use and post-exposure prophylaxis following sexual exposure if a woman does not have an undetectable viral load [16].

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, general practitioners, 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 multidisciplinary team

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 advocacy, clinical psychologists, psychiatrists, counsellors, health advisors, Citizens Advice Bureau workers, interpreters, community midwives, pharmacists, adult and paediatric clinical nurse specialists and health visitors [17].

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 management 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 mothers and improvements in clinical outcomes (such as adherence to prevention of vertical transmission interventions, and lower rates of depression) in randomised-controlled trials [18,19]. 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 of all the interventions they undertake [20,21]. 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 a multidisciplinary team 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 the long-term health of herself, her baby and her partner. In the case of newly diagnosed HIV in pregnancy, prompt linkage to HIV care may be beneficial [22], as is the offer of psychological support soon after an antenatal HIV diagnosis [23].

Confidence in telling others about HIV will vary from woman to woman, and there may be cultural factors that influence the patterns of telling partners and other social network members [17,24]. Talking about HIV should be encouraged in all women but should be viewed as a process that may take some time [25,26]. 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. There are situations where 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) [27] and General Medical Council (GMC) [28]. 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 [29].

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 NICE guidelines.	1D

We advise that HIV multidisciplinary teams follow existing NICE guidance on the detection of antenatal and postnatal depression [30]. 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?

If a mental health problem is suspected as a result of answers to these questions, then 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 recommended.	2C
5.1.3	Genital tract infections should be treated according to 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 STIs of 0–4% and of BV of 1–4% [1-3]. A London cohort 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, hepatitis B virus (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, additional considerations are the potential effects of the presence of a genital infection on vertical transmission of HIV-1. This could occur through an increase in the HIV-1 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 pre-term 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 bacterial vaginosis (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-1 RNA following treatment of gonococcal, chlamydial, and non-specific cervicitis [13,14].

Viral load in cervicovaginal specimens has been shown to correlate with vertical transmission of HIV-1 [15]. Genital tract HIV viral load will usually mirror the plasma HIV viral load [16], but there is increasing evidence of compartmentalisation of HIV-1 between the plasma and genital tract. Genital tract HIV-1 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] shows 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-1 vertical transmission (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 VL at delivery and cervicovaginal HIV VL 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 [24,25].

For pregnant women receiving ART, the data regarding the relationship between vertical transmission and HSV-2 is inconclusive. A Ukrainian study, where 96% of women were receiving antenatal ART and around half received 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 HIV with HSV-2 antibodies [26]. A Thai study of women living with HIV who were HSV-2 seropositive found that vertical transmission of HIV was independent of 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-1 and HSV-2 taking cART in Burkina Faso, which demonstrated that valaciclovir 500 mg twice a day further reduced genital HIV replication in those women with residual HIV shedding despite cART. However, vertical transmission of HIV was not reviewed [27]. 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% versus 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 [28].

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 HAART 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 daily suppressive aciclovir 400mg 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 [29].

5.1.2 Chorioamnionitis and bacterial vaginosis (BV)

Chorioamnionitis may lead to premature rupture of the membranes with the possibility of premature birth [30,31]. Chorioamnionitis, prolonged rupture of membranes and premature birth have all been associated with vertical transmission of HIV and may be interlinked [32-34]. However, a Phase III clinical trial of antibiotics to reduce chorioamnionitis related perinatal HIV-1 transmission showed no benefit in reducing vertical transmission in the context of single-dose nevirapine prophylaxis [35]. Although both *Chlamydia trachomatis* and *Neisseria gonorrhoeae* have been associated with chorioamnionitis, the organisms usually implicated are those associated with BV including *Ureaplasma urealyticum* [36,37]. A strong association between BV and premature delivery has been reported [38,39]. 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 [37]. A study in which mothers 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-fold risks, respectively [40]. It is not known how applicable this is in settings where mothers receive cART from earlier in pregnancy.

In HIV negative women, the data regarding the effect of screening for and treating BV on premature delivery are conflicting. There are scant pre-HAART data on women living with HIV therefore BV should be treated as per BASHH 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 sexually transmitted infections as per the routine management of newly diagnosed patients [41]. 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 (www.bashh.org/guidelines), 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 [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, then the colposcopy should not be delayed. If a pregnant woman requires colposcopy or cytology after treatment (or follow up of untreated CIN1), her assessment may be delayed until after delivery. Unless there is an obstetric contraindication, however, assessment should not be delayed if the first appointment for follow-up cytology or colposcopy is due following treatment for cervical glandular intraepithelial neoplasia (CGIN). 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 or defaulted 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 with each woman. ARVs may need to be changed postnatally to align with a woman's choice of contraception.

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. Women should be encouraged to continue cART 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

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.	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 should be performed as per routine initiation of cART and then at each antenatal visit.	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 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 that has not suppressed plasma viral load to <50 HIV RNA copies/mL at 36 weeks, the following interventions are recommended: • Review adherence 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 antiretroviral therapy in pregnancy and pregnancy outcomes

6.1 Conceiving on cART

6.1.1	It is recommended that women conceiving on a cART regimen should continue this.	1B
	Exceptions are: non-standard regimens, for example protease inhibitor (PI) monotherapy, regimens that have been demonstrated to show lower pharmacokinetics in pregnancy and protease inhibitors demonstrated to increase risk of pre-term delivery. These should be modified to include (depending on tolerability, resistance and prior antiretroviral history) one or more agents that cross the placenta.	2D

Despite the lack of 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 this throughout pregnancy and after.

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 minimal time required to overcome the issue. However, there are no data that specifically address this.

Although zidovudine remains the only antiretroviral agent with a license 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 [1], there are no data to support routinely switching to zidovudine, or adding zidovudine to a combination of ARVs that is suppressing HIV replication to less than 50 HIV RNA copies/mL in plasma. Analyses of data combined from two observational studies, the European Collaborative Study (ECS) and the UK and Ireland NSHPC, have shown no difference in pregnancy outcomes between zidovudine-based and zidovudine-sparing cART [2].

6.1.3 Evidence on teratogenicity and ART

The Antiretroviral Pregnancy Registry (APR) [3] provides the best data on teratogenicity and first trimester antiretroviral therapy exposure although it should be noted that births from the UK contribute to only 4.6% of collected data. This voluntary prospective database records rates of congenital birth defects in babies born to women with first-trimester exposure to antiretroviral therapy in comparison to background rates of congenital birth defects and second- and 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 ARV have been reported.

Table 6.1. Status of ART according to Antiviral Pregnancy Registry June 2017

Status with regards to congenital malformation	ARVs
Congenital malformation rates in expected range and a congenital malformation rate greater than two-fold higher than the general population has been excluded	Darunavir Efavirenz Indinavir Raltegravir Rilpivirine
Congenital malformation rates in expected range and an overall congenital malformation rate greater than 1.5-fold higher than the general population and two-fold higher risk in most common defects has been excluded	Abacavir Atazanavir Emtricitabine Lamivudine Lopinavir Nevirapine Ritonavir Tenofovir disoproxil fumarate Zidovudine
Insufficient data available to assess therefore this should be discussed with the patient prior to continuation of prescribing	Cobicistat Dolutegravir Elvitegravir Enfuvirtide Etravirine Fosamprenavir Maraviroc Saquinavir Tenofovir alafenamide Tipranavir
Not recommended in pregnancy	

In prospectively reported cases, infants exposed to 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 the general population has been excluded. For the other currently used agents abacavir, atazanavir, lamivudine, emtricitabine, lopinavir, nevirapine, ritonavir, tenofovir disoproxil fumarate (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 twofold higher rate than in the general population has been excluded) [3]. For the 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 antiretroviral pregnancy registry has shown no difference in risk of birth defects for abacavir/lamivudine and non-abacavir/lamivudine backbones [4].

The earlier recommendation that efavirenz be avoided in women who may conceive [5] was based on preclinical animal studies that had not been conducted on any other ART, the 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 in pregnancy without additional precautions and considerations over and above those of other antiretroviral therapies [6].

For further information and discussion regarding choice of ART, see section 6.4

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 continue lifelong.	1A

Current BHIVA treatment guidelines recommend treatment of all people living with HIV, regardless of CD4 cell count or clinical status [7]. Studies have shown 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 [8-10]. All pregnant women living with HIV should be counselled about the importance of continuation of cART postpartum.

6.2.2	Women should commence ART as soon as they are able to do so in the second trimester, but within the first trimester if VL >100,000 HIV RNA copies/mL and/or CD4 cell count is less than 200 cells/mm^3. All women should have commenced ART by week 24 of pregnancy.	1C

When considering the optimal time to start cART, the theoretical considerations for avoiding medication during pregnancy, and the first trimester in particular, must be considered in the light of the increasing safety data on first-trimester exposure to ART, the risk to maternal health (and foetal exposure to opportunistic infections), the risk of vertical transmission and the time required to achieve an undetectable viral load by the time of delivery.

Deferring treatment to the start of the second trimester is an option, particularly if the patient is experiencing nausea and/or vomiting of pregnancy. However, where the mother is at risk of, or has presented with an opportunistic infection, initiation of cART should not be delayed because of pregnancy.

Risk of vertical transmission of HIV is determined by maternal viral load, whether ART is taken in pregnancy, and the time on therapy prior to delivery.

Major determinants of the probability of suppressing to a viral load <50 HIV RNA copies/mL plasma 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 French cohorts, transmission events were significantly associated with starting treatment later in pregnancy. In the French cohort, the median duration of treatment was 9.5 weeks amongst women where vertical transmission occurred compared with 16 weeks for non-transmission (P<0.001) [11]. NSHPC Data also show an increased risk of transmission in those initiating treatment beyond 30 weeks, compared to those starting earlier [12].

In the Mma Bana study, plasma HIV viral load at delivery <400 HIV RNA copies/mL was observed in 96% (lopinavir/ritonavir-based) and 100% (abacavir/lamivudine/zidovudine) of women with baseline plasma viral load <1000 HIV RNA copies/mL, and in 86% (lopinavir/ritonavir-based) and 90% (abacavir/lamivudine/zidovudine) with a baseline viral load >100,000 HIV RNA copies/mL. When therapy was initiated therapy at 31–34 weeks, viral suppression was seen in only 78% of women on PI-based therapy [13].

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 data point used to make most delivery management decisions); this fell to 37% for baseline viral loads >100,000 HIV RNA copies/mL [14]. For all viral loads greater than 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. To address this, the Writing Group recommends that

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

6.3 Woman is not already on cART: what to start

6.3.1	Women are recommended to start tenofovir disoproxil fumarate or abacavir with emtricitabine or lamivudine as a nucleoside backbone as recommended in the BHIVA antiretroviral treatment guidelines.	2C

The PROMISE study [15] compared the efficacy of zidovudine/single dose nevirapine with combination therapy consisting of lopinavir/ritonavir and tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) to prevent vertical transmission. A higher rate of early neonatal death was reported in the combination therapy arm. The Writing Group does not consider this increase to be related to TDF/FTC backbone (www.bhiva.org/BHIVA-response-to-BMJ-article.aspx). 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 compared to non-tenofovir containing regimens [16-18]. In addition to these systemic reviews, prospective observational cohorts in pregnancy have shown no adverse outcomes between TDF/FTC and non-TDF/FTC backbones [19,20]. Zash *et al.* [20] found that the risk of adverse birth outcome was lowest amongst infants exposed to a combined regimen of TDF/FTC and safer than those with zidovudine/lamivudine as a backbone. The highest risks of adverse outcomes were observed in those women receiving lopinavir-based regimens. See also section 6.4.1 NRTI in pregnancy, Appendix 4 and www.bhiva.org/BHIVA-response-to-BMJ-article.asp

6.3.2	In the absence of specific contraindications, it is recommended that the third agent in cART should be in accordance with the BHIVA adult antiretroviral treatment guidelines, where there are sufficient clinical and pharmacokinetic data for use of the third agent in pregnancy.	1C

The Writing Group recommends that choice of therapy should always be discussed in full with every woman and be individualised for the patient in accordance with standard treatment guidelines. Boosted protease inhibitors are robust but have an increased risk of pre-term delivery (see section 6.4.4). They do not require prioritisation ahead of other preferred regimens in recommendation 6.3.2. 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.

6.3.3	It is recommended that an integrase inhibitor-based regimen is considered as the third agent of choice in patients with high baseline viral load (>100,000 HIV RNA copies/mL), where cART is being started late in pregnancy or where it is failing to supress the virus	2C

A retrospective cohort analysis of 101 pregnant women with HIV showed a more rapid viral suppression in those patients (*n*=32) on an integrase (INI) containing regimen versus women on ART without an INI [21]. Median time to VL reduction by greater than 1 log was 8 days in the INI containing ART arm and 35 days in the non-INI ART arm. This is comparable to studies comparing integrase and non-integrase based regimens in the general HIV population.

6.3.4	No routine dose alterations are recommended for ARVs during pregnancy if used at adult licensed doses	1C
	Consider third trimester TDM particularly if combining tenofovir and atazanavir	2C

	If dosing off licence, consider switching to standard dosing throughout pregnancy or regular TDM		2C
	Darunavir should be prescribed at the twice daily dose if known resistance and consideration should be given to using this higher dose if darunavir is initiated in pregnancy		2C
6.3.5	All women are recommended to commence lifelong cART. Where a woman declines cART despite on-going counselling and support to start therapy, zidovudine monotherapy is a non-preferred option in women refusing cART who have a baseline VL of <10,000 HIV RNA copies/mL and a CD4 cell count of >350 cells/mm^{3}. and who consent to a Caesarean section		1A

The data on the efficacy of zidovudine monotherapy for prevention of vertical transmission are well known: 0.8% transmission for women treated with zidovudine monotherapy and assigned to pre-labour CS in the Mode of Delivery study [22].

6.4 Antiretrovirals in pregnancy

Physiological changes that occur even during the first trimester of pregnancy may affect the kinetics of drug absorption, distribution, metabolism and elimination, thereby affecting the drug dosing [23]. Gastrointestinal pH is increased, transit time becomes prolonged, body water and fat increase throughout gestation 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.

Caution should be exercised if a woman falls pregnant on unlicensed doses of cART and consideration given to performing therapeutic drug monitoring (TDM) to assess trough levels, or reverting to licensed dosing, often twice per day, during pregnancy. Further consideration is required postpartum to ensure review of prescribed medications once physiological changes during pregnancy have resolved; for example darunavir 600mg with ritonavir 100 mg twice daily during pregnancy may be dosed more appropriately as darunavir 800mg/ritonavir 100 mg once daily postpartum.

6.4.1 NRTIs in pregnancy

Most data on the efficacy of cART in pregnancy are based on a three/four drug combination including a zidovudine/lamivudine backbone. Where treatment has been started at, or prior to, 28 weeks these studies have demonstrated transmission rates of 1% or less [4,13,22,24,25]. The adult prescribing guidelines now recommend tenofovir-DF/emtricitabine or abacavir/lamivudine as first-line therapy on the basis of safety, tolerability and efficacy [7].

Non-pregnant adults are now rarely prescribed zidovudine as part of cART. Despite the proven efficacy of zidovudine in preventing vertical transmission of HIV, particularly in the pre-cART era [1], there are no data to support routinely switching to zidovudine, or adding zidovudine to a combination of ARVs that is suppressing HIV replication to <50 HIV RNA copies/mL plasma. Analysis of data combined from two observational studies, the European Collaborative Study (ECS) and the UK and Ireland NSHPC, has shown no difference in pregnancy outcomes between zidovudine-based and zidovudine-sparing cART [3].

A *British Medical Journal* (*BMJ*) systematic review 'strongly recommended' that pregnant women living with HIV should not be treated with the combination tenofovir/emtricitabine/lopinavir/ritonavir due to higher rates of early neonatal death reported in the PROMISE randomised clinical trial [26]. The Writing Group

disagrees with this recommendation. The PROMISE trial compared the efficacy of zidovudine/single-dose nevirapine with combination protease inhibitor-based (lopinavir/ritonavir) ART using zidovudine/lamivudine or tenofovir/emtricitabine backbone to prevent vertical transmission in women with CD4 cell counts >350 cells/mm^3 [15]. PROMISE enrolled during two study periods and the analysis used as the main evidence base for the *BMJ* clinical practice guidelines was performed on women recruited only in the second study period, which considered only one-third of all women recruited to the PROMISE trial. The systematic review also made a 'weak recommendation' that zidovudine/lamivudine should be used preferentially over tenofovir/emtricitabine as the nucleoside backbone in pregnant women because of the lower number of stillbirths and early neonatal deaths in this arm of the PROMISE study. The endpoints of stillbirth and neonatal death were considered as separate endpoints in the PROMISE trial due to differing aetiologies associated with each outcome but were combined as a single outcome in the *BMJ* recommendation. Where the main difference between zidovudine/lamivudine- and tenofovir/emtricitabine-based ART emerged was in infants delivering <34 weeks, with more problems seen in the tenofovir/emtricitabine arm. Also, there was an unexpectedly low number of neonatal deaths in the second study period of the PROMISE trial (two *vs* 15 in the first period) and this, as well as the lack of any biological explanation, reduces the ability to interpret with any certainty why these differences may have occurred.

As both arms received lopinavir/ritonavir the *BMJ* panel postulated that tenofovir/emtricitabine was the cause of the difference. Despite the *BMJ* panel's assertion that pharmacokinetic interactions between tenofovir and lopinavir/ritonavir are not relevant, no specific studies were done as part of the PROMISE study to support the *BMJ* panel's assertion. Also, BHIVA does not recommend the use of lopinavir/ritonavir for the treatment of HIV in adults, including in pregnant women, and certainly not at the 50% higher dose used in the third trimester in the PROMISE trial [7]. In addition, PROMISE investigated outcomes in women initiating therapy. Most women in the UK will conceive on ART, most commonly with TDF/FTC backbone and this study does not address that cohort.

Three previous systematic reviews [16-18] reported no increase of birth adverse events or safety events (and no increased risk of congenital anomalies) in infants exposed to tenofovir- compared to non-tenofovir-containing regimens in HIV-exposed infants, although data remain limited and studies evaluating neonatal mortality, infant anthropometry and bone growth are required. WHO used these systematic reviews to inform their guidelines on HIV and pregnancy, which include the use of tenofovir-containing regimens [27].

In addition to these systematic reviews, there are numerous observational studies showing tenofovir/emtricitabine to be safe in pregnancy. For example, Zash *et al.* [20] published a birth surveillance study of 47,027 pregnant women in Botswana, including 11,932 women with HIV, where preterm birth, very preterm birth, small and very small size for gestational age, stillbirth, and neonatal death were evaluated. In this very large cohort, the risk for any adverse or severe adverse birth outcome was lowest among infants exposed to a combined regimen of tenofovir, emtricitabine and efavirenz but all tenofovir/emtricitabine-based regimens were found to be safer than those with zidovudine/lamivudine as a backbone and the highest risk of adverse outcomes with observed in those women receiving lopinavir-based regimens.

Pharmacokinetics

The pharmacokinetics of most NRTIs (zidovudine [28] , lamivudine [29], abacavir [30] are not significantly affected by pregnancy and dose adjustment is not required.

Tenofovir-DF (TDF) concentrations in the third trimester were reported to be reduced by about 15–25% compared with postpartum, but trough levels are adequate [31,32], although in a population-based study of tenofovir use, pregnant women appear to have 39% more clearance than non-pregnant women [33]. Higher rates of treatment failure during pregnancy with tenofovir-containing combinations have not been reported. A second study reported lower tenofovir-DF area under the curve and trough levels throughout pregnancy and found this linked to higher maternal weight. A single, 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 [34,35] (see section 9: Neonatal management). A review of antenatal patients with HIV attending a London hospital showed no decline in renal function during pregnancy in those women taking tenofovir-DF.

Tenofovir alafenamide (TAF) is a newer version of tenofovir-DF and whilst there are limited data on the safety and pharmacokinetics of TDF; no signals for concern with regard to birth defect have been seen [36]. The Writing Group does not recommend its routine use in pregnancy until further data are available. All women who conceive on TDF should have a discussion regarding this and consideration should be given to switching women who conceive on TDF if necessary 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 [32,37].

6.4.2 NNRTIs in pregnancy

The APR has sufficient evidence to suggest both efavirenz and rilpivirine are safe in pregnancy (see under section 6.1).

Pharmacokinetics

Rilpivirine is a recommended first line ART regimen with tenofovir-DF and emtricitabine in patients with VL<100K in the current BHIVA treatment guidelines. A pharmacokinetic study by the PANNA consortium [38] carried out intensive 24 hour pharmacokinetic (PK) profiles in women living with HIV receiving rilpivirine 25mg daily 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 an undetectable viral load <50 HIV RNA copies/mL at delivery and there was no vertical transmission. Based on this, it is recommended that women on rilpivirine containing regimens may remain on rilpivirine if they are able to take it with a meal to optimise pharmacokinetics and they are closely monitored.

Efavirenz 600 mg daily has been reported in one study of 25 pregnant women to result in third-trimester plasma concentrations that were similar to 6–12 week postpartum concentrations in the same women. Cord blood to maternal blood ratio was 0.49 resulting in transplacental concentrations that are in the therapeutic range [39].

A study of the pharmacokinetics of etravirine 200mg twice daily in 15 women found an increase in etravirine exposure during pregnancy but still within range of levels observed in previous studies of non-pregnant individuals with HIV treated with this dose [40]. Fourteen out of 15 women had an undetectable viral load during pregnancy and no vertical transmission was seen. A second study from the PANNA group has shown similar findings [41].

Nevirapine has been extensively studied in pregnancy and plasma concentrations are similar to those in non-pregnant adults [42,43]. 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 the consideration should be given to switching patients on 400mg prolonged release formulation to 200mg twice daily formulation during pregnancy. It should be noted that nevirapine is no longer a preferred treatment option for naïve patients in the current BHIVA Treatment Guidelines [7].

6.4.3 Integrase inhibitors

The APR has sufficient evidence to suggest raltegravir is safe in pregnancy although data on dolutegravir and

elvitegravir are still being collated.

Reproductive toxicity animal studies for dolutegravir have shown it to cross the placenta but do not indicate direct or indirect harmful effects of impaired fertility or fetal harm [44]. A recent, large, prospective cohort study has shown similar pregnancy outcomes to efavirenz for dolutegravir [20] in pregnant women living with HIV. Further observational cohort studies have not shown any signals of adverse clinical or birth outcomes [21,45,46].

Pharmacokinetics

A study of 10 pregnant women taking raltegravir 400 mg twice daily found adequate trough levels in all 10, although levels were very variable and lower than postpartum [47], while 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 [48]. A third study of 23 women receiving raltegravir 400mg twice daily, mostly as intensification of PI-based regimens during pregnancy showed no statistically significant change in raltegravir concentrations during pregnancy and postpartum [49]. The PANNA study has also shown similar results [50]. In an on-going 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 the children who are being followed up for 6 years [51].

No dose adjustment of raltegravir 400mg twice daily in pregnancy is required. Pharmacokinetics of the raltegravir 1200mg once daily formulation have not yet been studied in pregnancy and it is recommended that the 400mg BD dose is used until further information is available.

The IMPAACT P1026s study group is an on-going prospective study of antiretroviral pharmacokinetics in pregnant women living with HIV [52]. 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 studied and elvitegravir and cobicistat exposure was 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. The Writing Group therefore recommends that if a woman becomes pregnant with an undetectable viral load on elvitegravir/cobicistat, it may be continued, with close follow up of maternal viral load in the third trimester. There are not yet sufficient data to recommend the routine initiation of elvitegravir/cobicistat in women during pregnancy.

6.4.4 Protease inhibitors in pregnancy

While ritonavir-boosted protease inhibitor therapy can maintain suppression of viral load, vertical transmission of HIV would be almost entirely dependent on antiviral activity within the mother. With minimal transplacental transfer, the low to undetectable drug concentrations in the fetus provide no peri-exposure protection. In PHPT-5, the addition of ritonavir-boosted lopinavir to zidovudine monotherapy from 28 weeks' gestation was no better than maternal zidovudine with or without single-dose nevirapine provided neonatal nevirapine was administered [53]. The Writing Group therefore recommends that, where possible, patients who conceive on protease inhibitor monotherapy should have their regimen intensified with an agent that crosses the placenta.

Pharmacokinetics

Pharmacokinetic and safety data in pregnancy for cobicistat-boosted protease inhibitors are lacking. When given with elvitegravir, cobicistat has been shown to have lower levels during pregnancy and not to cross the

placenta [52]. For this reason, the Writing Group recommends that where women conceive whilst undetectable on a cobicistat-boosted PI regimen, consideration is given to a switch from cobicistat to ritonavir. When initiating protease inhibitors during pregnancy, it is recommended that ritonavir is the boosting agent of choice.

Protease inhibitors 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 99.04%, which results in 17% more unbound lopinavir [54]. 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 postpartum concentrations, third-trimester concentrations of lopinavir (lopinavir 400 mg/ritonavir 100 mg) 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 concluded that women taking three tablets twice daily (bd) (lopinavir 600 mg/ritonavir 150 mg) achieved similar area under the curve levels to non-pregnant adults taking the standard dose of two tablets bd [55]. 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 [56]. The Writing Group recommends that no dose adjustment is required in pregnancy for patients on lopinavir/ritonavir.

A study from Italy reported similar third-trimester and postpartum atazanavir concentrations at standard 300 mg dose with 100 mg ritonavir once daily [57]. However, recently third-trimester 24 h area under the curve (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, being approximately 50% of the postpartum values of women on atazanavir without tenofovir, 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 once daily) during the third trimester [58]. A systematic review has reported that grade 3–4 maternal hyperbilirubinaemia rates are doubled with atazanavir 400mg/ritonavir 100mg dose [59]. Data from the Europe-based PANNA study also reveals a 33% reduction in third trimester AUC and Clast 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 in an individual basis only if required [60].

Atazanavir/ritonavir 400mg/100mg is also recommended in women who require an H2 antagonist during pregnancy and the combination of atazanavir, tenofovir-DF and an H2 antagonist is not recommended [59].

When prescribed with zidovudine/lamivudine, plasma concentrations achieved with atazanavir 300 mg plus ritonavir 100 mg once daily are only 21% less (by AUC) than historic controls while trough concentrations were reported to be comparable to these controls. Increasing the dose of atazanavir to 400 mg daily during the third trimester increased trough concentrations by 39% and doubled the risk of hyperbilirubinaemia [61]. A case note review of 155 women in London receiving atazanavir did not report virological failure during pregnancy despite 96% receiving standard dosing of 300 mg with ritonavir 100 mg. Therapeutic drug monitoring was rarely performed and mostly if virological control was considered suboptimal [62].

The Writing Group recommends that no dose adjustment of atazanavir/ritonavir is required unless the mother is also taking an H2 antagonist.

For darunavir, a study from the USA reported reduced troughs and AUC 24h with once-daily dosing in pregnancy, whilst dosing twice a day produced levels more comparable to those in non-pregnant individuals [63]. They concluded that twice-daily dosing should be used in pregnancy and higher doses may be required.

For women receiving darunavir/ritonavir 800/100 mg the area under the curve (AUC) was reduced by 38% in the second trimester and by 39% in the third trimester when 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 sub-therapeutic trough concentrations reported with once-daily 800/100 mg dosing and no detectable darunavir in any of the cord blood samples [64]. 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 conclude that no dose adjustment is required when darunavir is prescribed at 600mg/ritonavir 100mg twice daily [65]. Other studies have also reported that although there is a reduction in darunavir levels during pregnancy, this is less pronounced when unbound darunavir levels are measured [64,66].

A pharmacokinetic study by IMPAACT P1026s study group showed no impact on third trimester darunavir levels by increasing dose further from 600/100mg BD to 800/100mg BD thus this is not recommended [67]. The clinical relevance of these pharmacokinetic studies has yet to be fully determined.

It is the view of the Writing Group that where a patient conceives on darunavir-based cART and has a fully suppressed viral load on a once-daily regimen, this 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. Whilst the pharmacokinetic data are consistent across studies, the virological impact during and post-pregnancy are unknown. Such outcome data are needed. Where the 600/100mg twice daily dose is used, women should be reviewed postpartum for appropriateness to switch to 800/100mg once daily 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, therapeutic drug monitoring (TDM) for PIs during pregnancy can be considered, but not 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.

Preterm delivery

The data on the association of cART and pre-term delivery (PTD) are conflicting. Some studies implicate boosted protease inhibitors, others do not.

The conflicting findings of these largely observational studies make it difficult to draw definitive conclusions. Importantly, a history of previous PTD, one of the most significant risk factors for subsequent PTD, is rarely, if ever collected. Additionally, there may be fundamental differences between cohorts precluding reliable comparison. For example, the USA has the highest background PTD rate of any industrialised country, peaking at 12.8% in 2006 [68].

Studies showing no association between boosted protease inhibitors in PTD

Several large studies from the USA have not found an association between cART and PTD [69,70] A US meta-analysis in 2007 did not find an association between PTD and PI-containing cART [71], and analysis of the NSHPC UK and Ireland data, although finding the increased risk of PTD in women on cART, similarly did not find a difference when comparing PI- and NNRTI- based regimens [72]. 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 [73]. Over 85% of these reports to the APR came from the USA.

Most studies that have looked at 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) [71,74-76]. However, the NSHPC UK and Ireland study did not find an association between timing of cART initiation and PTD [72]. A 2010 USA study attempted to overcome the potential confounding factors associated with timing of cART initiation by looking only at 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 [77]. 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/ritonavir. Further comparison between nelfinavir and the ritonavir-boosted lopinavir was unfortunately not possible. A small Canadian study retrospectively reviewed 384 women living with HIV comparing to a matched HIV-negative cohort [78]. A two-fold increase in pre-term birth, low birth weight and small for gestational age parameters was found, however when odds ratio was adjusted for race and history of preterm birth, no statistical difference between the two cohorts remained.

Studies implicating boosted PIs in PTD

The association between cART and PTD was first reported by the Swiss Cohort in 1998 [79], and subsequently by a number of other European studies including three analyses from the ECS [74,76,80,81]. Analysis of the NSHPC UK and Ireland data in 2007 found there to be a 1.5-fold increased risk of PTD when comparing women on cART with those on mono- or dual therapy [72].

In two American studies, one multicentre study from the Pediatric Spectrum of HIV Disease cohort and one single-centre study, an association between PTD and cART was found only if cART included a protease inhibitor [82,83]. Two of the earlier ECS reports had also noted that the increased risk of PTD in patients on cART was particularly marked in patients on PI-containing cART [74,76].

One single-centre UK study found the risk to be increased in those initiating cART in pregnancy compared to those conceiving on treatment [84].

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 when compared to those on a non-boosted PI regimen (HR 2.03; 1.06–3.89) [85].

Two randomised studies have now been published looking at the use of different antiretroviral regimens in breastfeeding populations in relation primarily to HIV MTCT. 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/ritonavir 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) [86]. 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 lopinavir/ritonavir and 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) [87]. A study of placental malaria data from PROMOTE of 391 Ugandan women randomised to lopinavir/ritonavir or efavirenz initiated during pregnancy shows no significant difference in preterm birth being 15.9% and 13.6%, respectively [88]. The randomised studies above are amongst the few studies that have been able to look at individual protease inhibitors. One additional analysis from the APR of 955 live births exposed to lopinavir/ritonavir reported a PTD rate of 13.4% [89]. A retrospective study from the UK reported a PTD rate of 10% in 100 women taking ritonavir-boosted atazanavir in pregnancy, of which 67% had conceived on their regimen [62]. The same group found no difference in PTD rates in a retrospective study comparing lopinavir/ritonavir and atazanavir/ritonavir as the third agent in cART [90].

Summary

The data regarding cART, individual components of cART and PTD remain conflicting. Some studies suggest that PIs, in particular ritonavir-boosted PIs, are associated with an increased risk of PTD but this is not confirmed by others. The Writing Group is therefore unable to make a definitive recommendation regarding use of boosted PIs in pregnancy and risk of PTD.

Where boosted protease inhibitors are required for ART in the treatment of pregnant women, the risk of PTD should always be balanced with the benefit of prevention of vertical HIV transmission. The PROMISE study for example showed that overall use of an ART regimen improved overall HIV-free infant survival rates [15].

6.4.5 Other agents

The pharmacokinetics of enfuvirtide in pregnancy, as well as tipranavir and maraviroc, have not been described. It is worth noting that enfuvirtide does not cross the placenta [91].

6.5 Late-presenting woman not on treatment

6.5.1	A woman who presents after 28 weeks should commence cART without delay.	1B
6.5.2	If the viral load is unknown or >100,000 HIV RNA copies/mL a three- or four-drug regimen that includes raltegravir 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 6.3.3, an integrase inhibitor-based cART regimen is recommended due to more rapid viral load decline compared to other drug combinations.

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. A recent Thai study [92] in 57 pregnant women has shown that intensification of a standard three-drug ART regimen in women with detectable viral load after 28 weeks resulted in a significant reduction in viral load at delivery.

A second pilot study in 40 women, demonstrated that initiation of raltegravir based therapy, compared to lopinavir/ritonavir based therapy resulted in significantly more women with undetectable viral load <50 HIV RNA copies/mL at delivery and a faster time to viral load reduction to <50 HIV RNA copies/mL of 44 days in the raltegravir arm and 69 days in the lopinavir/ritonavir arm [93]. Adverse events 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.

6.5.3	For details on how to manage an untreated woman presenting in labour at term, please see section 8.6.1 (high-risk neonatal management). All women should be given a stat dose of nevirapine 200 mg;	1B
	and commence fixed-dose zidovudine with lamivudine;	1B
	and raltegravir and receive IV zidovudine for the duration of labour.	2D

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 [42,94]. cART should be commenced immediately with fixed-dose zidovudine and lamivudine and with raltegravir as the preferred additional agent because it also rapidly crosses the placenta [95]. Intravenous zidovudine can be administered for the duration of labour and delivery [96]. Data from the French cohort indicate that peri-partum 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 [97]. If delivery is not imminent, a Caesarean section should be considered.

6.5.4	In preterm labour, if the infant is unlikely to be able to absorb oral medications consider the addition of double-dose tenofovir disoproxil fumarate to the treatment described in recommendation 6.5.3 to further load the baby.	2C

Nevirapine and raltegravir should be included in the regimen as they cross the placenta rapidly (see above). In addition, double-dose tenofovir disoproxil fumarate (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 PEP in the first few days of life [34].

6.5.5	Women presenting in labour/ROM/requiring delivery without a documented HIV result must be recommended 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 mother'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 on-going risk for HIV should also have a POCT if presenting in labour. If the test is positive (reactive) a confirmatory test should be sent but treatment to prevent vertical transmission should commence immediately. Where 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 taken. Treatment should be commenced immediately as per recommendation 6.5.3 above. Three-drug PEP should be given to the neonate (see section 9: Neonatal management).

6.6 Stopping ART postpartum

6.6.1	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 antiretroviral treatment of adults living with HIV [7].	1B

6.7 References

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7. HIV and hepatitis virus co-infections

7.1 Hepatitis B virus (HBV)

The combination of HIV, chronic hepatitis B virus (HBV) infection and pregnancy presents unique management questions. Referral to the local designated specialist should be undertaken to ensure that all aspects of care, including the effects of HBV/HIV on pregnancy, effects of pregnancy on the course of co-infection, drug management for both HBV and HIV, and prevention of mother-to-infant transmission for both viruses are addressed. 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: RR 1.40; 95% CI 1.16–1.69) [1]. Up to one-third of HBsAg are wild type (HBeAg-positive) and, depending on region, up to 6% 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% amongst Asian women in the USA *vs* 0.6% in white women) [5]. The same is true for injecting drug use (prevalence <0.1% in North-West Europe compared to 1–4% in Southern Europe) and sexual transmission (prevalence is higher in MSM).

Although plausible because of higher levels of HBV-DNA in co-infected women, there is no evidence of increased vertical transmission of HBV in co-infection over 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 transferase (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 $\log_{10}$. 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 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 HAV, HCV and HDV screening and tests to assess hepatic inflammation/fibrosis and liver function are recommended.	1C
7.1.2	Liver function tests 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, 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, AST, albumin, INR), an assessment of fibrosis, and the exclusion of additional causes of liver disease (e.g. haemochromatosis, autoimmune hepatitis) are indicated. Additionally, patients should be assessed for the need for HAV (HAV IgG antibody) immunisation 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], so where there is suspicion of advanced liver disease, 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 performed. 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 ARV-related hepatotoxicity and a hepatitis flare from immune reconstitution, it is important to repeat liver function tests (LFTs) at 2 weeks and 4 weeks post-initiation of ART and then periodically thereafter. Through pregnancy, it is routine to monitor LFT tests at each antenatal clinic appointment as a marker for potential obstetric complications (HELLP, preeclampsia, 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 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 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 transmission combined with the potential for acute hepatitis and threat to maternal and fetal health, the presumption would be that this would be abrogated by the patient already being on ART incorporating tenofovir and either emtricitabine or lamivudine. Where the woman is not on ART, a tenofovir-based ART regimen should be commenced immediately.

7.1.3	Since 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, APR [10] and the Development of Antiretroviral Therapy Study (DART) [11] have not identified any increased risk in prevalence or any specific pattern of anomaly, even when administered in the first trimester. Hence, when a patient becomes pregnant on an anti-HBV viral agent as part of their ART (tenofovir-DF, lamivudine or emtricitabine), as for HIV management, ART 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 MTCT. Because entecavir has activity against HIV, it is not recommended unless given with active cART in a co-infected patient. 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 lamivudine and telbivudine have been used in HBV mono-infected pregnant women and all have been found to be safe. Whilst the experience with tenofovir-AF in pregnancy is limited, animal data do not indicate direct or indirect harmful effects with respect to reproductive toxicity [12]. 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 infection and no contraindication to any drug.	1B
7.1.5	If tenofovir is not currently part of ART it should be added.	1B
7.1.6	Lamivudine/emtricitabine may be omitted from the antiretroviral regimen and tenofovir 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 potential antiviral benefits over lamivudine, is co-formulated with tenofovir (TDF and TAF), and appears to be equally safe during pregnancy and hence is the preferred option to be given with tenofovir in co-infection.	2D

All HBV/HIV co-infected women should receive cART containing tenofovir with emtricitabine or lamivudine treatment during pregnancy, unless contraindicated. Although lamivudine and emtricitabine are potent anti-HBV agents, 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-AF, 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]. Phenotypic HBV resistance has not been ascribed to tenofovir in co-infected patients with up to 5 years of follow-up and has only been demonstrated in vitro in treated individuals with sub-optimal control [19]. In combination with lamivudine or emtricitabine tenofovir has been demonstrated to be effective at suppressing HBV DNA and may induce HBeAg seroconversion. Combining lamivudine/emtricitabine with tenofovir may also reduce the risk of breakthrough HBV viraemia [13], however the biggest advantage is that currently emtricitabine is co-formulated with tenofovir and therefore, convenient to dose.

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 [20]. Although not currently approved for HBV treatment, it induces a sharp reduction of HBV DNA in both mono and co-infected patients. In co-infected patients naïve to antivirals, in an RCT, combining emtricitabine with tenofovir has been shown to be more effective than emtricitabine alone (median TWAC decrease was -5.32 $\log_{10}$ IU/mL in the tenofovir/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/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 HIV and HCV, whilst a strong association with hepatic steatosis was found with didanosine and stavudine 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 section 7.2.2).

7.1.9	In all HAV non-immune HBV co-infected women, 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 vaccines. Data for HAV vaccine in pregnancy are limited. Nevertheless, several guidelines indicate that pregnancy is not a contraindication for HAV immunisation, including in HBV co-infected pregnant women [24]. For HAV vaccines, patients with higher CD4 cell counts

and on cART generally show improved responses to vaccination. People living with HIV with CD4 cell counts <300 cells/mm3 should receive three doses of HAV vaccine over instead of the standard two.

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

Inflammatory flares, which may be severe, particularly in persons with cirrhosis can occur as a result of viral escape and HBV viraemia, if drugs with anti-HBV activity are stopped. In an RCT comparing lamivudine with placebo for reducing vertical transmission of HBV in patients with HBV mono-infection, an immediate increase in HBV DNA levels was observed on discontinuation of lamivudine postpartum [25]. Similarly, hepatitis flares among HIV/HBV co-infected patients have been reported upon the discontinuation of lamivudine, emtricitabine and tenofovir. 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. Whilst rarely leading to fulminant hepatitis, care needs to be exercised in careful monitoring 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 antiHBe seroconversion in HBeAg-positive women [28].

| 7.1.12 | In the absence of obstetric complications, normal vaginal delivery can be recommended if the mother has fully suppressed HIV viral load on cART, irrespective of HBV viral load. | 1C |

7.1.1 Postpartum management of HBV co-infection

| 7.1.13 | Neonatal immunisation with or without HBIG should commence within 24 hours of delivery. | 1A |

No data exist to support any benefit from pre-labour Caesarean section (PLCS) in mothers with HBV/HIV co-infection and no robust RCT exists in HBV mono-infected women. In a meta-analysis of HBV mono-infected women (four randomised trials all from China involving 789 people were included) 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 confirms that there may not be additional benefit beyond appropriate vaccination and HBIG use [30].

Another meta-analysis suggests 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 co-infected patients, 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 co-infected.

Immunoprophylaxis with HBV vaccine with or without hepatitis B immunoglobulin (HBIG) given to the neonate has been shown in separate meta-analyses of RCTs to significantly reduce vertical transmission from HBV mono-infected women. HBIG should be administered to the neonate if maternal HBV DNA

concentration is >10^6 IU/mL and/or mother is HBeAg-positive, or anti-HBe-negative [32]. In the absence of neonatal immunisation with HBV vaccine with or without HBIG, the rate of vertical transmission from a mono-infected mother who is HBsAg and HBeAg-positive is 70–90% and for women who are HBsAg-positive but HBeAg-negative, 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 [33].

Therefore, maternal ART together with prompt post-delivery neonatal immunoprophylaxis is the ideal approach for preventing vertical transmission of HBV.

7.2 Hepatitis C virus (HCV)

It is recommended practice that all pregnant women with active HCV (HCV RNA positive)/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 come from high HCV prevalence areas in the cohorts studied [34,35]. Several meta-analyses and systematic reviews have shown the overall rate of vertical transmission for HCV approximates 5% (range 2–10%) if the mother is anti-HCV-positive only.

HIV co-infection is associated with a significant increase in HCV transmission (OR up to 2.82) compared to HCV mono-infection [36,37]. In addition, a higher rate of HCV vertical transmission is seen in mothers who are co-infected and HCV viraemic compared to those who are co-infected and non-viraemic (OR 2.82), as well as to HCV viraemic but HIV-negative women (OR 1.97) [36,37]. Acquisition of infection of HCV is more likely in infants also becoming infected with HIV, and vertical transmission of HIV occurs more often from women co-infected with HIV and HCV than from those infected with HIV only (OR 1.82) with a modest association with HCV viral load [38].

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 VL and transmission as for HIV [39-41]. 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 mono-infected mothers [42,43]. Effective cART significantly reduces the rate of HCV transmission, possibly by reducing HCV viraemia [42,44]. Lack of immuneregulation during pregnancy may also facilitate HCV transmission via peripheral blood monocytes (PBMCs) [45]. No correlation with HCV genotype or interleukin-28 polymorphisms and transmission has been identified [41,46,47]. 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 [48].

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	Liver function tests 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 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, INR), an assessment of fibrosis, and the exclusion of additional causes of liver disease (e.g. haemochromatosis, autoimmune hepatitis) are indicated. Additionally, patients should be assessed for the need for HAV (HAV IgG antibody) and HBV (anti- HBs) immunisation as well as for HBV co-infection (HBsAg).

Liver biopsy and hepatic elastometry (FibroScan) are relatively contraindicated during pregnancy [7] so that where there is suspicion of advanced liver disease, 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 performed. 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 post initiation of cART. Through pregnancy, it is routine to monitor LFT results 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 hepatitis C 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 hepatitis C 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 chronically infected patients there is unlikely to have been significant change in the HCV viral load. However, the prenatal viral load will give some idea as to the risk of transmission and may be worth repeating near delivery. If pregnancy has occurred during treatment for HCV with pegylated interferon (IFN) and ribavirin, or during directly acting antiviral (DAA)-based therapy, in addition to immediate discontinuation of treatment, thyroid function test should be included in the routine bloods as thyroid dysfunction occurs in approximately 7% of patients on IFN therapy. Ribavirin is teratogenic, 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 [49]. Women about to embark on ribavirin therapy, or female partners of men on ribavirin therapy should be counselled about avoiding pregnancy for at least six months post cessation of therapy. Those that become pregnant on ribavirin or DAA-based therapy should have detailed discussions with the obstetrics team with regards to enhanced fetal monitoring.

Finally, it is recognised that a small number of co-infected patients 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 | Co-infected mothers with HCV should not be treated for HCV with ribavirin-based DAA therapies, and all women who discover they are pregnant while receiving treatment should discontinue both therapies immediately. | 1B |
| 7.2.4 | Co-infected women of child-bearing age wishing to get pregnant should be prioritised for DAA-based HCV therapy. | 2D |

There is no evidence that HCV can be transmitted vertically in the absence of HCV viraemia so 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 [50]. There are no definitive studies on the safety of HCV antiviral therapy during pregnancy.

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 [51]. 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.

There are limited data on the possible teratogenicity of non-ribavirin containing IFN-free DAA-based therapies. 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 [52-56]. Paritaprevir/ribavirin/ombitasvir FDC and daclatasvir have both shown risk of malformations in small-animals at supranormal dose exposures [57,58].

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 get pregnant should be prioritised for DAA-based anti-HCV therapy regardless of fibrosis stage, and to 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 HCV co-infected women after the first trimester, unless already immune.	1C

Immunisation for HBV uses an inactivated vaccine. Limited data are available on the use of hepatitis B vaccination in pregnancy and none in pregnant women living with HIV. Moreover, no randomised trial has been performed on the optimum dosing schedule for use in pregnancy [59]. Nevertheless, several guidelines indicate that pregnancy is not a contraindication for HBV or HAV immunisation, including in HCV co-infected pregnant women [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, well tolerated, and had the advantage of potential completion prior to delivery [60]. 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 [61].

7.2.6	In all HAV non-immune HBV co-infected women, 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 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 doses of HAV vaccine over 6–12 months instead of the standard two [24].

7.2.7	In the absence of obstetric complications, normal vaginal delivery can be recommended if the mother 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 mono-infection, two meta-analyses failed to show a significant decrease in HCV vertical transmission among study mothers who underwent CS compared with mothers who gave birth vaginally (OR 1.1 [62] to OR 1.19). In the first European Paediatric Hepatitis Network cohort, a subgroup analysis of women co-infected with 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)[63]. However, in a later analysis from the EPHN (n = 208, 15.0%) no such association was found (OR 0.76; 95% CI 0.23–2.53) [42]. In the later analysis, vertical transmission of HCV was less (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 monotherapy or no therapy (OR 0.26; 95% CI 0.07–1.01). There was also a trend to lower HCV viral load in this group, which may go some way to explaining this. Also, in a small French cohort of co-infected women (29% on cART), rate of transmission did not differ significantly between children born by vaginal delivery or CS [64]. A recent systematic review concludes that no intervention, in terms of mode of delivery or obstetric intervention or avoidance of breastfeeding reduces the risk of HCV transmission [65]. cART should be given to all HCV/HIV co-infected pregnant women, regardless of CD4 cell count or HIV viral load because of the evidence of increased HIV transmission in co-infected mothers.

7.2.8	cART should be continued postpartum in all HCV/HIV co-infected women regardless of HCV viraemia, fibrosis stage or CD4 cell count.	1A

Recommendations for lifelong ART are in line with current BHIVA guidelines [66] and section 6 above. Furthermore, effective HIV suppression improves liver histology even in the absence of effective HCV treatment [67,68].

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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 antiviral pregnancy registry (APR) [3] does not support the need for increased surveillance with the most commonly prescribed therapies (listed in Appendix 4), 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 trisomy 21 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 trisomy 21. The most effective screening is with the combined test at 11 + 0 to 13 + 6 weeks' gestation. This includes maternal age, nuchal translucency, 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 and cost-effective serum screening test (triple or quadruple test) should be offered between 15 weeks 0 days and 20 weeks 0 days [2]. However, significantly increased levels of βHCG, αFP and lower levels of UE3 (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 with NNRTI-based cART has been reported. Since Down's syndrome is associated with increased βHCG, 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 antiretroviral therapy [10] and thus are the preferred screening modality for women presenting between 15 and 20 weeks.

8.1.3	Invasive prenatal diagnostic testing should not be performed until after the HIV status of the mother 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 amniocentesis is safe in women on cART. There are minimal data on other forms of prenatal invasive testing. It is now possible to use non-invasive prenatal testing (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 Pediatric HIV Infection Study Group observed a relative risk of HIV transmission of 1.9 (95% CI 1.3–2.7; P=0.003) with 'antenatal procedures' that included amniocentesis, cerclage, laser therapy and amnioscopy [11]. This study was conducted between 1985 and 1993 and, of the 1632 mother–infant pairs (overall transmission 19%), only 100 mothers 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 (of which 166 had an amniocentesis) showed that the risk of vertical transmission of HIV in the untreated rose from 16% to 25% in those who had an amniocentesis, in those on zidovudine alone the risk rose from 3.3% to 6.1% and in those on cART there were no transmissions in 81 mothers who underwent amniocentesis [12]. Viral load data were not reported, but in other settings suppression of viral load reduces transmission.

A further study of nine women in France on cART in 2008 [13] and 17 women on cART in Portugal (1996–2009) showed no transmissions, while 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 reporting on chorionic villus sampling (CVS) or cordocentesis [14]. For evidence relating to choice of ART to reduce transmission risk associated with amniocentesis, see section 6.5: Late-presenting woman not on treatment.

8.1.5	External cephalic version (ECV) can be performed in women with HIV.	2D

ECV should be offered at term from 37+0 weeks of gestation. 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 mother when the fetus is head-down at the time of birth. External cephalic version (ECV) is a procedure by which the fetus, which is lying bottom first, is manipulated through the mother'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]. The question of whether ECV might increase the risk of vertical transmission of infections such as HIV is important and, in the absence of direct evidence, we have reviewed the relevant biological evidence and concluded that materno-fetal transfusion, as a consequence of this procedure, is very uncommon, and unlikely to be precipitated by ECV [15]. It is also reassuring that in a randomised trial of fundal pressure to expel the baby during Caesarean section, no evidence of materno-fetal transfusion was found [16].

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, a planned vaginal delivery is recommended.	1C
8.2.2	For women with a plasma viral load of 50–399 HIV RNA copies/mL at 36 weeks, 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

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 [17-21]. 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 NSHPC UK and Ireland surveillance study reported on vertical transmission of HIV in women delivering 2000–2011 [22] 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), excluding two in-utero transmissions; there was no significant difference between elective Caesarean section 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 50–399 HIV RNA copies/mL, vertical transmission rates were 0.77% following elective Caesarean section and 1.6% following planned vaginal delivery (*P*=0.39). Women delivering by elective Caesarean section had 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 50–399 HIV RNA copies/mL was 0.26% (2/777) following elective Caesarean section and 1.1% (2/188) following planned vaginal delivery (*P*=0.17).

A recent analysis from the ANRS French Perinatal cohort looked at Caesarean section in 8977 women on cART delivering 2000 to 2010. They 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 elective Caesarean sections and 0.3% for non-elective Caesarean section, *P*=1) or 707 women delivering at term with viral load 50–399 HIV RNA copies/mL (1.0%, 1.0% and 2.5% respectively, *P*=0.24). There was no comment on the timing of transmission in the infants diagnosed with HIV [23].

Older data from the ANRS French Perinatal cohort reported on 5271 women delivering between 1997 and 2004, of whom 48% were on cART. In women on cART with a delivery viral load of <400 HIV RNA copies/mL there was no significant difference in vertical transmission rates according to mode of delivery, with 3/747 (0.4%) transmission in the PLCS group compared with 3/574 (0.5%) transmissions in the vaginal delivery group (*P*=0.35). The effect of mode of delivery was also analysed for women delivering with a viral load of >10,000 HIV RNA copies/mL and no significant protective effect of PLCS was seen (OR 1.46; 0.37–5.80). Vertical transmission of HIV was low at 0.4% in women delivering with a viral load of <50 HIV RNA copies/mL but mode of delivery data for this subset were not provided [21].

In contrast, data from the ECS of 5238 women delivering between 1985 and December 2007 showed that in 960 women delivering with a viral load of <400 HIV RNA copies/mL, elective Caesarean section was associated with an 80% decreased risk of vertical transmission (AOR 0.2; 95% CI 0.05–0.65) adjusting for cART and prematurity. There were only two transmissions amongst 599 women delivering with viral loads of <50 HIV RNA copies/mL (transmission rate 0.4%) with one delivering vaginally at <34 weeks and one by ECS at 37 weeks, but further analysis was not possible [17].

A potential explanation for the differing conclusions of the effect of mode of delivery on vertical transmission in women with delivery plasma viral loads of <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 which could account for the contrasting findings. 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 of <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 having vaginal delivery is

about twice that of PLCS, and this rises to four-fold when in utero transmissions are excluded. The Writing Group therefore recommends that PLCS 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 PLCS in women not on effective antiretroviral therapy, reducing the risk of vertical transmission by two-thirds in the pre-cART era. More recent observational studies only have very small numbers of women delivering vaginally with a viral load above 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 PLCS 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 of <400 HIV RNA copies/mL, together with the data from the UK study showing a 2.4-fold increased risk of transmission for every $\log_{10}$ increase in viral load associated with mode of delivery, the Writing Group continues to recommend PLCS for all women with a viral load of >400 HIV RNA copies/mL.

8.2.4	In women for whom a vaginal delivery has been recommended and labour has commenced, obstetric management should follow the same guidelines as for the HIV-negative population.	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. These show little or no risk for many of these procedures. Data from the cART era are scant.

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 [11]. In a retrospective study from Spain, in predominantly 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% who had neither (RR 1.94; 95% CI 1.12–3.37) [24]. 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 [25]. In the 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 [26].

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 Management of spontaneous rupture of membranes) would appear to be reassuring on this point.

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) [11]. Data from the smaller Swiss cohort (n = 494, 1986–1996, transmission rate 16.2%) also failed to identify instrumental delivery as a risk factor (RR 1.82; 95% CI 0.81–4.08) despite less than 20% of the cohort taking any antiretroviral therapy for prophylaxis [25].

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 [27]. 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 undertake a vaginal operative delivery, evidence to support a benefit of any type of operative vaginal delivery over Caesarean section for them or their infants is limited to expert judgement and extrapolation from other data sets 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 of <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 [28]).

The importance of the use of ART in the prevention of vertical transmission of HIV is clear and undisputed. Good 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 [29] and HIV RNA [30] in cervicovaginal lavage have been identified as independent transmission risk factors. Large cohort studies from the UK and Ireland, and France have concluded that there is no significant difference in vertical transmission in women with an undetectable viral load when comparing those who have a planned vaginal delivery and those who have a PLCS. 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 [31-34]. 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 VL of <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 felt that there was 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 conclude 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 [28]. 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 her 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 Caesarean section (VBAC) should 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 elective Caesarean section 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 Caesarean section in the face of any difficulty, the outcome of trial of labour for mother and neonate is good, even if scar dehiscence occurs [35]. In the general maternity population, 70% of VBACs 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 PLCS is the prevention of vertical transmission, PLCS 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 timing will usually be at between 39 and 40 weeks.

The timing of PLCS is a balance between the risks of transient tachypnoea of the newborn (TTN) and the likelihood of labour supervening before the scheduled Caesarean section [36]. Where the indication for PLCS 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 rupture of the membranes is considered to outweigh the risk of TTN. Where PLCS is undertaken only for obstetric indications, the optimal timing of PLCS is between 39 and 40 weeks [35]. 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 mother to reduce the risk of TTN should be considered for PLCS prior to 38 completed weeks.

8.3 Management of spontaneous rupture of membranes

8.3.1	In all cases of term pre-labour spontaneous rupture of the membranes (ROM) delivery should be expedited.	1C
8.3.2	If maternal HIV viral load is <50 HIV RNA copies/mL immediate induction of labour is recommended, with a low threshold for treatment of intrapartum pyrexia.	1C
8.3.3	For women with a last measured plasma viral load of 50–999 HIV RNA copies/mL, immediate Caesarean section 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
8.3.4	If maternal HIV viral load is ≥1000 RNA copies/mL plasma immediate Caesarean section is recommended.	1C

In the pre-cART era several studies [26,37,38] suggested that prolonged duration of ruptured membranes, usually analysed as greater 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 (AOR 1.02). Transmission increased from 12% with <1 hour membrane rupture to 19% with >12 hours of membrane rupture [39].

There are few published studies 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 finally in those on cART. Ruptured membranes >6 hours compared to <6 hours was only significantly associated with transmission in the group of women on no treatment (26.6% *vs* 11.9%; *P*=<0.01). Corresponding transmission rates for the mono–dual therapy group were 14.3% versus 7.1% (*P*=NS) and in the women on cART (0.8% *vs* 0.0%; *P*=NS) [40].

The NSHPC reported on 1050 women where length of time of ROM was recorded from 2007. In 618 women delivering with a viral load of <50 HIV RNA copies/mL when comparing those with ROM ≤4 hours to >4 hours the vertical transmission rate was 0.3% (1/326) and 0.0% (0/292), respectively (*P*=0.34). Restricting the

analysis to the 386 women with a viral load of<50 HIV RNA copies/mL who delivered vaginally did not alter this conclusion [41]. Data from North America in 2012 showed similar results. In over 700 women with HIV on ART, the perinatal transmission rate was 1% in those with ROM <4 hours and 1.9% in those with ROM for >4 hours. In those with a viral load of <1000 HIV RNA copies/mL there were no cases of perinatal transmission (493 cases with ROM of up to 25 hours). Only viral load of >10,000 HIV RNA copies/mL was shown to be an independent risk factor [42]. Therefore, for women on cART who rupture their membranes at term with a viral load of <50 HIV RNA copies/mL and who do not have an obstetric contraindication to vaginal delivery, a Caesarean section is not recommended.

As both acute and chronic chorioamnionitis have been associated with perinatal transmission [38,43-45], albeit from studies largely performed in the pre-cART era, it is recommended that labour should be expedited for all women with ROM at term. Hence women with ROM at term with a viral load of <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[46] and the NICE intrapartum guidelines [28] should be followed with regard to use of antibiotics and mode of induction.

NSHPC data for the effect of ROM greater or less than 4 hours for women with a viral load of >50 HIV RNA copies/mL are more difficult to interpret as the numbers are currently small. In women with VL 50–999 HIV RNA copies/mL there were two transmissions with ROM >4 hours (2/51) and none in the women with ROM ≤4 hours (0/43). The two transmissions occurred in women who had emergency Caesarean sections but the timing of this is not known. Although not statistically significant (*P*=0.19), these limited unpublished data suggest a possible trend towards greater transmission risk with ruptured membranes >4 hours for those with viral loads ≥50 HIV RNA copies/mL, and until further data are available, it is the recommendation of the Writing Group that Caesarean section should be considered for women with a viral load of 50–999 HIV RNA copies/mL at term. Again, if Caesarean section is not undertaken, delivery should be expedited, as above.

Data from the NSHPC for women with a viral load of >1000 HIV RNA copies/mL are sparse at present, with 1/14 (7.1%) transmitting with ROM ≤ 4hours compared to 3/15 (20%) with ROM >4 hours. A single-centre study from Miami of 707 women on ART showed ROM >4 hours to be associated with an increased risk of vertical transmission if the VL 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. Until further data are available, an urgent (category 2) Caesarean section is recommended where the viral load is >1000 HIV RNA copies/mL regardless of treatment [47].

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 prolonged premature rupture of membranes (P-PROM) at ≥34 weeks is the same as term ROM (see section 8.3 Management of spontaneous rupture of membranes) except women who are 34–37 weeks' gestation will require group B streptococcus prophylaxis in line with national guidelines.	1C
8.3.6	When P-PROM occurs at <34 weeks. • Intramuscular steroids should be administered in accordance with national guidelines • Virological control 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 or P-PROM. Decisions regarding the optimum management of early preterm ROM require the assessment of a number of factors including the exact gestation, the facilities available, maternal viral load and the presence of other co-morbidities 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 [48]. Decisions regarding timing of delivery should be made in consultation with the full multidisciplinary team including the neonatal unit. There is no evidence that steroids for fetal lung maturation (with the associated 24-hour delay in induction) are of overall benefit at 34–37 weeks' gestation in women with ruptured membranes, thus delay for the optimisation of fetal lung maturity is not recommended. For this reason, and also to minimise the risk of developing chorioamnionitis, induction is recommended from 34 weeks' gestation in women with ruptured membranes who are not in labour.

If the maternal 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 therapy is recommended (See section 6 for further information on ART in pregnancy). There is most experience with maternal oral nevirapine 200 mg stat >2hours prior to delivery, but double-dose tenofovir and standard-dose raltegravir can 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 of >1000 HIV RNA copies/mL plasma who present in labour, or with ruptured membranes or who are admitted for planned CS	1C
	For untreated women presenting in labour or with ruptured membranes in whom the current viral load is not known.	1C
	There are no data to support the use of intrapartum intravenous zidovudine infusion in women on cART with a plasma HIV viral load <1000 HIV RNA copies/mL.	1C

The use of intravenous zidovudine is suggested for women taking zidovudine monotherapy as per Recommendation 6.3.4. 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 6.3.4) has also been recommended for women who present in labour, having not received ART. However, data from the New York State HIV diagnostic service (1995–1997) suggest that intrapartum iv zidovudine alone does not significantly reduce transmission (10%; 95% CI 3.3–21.8%) since, provided neonatal prophylaxis is commenced within 48 hours of delivery (this being the only intervention accessed), the latter has similar efficacy (9.3%; 95% CI 4.1–17.5%) [49].

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 [50]. However, individual circumstances vary, and intravenous zidovudine may be considered as one of a number of maternal intrapartum antiretroviral options for women with viral loads >50 HIV RNA copies/mL who present in labour, or with ruptured membranes or who are admitted for planned CS provided this does not delay other interventions.

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9. Neonatal management

9.1 Infant post-exposure prophylaxis (PEP)

All infant PEP should be started within 4 hours of delivery. Please see Figure 9.1 and Appendix 4

9.1.1	VERY LOW RISK	1C
	Two weeks' zidovudine monotherapy is recommended if all the following criteria are met: • Mother 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 zidovudine monotherapy: • If the criteria in 9.1.1 are not all fulfilled but maternal HIV VL is <50 HIV RNA copies/mL at or after 36 weeks • If baby born prematurely (<34 weeks) but most recent maternal HIV VL is <50 HIV RNA copies/mL	
9.1.3	HIGH RISK	1C
	Use combination PEP if maternal birth HIV VL known to be or likely to be >50 HIV RNA copies/mL on day of birth, if uncertainty about recent maternal adherence or if VL not known.	
9.1.4	Neonatal PEP should be commenced very soon after birth, certainly 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 not immediately available, commence standard three-drug PEP (zidovudine, lamivudine, 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 be available as early as possible and certainly within 72 hours of delivery.
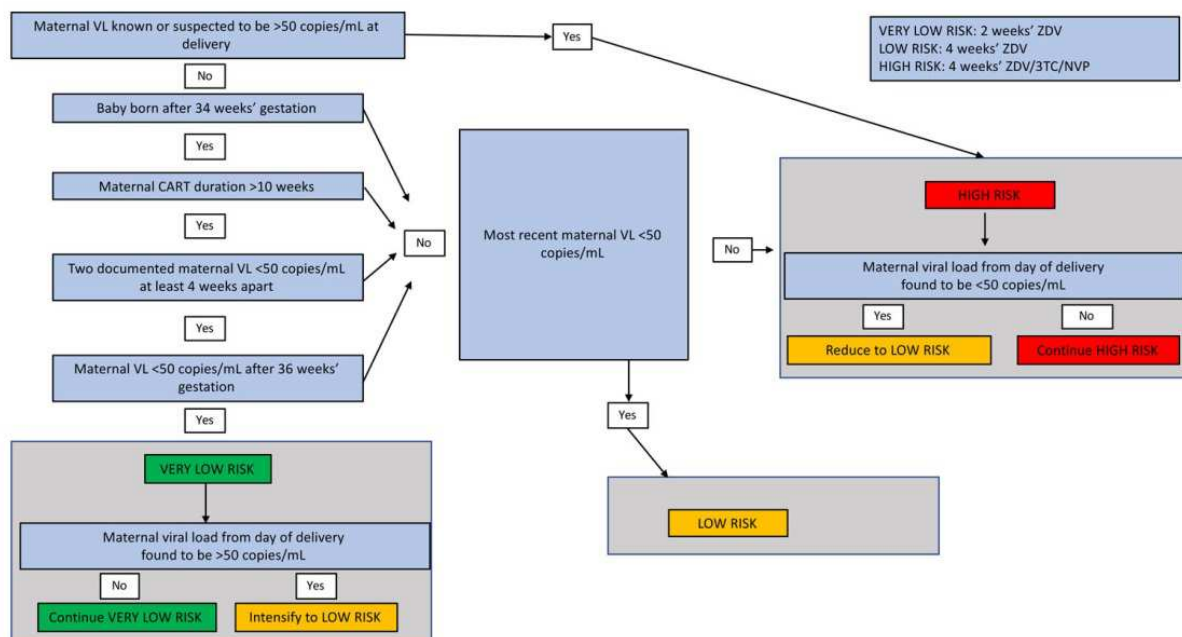
Figure 9.1. Algorithm for infant treatment

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 ACTG 076 [1]. The relative contributions of the antenatal, peripartum and infant components have been difficult to quantify. In ACTG 076 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 has 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 delivering with an HIV VL <50 HIV RNA copies/mL (upper 95% CI 0.1%) [5].

In the pre-cART era, a randomised placebo controlled trial in Thailand compared 4 strategies for the prevention of vertical transmission of HIV:

- Maternal zidovudine monotherapy from 28 weeks 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, neonatal zidovudine for 6 weeks (short-long).

Analysis demonstrated the efficacy of the 'long-short' regimen to be equivalent to the 'long-long' regimen. This led the authors to conclude that a regimen of 3 days PEP would be sufficient when the mother 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 HIV viral load <50 HIV RNA copies/mL, 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 mothers on cART with documented VL <50 HIV RNA copies/mL on the 2 most recent measurements prior to delivery. For all other situations 3 drug combination PEP is recommended [8].

It is the Writing Group's opinion that caution should be taken when extrapolating from adult 'treatment as prevention' studies to the prevention of vertical transmission. The HIV transmission risk of peripartum exposure is much higher than that 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 time of delivery being 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 hepatitis B virus [11]. Of note, this was the justification for 6 weeks neonatal PEP in the original ACTG 076 trial [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 indicates 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 the mother has been on cART for more than 10 weeks, with HIV VL <50 HIV RNA copies/mL on the most recent 2 occasions during pregnancy prior to delivery (at least 4 weeks apart) and an HIV VL <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 VL 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 separate out 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 mother commenced ART in pregnancy and delivers prematurely (<34 weeks) with an HIV 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 VL 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 RCT of combination therapy in neonates born to mothers who did not receive ART prior to delivery [14]. Infants were randomised at less than 48 hours of age to: 6 weeks of zidovudine monotherapy; or 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. HIV transmission rate was 8.5%, and in multivariate analysis only ART arm and maternal viral load were significantly associated with transmission. For infants who did not acquire HIV at birth, 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 mothers 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): a protective efficacy of 36% for the dual combination [15].

However, in two other randomised African studies where the mothers 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 to 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, and for the 86% with data on type of PEP, 3% received dual and 11% triple. 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 mothers 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 mothers), compared to 1% of those who received any PEP (72 of 7286). Among infants born vaginally to untreated mothers, 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% detectable VL at delivery despite antenatal ART), 23.9% 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-therapy PEP for infants where mothers are receiving cART. In a French study, transmission rates with dual therapy (zidovudine and lamivudine) given to both the neonate and mother (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 mothers 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 premature neonates have even less efficient metabolism. Due to a lack of neonatal pharmacokinetic and efficacy studies and suitable formulations, ART dosing regimens remain restricted to a small proportion of ARVs (Appendix 4).

For infants born to ART-naïve women, or where drug resistance is unlikely, zidovudine, lamivudine and nevirapine is a well-tolerated combination-therapy regimen with which we have the most experience [18,19,21-24] (see Appendix 4 for dosing).

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

The pharmacokinetics of nevirapine in neonates has 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 mother has taken it for 3 or more days, the full dose of 4 mg/kg per day should be started at birth, rather than the induction dose of 2 mg/kg per day (Appendix 4). 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 4.

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 dosing Appendix 4). 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.

PK-supported dosing is available for ritonavir-boosted lopinavir based on HIV-1 infected infants 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/ritonavir, particularly when preterm [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/ritonavir [43]. No effects have been observed with maternal lopinavir/ritonavir in the absence of neonatal dosing. It remains unclear whether these effects are related to lopinavir/ritonavir specifically or could be seen with other ritonavir-boosted PIs.

The Writing Group therefore recommends that lopinavir/ritonavir 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 i.v. use in sick and/or premature neonates who are unable to take oral medication, is zidovudine [25,44]. Reduced oral and i.v. dosing schedules for premature infants are available (Appendix 4).

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 mother 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 i.v. zidovudine, until enteral feeding is established, when zidovudine may be given enterally. The premature dosing regimen should be used (Appendix 4).

The fusion inhibitor enfuvirtide (T20) is the only other antiretroviral that is administered parenterally, usually subcutaneously, in adults and children. Enfuvirtide does not cross the placenta. Although i.v. enfuvirtide has been given to a small number of infants born to mothers with multidrug resistant HIV, no formal neonatal pharmacokinetic studies have been conducted to date. An unlicensed i.v. dosing regimen for infants at risk of multidrug resistant HIV has been adapted from the paediatric subcutaneous treatment study [46] and an adult i.v. dosing study [47] (See Appendix 4 and seek expert advice).

When an infant has been started on triple-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 AZT 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 [48-50]. Immediate administration of PEP is especially important where the mother has not received any ART.

9.1.7 Maternal genotypic resistance

For infants born to mothers on fully suppressive ART, zidovudine monotherapy PEP remains reasonable even where the mother has a previous history of zidovudine exposure with resistance (thymidine-associated mutations). On cART, the risk of transmission from a mother 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 6 infants born to mothers with zidovudine resistant virus [52]. A substudy of the ACTG 076 showed that low level zidovudine resistance was not associated with an increased risk of transmission [53]. Retrospective data from the U.S. 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 mother-infant pairs, although in all those cases (where data was available) the mother had detectable viral load at time of delivery [55]. In the Women and Infants Transmission Study (WITS), 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 virus 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 has 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 then the likelihood of developing new resistance on AZT monotherapy is likely to be less than with NVP or 3TC.The dosing and safety issues with lopinavir/ritonavir 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, an advantage of zidovudine.

Neonatal zidovudine monotherapy therefore remains a reasonable approach for infants born to mothers

with a HIV RNA viral load <50 HIV RNA copies/mL plasma, 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 mother known to be HIV-2 infected follow the above advice but if HIGH RISK (combination PEP indicated), nevirapine will not be effective. Seek expert advice. If advice not immediately available commence zidovudine, lamivudine and raltegravir until guidance available.	2C

There are no data available to suggest that babies born to HIV-2 infected mothers who are VERY LOW or LOW RISK should be managed any differently from those born to HIV-1 infected mothers. 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-1 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 3 drug PEP should be followed as in section 9.1.3 should be followed, replacing nevirapine with ideally raltegravir. If raltegravir is not available then lopinavir/r could be used. Infants receiving raltegravir or lopinavir/ritonavir PEP should be monitored for toxicity in the first few days of life as per Appendix 4. 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 be stopped at 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 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 mother with a HIV RNA 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 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 4 for dose).

9.3 Immunisation

9.3.1	Immunisations should be given as per national schedule.	1C
9.3.2	Rotavirus vaccine is not contraindicated (unless HIV diagnosis has been confirmed and 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 HIV RNA viral load <50 copies/mL at or after 36 weeks' gestation) may be given BCG at birth if indicated according to guidelines for HIV unexposed infants.

9.4. Infant feeding

9.4.1 HIV transmission through breast milk

9.4.1	In the UK and other resource rich settings the safest way to feed infants born to mothers with HIV is with formula milk, as this eliminates on-going risk of HIV exposure after birth.	1D

There are no data on the risk of HIV transmission via breast milk in resource rich settings. In resource poor 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 most of the studies women only received cART for 6 months and often breastfed for longer [57]. 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 [58].

Factors that increase the risk of breast milk HIV transmission when women are not on cART include detectable viral load; advanced maternal HIV disease; longer duration of breastfeeding; breast and nipple infection/inflammation; infant mouth or gut infection/inflammation; and mixed feeding, in particular solid food given to infants less than 2 months of age [59].

Where a mother 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. Exclusive breastfeeding has a transmission risk of 9/100 child-years; predominantly breast milk with other liquids transmission risk is 9.5/100 child years; and early solid foods transmission risk is 41.2/100 child-years. Thus, women with HIV have been advised to exclusively breastfeed [59]. Whether this risk still holds when women breastfeed on cART with full viral suppression is not yet known.

The risk of transmission in women on cART may still increase according to the duration of breastfeeding. Therefore, women are advised to breastfeed for as short a time as reasonable. 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 [60]. However, this estimated transmission risk is at least twice that seen in infants enrolled in the PROMISE trial at 12 months of age [58].

9.4.2 Breastfeeding advice for women with HIV living in Resource Poor Settings

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 it lifelong. They are advised to breastfeed their infants whilst adhering to cART exclusively for the first 6 months, 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 [61].

9.4.3 Breastfeeding advice for women with HIV living in the UK

9.4.2	Abstaining from breastfeeding can have financial and psychological repercussions for women, requiring support from the HIV MDT.	1C

Suppressive maternal cART significantly reduces, but does not eliminate, the risk of vertical transmission of HIV through breastfeeding. The Writing Group therefore continues to recommend formula feeding by mothers living with HIV to eliminate the risk of postnatal transmission. It is important to be aware that not breastfeeding can come at an emotional, financial and social cost to women living with HIV (see section 10.4), and we advise that women receive appropriate support from their HIV MDT (which may include peer-support, psychology, practical and financial support for formula) [62-64].

9.4.4 Choosing to breastfeed in the UK

9.4.3	Women who are virologically suppressed on cART with good adherence and who choose to breastfeed may be supported to do so, but should be informed about the low risk of transmission of HIV through breastfeeding in this situation.	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 have the following: 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 multi-disciplinary team; are prepared to attend for monthly clinic review and blood HIV viral loads for themselves and their infant during, and for 2 months after stopping breastfeeding.

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 Appendix 5).

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 [62,65]. Ideally, women 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 gastro-intestinal 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. They should be reviewed monthly with their baby for HIV RNA viral load testing until they stop breastfeeding.

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 they are putting their infant at significant risk of HIV infection.

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).

9.4.4	Maternal cART (rather than neonatal PEP) is advised to minimise HIV transmission through breastfeeding.	1D

In resource-poor settings, neonatal PEP is equally effective to maternal cART in preventing HIV transmission via breast milk. In the PROMISE-PEP trial (ANRS 12174), infant regimes of daily lamivudine or lopinavir/ritonavir were equally effective to 50 weeks (transmission rate on lopinavir/ritonavir 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 [66]. In the PROMISE trial, daily nevirapine for the infant was comparable to maternal cART 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 [58].

As lifelong maternal cART is now the WHO recommendation, these infant PrEP regimes are less likely to be used large scale. There are no clinical trials of prolonged combined treatment for the breastfeeding mother and infant, although it has suggested that this could be a feasible approach in resource poor settings where mothers may not have fully suppressed viral load and may be more likely to give medication to the infant than take it themselves [67]. We therefore recommend that maternal cART (rather than infant PrEP) be used in cases where a woman chooses to breastfeed.

9.4.5 Communication with health professionals

With sensitivity to concerns about confidentiality, families should be strongly encouraged to inform primary health care providers (including midwives, health visitors and family doctors) about maternal HIV status and infants of indeterminate HIV status. This will enable the 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	Exclusively 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 (at least 2 weeks post cessation of infant prophylaxis*) - at 12 weeks (at least 8 weeks post 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 positives has been reported [68,69].

Infants infected 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 [68].

Although HIV RNA and DNA assays have similar sensitivity, RNA assays commonly require 1 mL of plasma. 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). Ideally, the lower limit of detection should not exceed 100 HIV RNA copies/mL following dilution. In addition, where transmission may have occurred in utero, subsequent maternal antiretroviral therapy with agents that cross the placenta could lead to a false-negative RNA result in an infected infant. This risk would be highest in a late-presenting mother. In this situation, the infant should be tested using DNA PCR. As HIV DNA PCR is not widely available, a faster result will 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 then a different primer set and/or test should be used. There has been an increase in the number of cases, usually in mothers established on antiretroviral therapy with fully suppressed HIV, where it has not been possible to amplify maternal DNA using four different primer sets. HIV DNA/ RNA results on their infants should therefore be interpreted with caution and in the light of clinical and serological findings.

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 [69]. 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 6 weeks and 12 weeks of age. If all tests are negative and the baby is not being/has not been breastfed, then parents can be informed that the child does not have HIV. For infants at high risk of infection an additional early HIV test maybe undertaken at 2–3 weeks of age. For infants breastfeeding from mothers on cART (see above), HIV viral diagnostic tests should be undertaken at least monthly on mother and infant while breastfeeding, and then additionally on the infant, ideally 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. HIV Ag/Ab tests (4th generation and above) are highly sensitive and may give a positive HIV result until up to 2 years of age [70]. 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) [71]. 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 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 Network (CHIN) and contacts for local paediatricians can be found on the CHIVA website (www.chiva.org.uk).

9.6. 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 hepatitis B immunoglobulin (HBIG) given to the neonate has been shown in separate meta-analyses of RCTs to significantly reduce vertical transmission from HBV mono-infected women. HBIG should be administered to the neonate if maternal HBV DNA concentration is >10^6 IU/mL and/or mother is HBeAg-positive, or anti-HBe-negative [72]. In the absence of neonatal immunisation with HBV vaccine with or without HBIG, the rate of vertical transmission from a mono-infected mother who is HBsAg and HBeAg-positive is 70–90% and for women who are HBsAg-positive but HBeAg-negative, 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 [73].

It is therefore imperative that maternal ART together with prompt post-delivery neonatal immunoprophylaxis should be the ideal approach for preventing vertical of HBV.

Recommendations for prevention of HBV infection in infants of HBV mono-infected mothers should be followed [72,74] as HIV infection is not considered an additional risk factor.

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 HCV infected mothers. Testing and follow up of these infants should follow usual practice recommended for infants of HCV mono-infected mothers with consideration of combining HIV and HCV follow up assessments in the first 18 months to 2 years.

9.7 HIV exposed but uninfected (HIVEU)

9.7.1	In light of evidence for possible increased infectious morbidity in HIVEU, timely routine vaccination should be ensured and GPs, health visitors and secondary care physicians should be made aware of possible increased risk in order to inform decisions when risk assessing in primary care.	1D

With increasingly successful rollout of prevention of vertical transmission of HIV interventions across the globe, the number of HIVEU 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 [75] and [76]). 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 HIVEU neonatal immunity [76]. Much less information is available from high incoming settings and findings are inconsistent [77-80].

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

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10 Postpartum and postnatal 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] but for women who start on ART in pregnancy there may be an opportunity to simplify regimens, for example to once daily co-formulated regimens. Another example would be that women started on darunavir BD in pregnancy should be switched to OD 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 Postnatal follow up of women

10.2.1	All women should be reviewed in the postnatal period by a named member of the multidisciplinary team 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 NSHPC data 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 multidisciplinary team 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 multidisciplinary team and to ensure pregnancy pathways are working well. This will also allow women to receive support around any difficult experiences they may have had. Should a woman miss her first postnatal appointment then every effort should be made by the HIV MDT to contact her in order to re-establish care.

10.3 Suppression of lactation

10.3.1	Women not breastfeeding their infant by choice, or because of HIV RNA>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 [11,12]. Cabergoline is a dopamine agonist with a higher affinity and specificity for the dopamine D_2 receptor than bromocriptine [13]. The suppression of prolactin release is more prolonged with cabergoline than with bromocriptine [14]' such that a single dose of 1 mg of cabergoline may be used to inhibit lactation on Day 1 postpartum giving the equivalent effect of two weeks of bromocriptine. Adverse effects are similar to other ergot derivatives, but cabergoline appears to be better tolerated [15].

A small prospective study in Canada looked at 22 women who received cabergoline postpartum [16]. Taken at Day 2 and Day 15 lactation was successfully suppressed with absence of pain, swelling or nipple discharge in over 86% of women. However, side effects were common and seen in 9 women at Day 2 and 10 women at 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. It should be made clear that it will reduce the discomfort of lactation if not breastfeeding but will also prevent her from breastfeeding once taken.

10.4.1	Women advised not to breastfeed for their baby's health should be provided with free formula feed to minimise vertical transmission of HIV.	1D

10.4 Support services

10.5.1	Women should have 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 multidisciplinary team 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.

10.5 Mental health assessment and support

10.6.1	Women should have 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 also be offered as additional support.

10.6 Contraception

10.7.1	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

A plan for contraception postnatally should have been discussed in advance of delivery (see section 5.1.5). Ovulation usually resumes at 6 weeks postpartum but may occur earlier in non-breastfeeding women. 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 [17]. It is important to try to accommodate both the contraceptive and ART wishes of each woman. There are multiple ARVs available which do not interact with systemic oestrogens and/or progestogens such as all NRTIs, raltegravir, dolutegravir, rilpivirine and maraviroc (www.hiv-druginteractions.org). 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.

10.7 Cervical cytology

10.8.1	Cytology should be scheduled as per the Guidelines for the NHS Cervical Screening Programme 2016, 3 months post-delivery.	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 [18,19].

10.8 Testing of partner and/or older children

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

Women newly diagnosed in pregnancy should be counselled and supported regarding testing of her partner and her older children if appropriate. She should be informed that being on cART will significantly reduce her risk of vertical transmission of HIV [20] and that 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 [21].

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Appendix 4: Drug dosing for infants

DRUG	DOSE	COMMENTS/SIDE EFFECTS
NRTIs: nucleoside reverse transcriptase inhibitors		
Zidovudine (ZDV) (Retrovir®) Also known as azidothymidine (AZT) Liquid – 10 mg/mL	**Oral:** {{dose table below}} **Duration oral dosing:** • **Mono therapy - 2 weeks** • **Combination therapy - 4 weeks** **Intravenous:** • **≥34/40 gestation** – 1.5mg/kg QDS • **<34/40 gestation** – 1.5mg/kg BD, change to QDS at 34/40	Anaemia, neutropenia {{weight band table below}}

Oral dose banding:

Gestation +/- weight	Dose
<30/40 **gestation at birth**	2mg/kg BD
30–34/40 **gestation at birth**	2mg/kg BD for 2/52 then 2mg/kg TDS
≥34/40 **gestation at birth and** ≤2kg	4mg/kg BD – round dose _up_ to the nearest 0.5 mg to assist administration
≥34/40 **gestation at birth and** >2kg	See dose banding table

Weight range (kg)	Oral dose (equivalent to 4mg/kg)	Volume to be given orally
2.01–2.12	8.5mg BD	0.85mL BD
2.13–2.25	9mg BD	0.9mL BD
2.26–2.37	9.5mg BD	0.95mL BD
2.38–2.50	10mg BD	1mL BD
2.51–2.75	11mg BD	1.1mL BD
2.76–3.00	12mg BD	1.2mL BD
3.01–3.25	13mg BD	1.3 mL BD
3.26–3.50	14mg BD	1.4 mL BD
3.51–3.75	15mg BD	1.5 mL BD
3.76–4.00	16mg BD	1.6 mL BD
4.01–4.25	17mg BD	1.7 mL BD
4.26–4.50	18mg BD	1.8 mL BD
4.51–4.75	19mg BD	1.9 mL BD
4.76–5.00	20mg BD	2 mL BD

DRUG	DOSE	COMMENTS/SIDE EFFECTS
Lamivudine (3TC) (Epivir®) Liquid 10 mg/ mL	**Oral: usually as part of combination therapy** 2mg/kg BD – round dose _up_ to nearest 0.5 mg to assist administration	Anaemia, neutropenia (much less common than with ZDV)
Abacavir (ABC) (Ziagen®) Liquid 20mg/mL	**Oral: usually as part of combination therapy** 2mg/kg BD– round dose _up_ to nearest 1 mg to assist administration	Hypersensitivity reactions have not been noted in neonates
Tenofovir (TDF) (Viread®) 245mg tenofovir disoproxil = 300mg TDF	**Oral:** usually as part of combination therapy All doses now based on tenofovir disoproxil salt (TD) **(*245mg TD tablet dissolved in 24.5 mL water gives 10mg/mL)** 4.9mg/kg (0.49 mL/kg*) OD⁻ (round dose _up_ to the nearest 0.5 mg (<10 mg) or 1 mg (≥10 mg) to assist administration)	Renal dysfunction: consider monitoring renal function weekly.
NNRTI: Non-nucleoside reverse transcriptase inhibitor		

Nevirapine (NVP) (Viramune®) Liquid 10mg/mL	**Oral: usually as part of combination therapy** 2 mg/kg OD for 1 week, then 4 mg/kg OD for 1 week – round doses *up* to the nearest 0.5 mg to assist administration *If mother has already received >3 days of nevirapine:* 4 mg/kg OD – (round doses *up* to the nearest 0.5 mg)	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.
INSTI: Integrase strand transfer inhibitor		
Raltegravir (RAL) (Isentress®) 100 mg sachets for oral suspension (20 mg/mL)	**Oral: 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 – round doses *up* to the nearest 1 mg to assist administration	Rash and liver dysfunction: monitor liver function tests at 5–7 days of age
PI - Protease inhibitor		
Lopinavir/ritonavir (Kaletra®) Liquid: 5 mL = (Lopinavir 400 mg + ritonavir 100 mg)	**Oral: usually as part of combination therapy** $300mg/m^2$ (of lopinavir) BD – use dose banding table below	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.

Weight range (kg)	SA range (m^2)	Kaletra dose
1–1.5	0.1–0.13	0.5 mL BD
1.51–2	0.14–0.16	0.6 mL BD
2.01–2.5	0.17–0.19	0.75 mL BD
2.51–3	0.20–0.21	0.8 mL BD
3.01–3.5	0.22–0.24	0.9 mL BD
3.51–4	0.25–0.26	1 mL BD
4.01–4.5	0.27–0.28	1.1 mL BD
4.51–5	0.29–0.30	1.2 mL BD

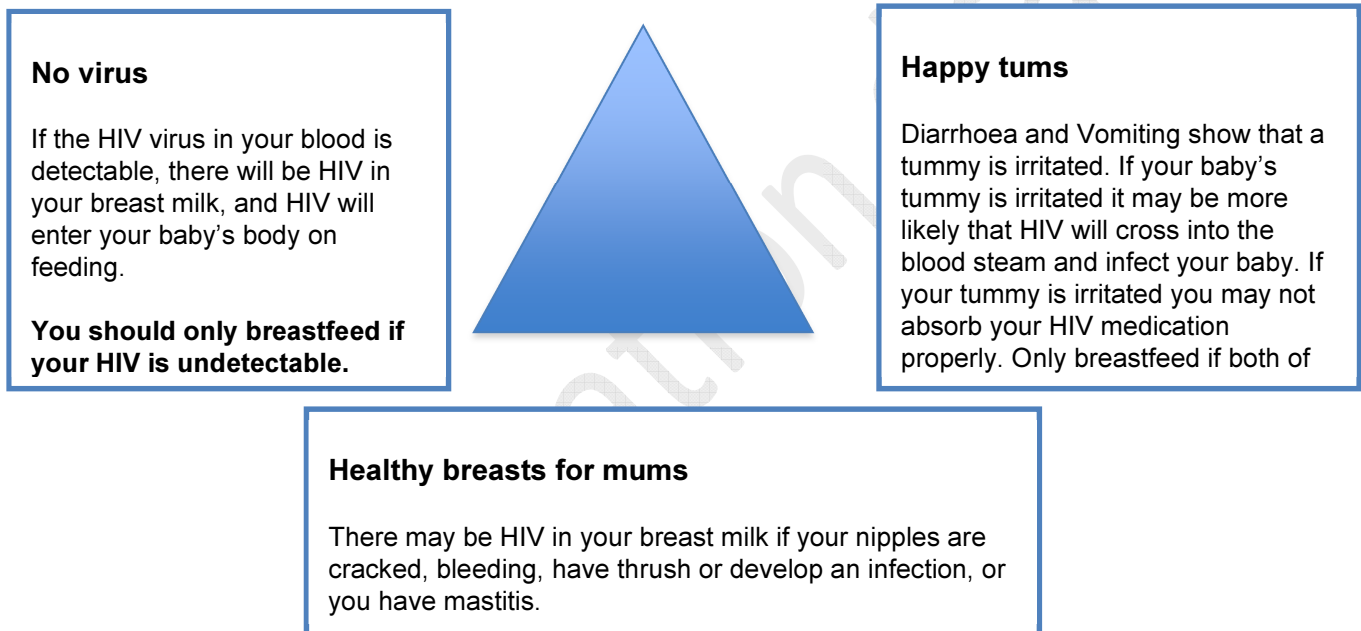| **FI: Fusion inhibitor**		
Enfuvirtide (Fuzeon®) (T-20)	**Intravenous: usually as part of combination therapy** 2mg/kg IV every 12 hours (as infusion over 30 minutes) **Method:** To reconstitute the 108mg vial slowly add 1.1 mL of water for injections from the vial of diluent provided to the vial of enfuvirtide powder, do not shake or invert the vial. The powder will 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.	Experimental IV dosing regime **Use only, as per birth plan, when benefit of giving outweighs the potential risks**
PCP prophylaxis		
Co-trimoxazole (Septrin®) 240 mg in 5 mL liquid	**BW ≥2kg** 120mg = 2.5 mL ONCE daily 3 days per week **BW <2kg** 60mg = 1.25 mL ONCE daily 3 days per week	Only HIV infected infants, start at 4 weeks of age. May rarely cause rash and bone marrow suppression.

Appendix 5. Information on infant feeding

St Mary's Family Clinic

HIV and breastfeeding your baby

Information for mothers

The safest way for a mother living with HIV in the UK to feed her baby is to bottle feed using formula milk. If you are on treatment with an undetectable viral load and choose to breastfeed your baby we can help you make it as safe as possible for your baby, but it will not be as safe as using formula. You will need to protect your baby using '*The Safer Triangle*' below:

No virus

If the HIV virus in your blood is detectable, there will be HIV in your breast milk, and HIV will enter your baby's body on feeding.

You should only breastfeed if your HIV is undetectable.

Happy tums

Diarrhoea and Vomiting show that a tummy is irritated. If your baby's tummy is irritated it may be more likely that HIV will cross into the blood steam and infect your baby. If your tummy is irritated you may not absorb your HIV medication properly. Only breastfeed if both of

Healthy breasts for mums

There may be HIV in your breast milk if your nipples are cracked, bleeding, have thrush or develop an infection, or you have mastitis.

The Safer Triangle means
No Virus + Happy Tums + Healthy Breasts for Mums

Only breastfeed if your HIV is undetectable AND both you and your baby are free from tummy problems AND your breasts and nipples are healthy with no signs of infection.

If HIV virus becomes detectable in your blood: Stop breastfeeding and start using formula milk. Do not use breast milk you have expressed and stored. Feed your baby using formula only until you have spoken with your HIV clinic.

If your baby has diarrhoea or vomiting: Feed your baby with formula milk only. Keep feeding your baby using formula milk even after their tummy is healed.

If you have diarrhoea or vomiting, or your breasts have an injury or infection: Stop breastfeeding and feed your baby with formula milk OR use breast milk that you expressed more than 2 days (48hrs) before your tummy or breast problem began. If your baby has formula milk while you are ill, continue feeding your baby formula milk only. If your baby did not receive formula milk you may return to breastfeeding two days (48hrs) after your breast problem is healed. If you had tummy problems you must contact your HIV clinic before breastfeeding.

These four golden rules will help to protect your baby from HIV while breastfeeding.

(1) Taking Your Meds = Giving Your Love

The HIV medicines you take protect your baby as well as you. You need to be 'undetectable', with no HIV detectable in your blood, to breastfeed your baby. The only way to do this is to take your HIV medications at the right time every day.

Every day you are already caring for your baby keeping them clean, warm and comforted. Taking your HIV medication as perfectly as possible is just another part of the love that you are already giving to your child.

(2) Short and sweet

The fewer breastfeeds your baby ever has, the lower the chance your baby will have of becoming HIV positive. Even if you are taking your HIV medication, your baby has double the chance of becoming infected with HIV if you breastfeed for 12 months rather than stopping before your baby is 6 months old.

By 6 months babies are ready to start first (weaning) foods. Good first foods are cooled mashed vegetables like potatoes or carrots, soft fruits or baby cereals mixed with formula milk. Babies' tummies are more irritated during weaning. Using formula milk only while weaning means your baby will get the vitamins and calories he or she needs to grow, while being completely protected from any risk of HIV infection.

If your baby doesn't like the bottle at first, try having someone else apart from you give them the bottle – what your baby won't accept from mum, he or she may take from someone else!

(3) Breast milk only

If you choose to breastfeed you should give breast milk **only**. This is known as exclusive breastfeeding. Giving breast milk and other foods may irritate the baby's tummy and increase the risk of HIV infection. If you are 'exclusively breastfeeding', it means your baby is receiving no other food or drink. You can still give your baby vitamins or prescribed medicines. Your baby can also have bottles of your own expressed breast milk. We recommend starting to do this early on, so your baby gets used to a bottle as well as the breast.

(4) Be prepared

Breastfeeding doesn't always go to plan. A mother living with HIV faces the same challenges during breastfeeding as any mother. Living with HIV means these situations need to be managed with extra planning. Advice for a breastfeeding mother who does not have HIV may not be correct for you and your baby. We encourage you to tell your community midwife about your HIV to help make sure they are giving you the right advice for you and your baby. If you are uncertain about something ask your specialist midwife, your specialist children's nurses, or your HIV doctor.

Get comfortable

Good feeding positions are better for you and your baby. They will reduce the chance of injuries to your nipple. An injured nipple or inflamed breast (known as mastitis) can increase the amount of HIV in your milk. Ask your specialist midwife and community midwife for help with breastfeeding positions.

Expressing milk

'Expressing' milk means gently squeezing or pumping your milk from your breast into a sterile container to use either right away or save for later.

One of the most useful ways to prepare for any breastfeeding difficulties is to express and freeze your breast milk while your breasts and tummy are healthy and free from problems and your viral load is undetectable.

You can express your milk by hand into a cup that has been boiled in water for 10 minutes and then allowed to cool. You can also use a breast pump. You can rent one from the hospital or buy one from places such as Boots or Argos. Pumps can be by hand or electric and cost from £10 to more than £200.

Your milk can be safely stored in a sterilised container or individual pre-sterilised plastic breast milk bags (about £7.50 for 30). Write the date and the amount of milk on the container before you store it.

You can keep your expressed milk:
- in the fridge for up to five days at 4 degrees centigrade or lower. Using a fridge thermometer (about £5 from places like Tesco or Curry's) is the best way to make sure your milk is kept at the right temperature.
- for two weeks in the ice compartment of a fridge
- for up to six months frozen in a freezer

Ask your community midwife for more advice on expressing and storing milk.

Formula feeds for back-up

If a side of the Safer Triangle breaks (No Virus + Happy Tums + Healthy Breasts for Mums) you may need to stop breastfeeding and give your baby formula milk. Even if you are breastfeeding, keep a small supply of formula milk at home for your baby in case of an emergency.

You will need

- The right stage formula milk for your baby (stage 1 for 0–6 months, stage 2 follow on milk for 6–12 months)
- Two bottles or more
- Two teats or more
- A method to sterilize the bottles and teats

How to stop breastfeeding

You may stop breastfeeding abruptly to protect your baby from HIV. This can make your breasts feel full of milk and uncomfortable. It may also increase your risk of a breast infection. Two things can help:

(1) Hand expressing just enough milk to keep your breasts comfortable. Each day, make the amount you express less and less, and the length of time between when you are expressing longer and longer. Do one less session every 2-3 days depending on how your breasts feel. If normally you breastfeed your baby six times a day reduce this to five times a day, wait a day or two and reduce this to four times a day. Keep going until you have stopped breastfeeding. This will help your breasts to gradually stop making so much milk.

(2) *Cabergoline* is a tablet that stops your body making breast milk. You may need to take one tablet once, or a smaller dose four times over two days. This can make ending breastfeeding more comfortable for you. Contact your HIV clinic (The Family Clinic if you are cared for at St. Mary's Hospital) or your GP to prescribe *cabergoline* for you. You can keep this medicine at home for when you want to stop breastfeeding.

Help with breastfeeding problems for women living with HIV

This section lists some of the problems that may come up whilst you are breastfeeding. It gives advice on how to manage them. This advice may be different than for women who do not have HIV.
If you have a problem breastfeeding, and this leaflet does not help and you cannot reach a healthcare professional who understands HIV and breastfeeding, use the *Safer Triangle* and ask your community midwife or GP for advice.
Once you begin feeding your baby formula milk do not return to breastfeeding.

Mastitis

When milk stays in the breast for longer than usual, or the whole breast isn't being fully emptied of milk, you can get a blocked milk duct. This can become inflamed and / or infected. This infection is called *mastitis*. Mastitis is very common. One in ten, and up to one in three, breastfeeding women develops mastitis. Speak with your community midwife about how to prevent and treat a blocked duct so it does not become mastitis.

Symptoms of mastitis

- A red, swollen area on your breast that may feel hot and painful to touch
- A breast lump or area of hardness on your breast
- A burning pain in your breast that may be continuous or may only occur when you are breastfeeding
- Nipple discharge, which may be white or contain streaks of blood

- You may also feel achy, have a high temperature, chills and be very tired.

Mastitis can develop quickly. See your GP or go to A & E if you have symptoms of mastitis to avoid a breast-abscess forming.

How to manage mastitis

Mastitis causes the amount of virus in breast milk to increase.
If you develop mastitis, do not breastfeed your baby.
The safest thing you can do if you develop mastitis is to stop breastfeeding and change to formula milk. Express and throw away milk regularly from both breasts.

- Throw away any milk expressed from the two days before the breast became sore.
- Your doctor may give you antibiotics. Some will enter your breast milk. If you continue to breastfeed your baby against advice, the antibiotics may cause your baby to have diarrhoea. This is a sign that your baby's tummy is irritated and can increase the risk that HIV will enter your baby's body.
- Rest and drink lots of fluids
- You can use paracetamol or ibuprofen. **Do not use** aspirin if breastfeeding.
- Avoid tight clothes or bras
- Warm baths and directing a hot shower onto the affected breast can help.

Feeding your baby after the mastitis is healed

- If you start formula feeding, do not return to breastfeeding. Continue to only feed your baby formula milk even after the mastitis has healed.
- If you had enough stored breast milk to feed your baby with while you were unwell, and did not feed your baby formula, you may return to breastfeeding two days (48hrs) after your mastitis is completely healed.
- If your baby has runny poos or other signs of tummy irritation do not feed your baby with any breast milk – neither stored expressed milk, nor straight from your breast. Continue to feed your baby with formula milk after their tummy irritation has improved.

Cracked or bleeding nipples

Sore and injured nipples are usually because the baby is not latching onto the nipple well. Please ask your community midwife or health visitor for help with this.
Irritated and broken skin can allow your blood to get into your breast milk. This could increase the chance your baby maybe infected with HIV.

- Do not feed your baby from the sore breast while the nipple is cracked.
- Hand express or pump milk from the sore breast and throw this milk away.
- Do not feed you baby from the sore breast until the breast is healed and has been blood and pain free for at least two days (48hrs).
- Breastfeed your baby from the other breast.
- If both breasts are cracked and sore – even if there is no blood – then do not breastfeed your baby.
- Use your supply of stored expressed milk instead.
- If you do not have enough stored expressed milk, feed your baby using baby formula.

Feeding your baby after cracked nipples have healed

If you start formula feeding, do not return to breastfeeding. Continue to only feed your baby formula milk.
If you had enough stored expressed breast milk to feed your baby with while your nipples were cracked or irritated, and did not feed your baby formula, you may return to breastfeeding two days (48hrs) after your nipples are completely healed.

Thrush: Candida yeast infection

Thrush is a yeast infection in your nipple. It can be passed from mother to baby and baby to mother. Sore and cracked nipples are more likely to develop thrush and nipples with thrush are more likely to stay sore and cracked. You are more likely to develop nipple thrush if you, or your baby, have been on antibiotics. If you, or your baby, have signs of thrush you are likely to pass it back and forth to each other until both of you are successfully treated.

Symptoms of nipple thrush in the mother

- Breastfeeding is painful in both breasts, when previously it felt ok.
- It is less likely to be nipple thrush if the pain is only on one side, you have a fever, or there is a warm red patch on one of your breasts.

Managing nipple thrush

- Treat thrush with anti-fungal medicine for you and your baby and painkillers such as paracetamol or ibuprofen (not aspirin). Your GP can prescribe this for you.
- If your nipple is cracked or bleeding do not breastfeed from the sore breast.
- You can continue to breastfeed from the healthy breast, although it is likely that both nipples will have thrush.
- Use your supply of frozen milk instead.
- If you do not have enough frozen milk, feed your baby using baby formula.
- Express and discard milk from the sore breast until 48hrs after it is recovered.

Feeding your baby after the nipple thrush has healed

- If you start formula feeding, do not return to breastfeeding. Continue to only feed your baby formula milk
- If you had enough stored expressed breast milk to feed your baby with while your nipples were cracked or irritated, and did not feed your baby formula, you may return to breastfeeding two days (48hrs) after your nipples are completely healed.

Diarrhoea and vomiting in the mother

You may not absorb your HIV medicine well if you have diarrhoea or are vomiting. This may cause a temporary increase in the amount of HIV in your breast milk.

- Do not breastfeed your baby if you have diarrhoea or are vomiting because you may not have absorbed enough of your anti-retroviral medicine.
- Use your supply of stored expressed breast milk instead.
- Express your milk and throw it away it until at least two days (48hrs) after you last had diarrhoea or vomited.
- Tell your clinic team, as they may want to check that the virus in your blood is still undetectable.
- Your HIV clinic team may ask you not to breastfeed your baby and throw away any expressed breast milk, until they have been able to check the amount of virus in your blood.
- If you do not have enough stored expressed breast milk then feed your baby with formula milk.
- If you start formula feeding, do not return to breastfeeding. Continue to only feed your baby formula milk.
- If you had enough stored expressed breast milk to feed your baby with while you were unwell and did not feed your baby formula, you may be able return to breastfeeding after you have spoken with your HIV clinic team.

Diarrhoea and vomiting in the baby

If your baby is having diarrhoea or vomiting, it is safer to feed your baby formula milk and not breast milk. Diarrhoea and vomiting are signs that your baby's tummy and intestines are irritated. This will make it more likely that any HIV in your breastmilk can enter into your baby's blood and cause infection.

- Start formula feeding and do not return to breastfeeding. Continue to only feed your baby formula milk.

If your baby is not putting on weight

You may be told to give your baby additional feeds of formula milk.

- Start formula feeding and do not return to breastfeeding. Continue to only feed your baby formula milk.

If HIV becomes detectable in the mother's blood (detectable viral load)

If your HIV viral load becomes detectable in your blood stop breastfeeding and start formula milk feeding.

You may be eligible for free formula milk if the amount of HIV in your blood increases while you are breastfeeding.

And finally…

We are learning more all the time about how to keep mothers and babies with HIV healthy. You may have a question for which we do not yet have a definite answer. If this happens we will use our experience to guide you. We will tell you when we know new scientific evidence. If you have a question and cannot reach us, use the Safer Triangle.

St Mary's Family Clinic Team
2017

Contact details:

Children's Clinical Nurse Specialists
Paula Seery and Natalie Kirkhope
Telephone number: 0203 312 6349
Email address: family.clinic@nhs.net
Specialist Midwife
Moira Marks
Telephone number: 0203 313 5179
Bleep 0203 311 1000 pager number 9601
Email address: moira.marks@imperial.nhs.uk
moira.marks@nhs.net

Mentor Mother at Positively UK http://positivelyuk.org/pregnancy/
Helen Rogers
Telephone number: 020 7713 0444
Email address: hrogers@positivelyuk.org

For other organisations that can give basic breastfeeding advice please see *NHS choices 'Breastfeeding Help and Support'* for a list of websites and helplines.

Helplines

National Breastfeeding Helpline – 0300 100 0212
Association of Breastfeeding Mothers – 0300 330 5453
La Leche League – 0345 120 2918
National Childbirth Trust (NCT) – 0300 330 0700

The Safer Triangle =
No Virus + Happy Tums + Healthy Breasts for Mums
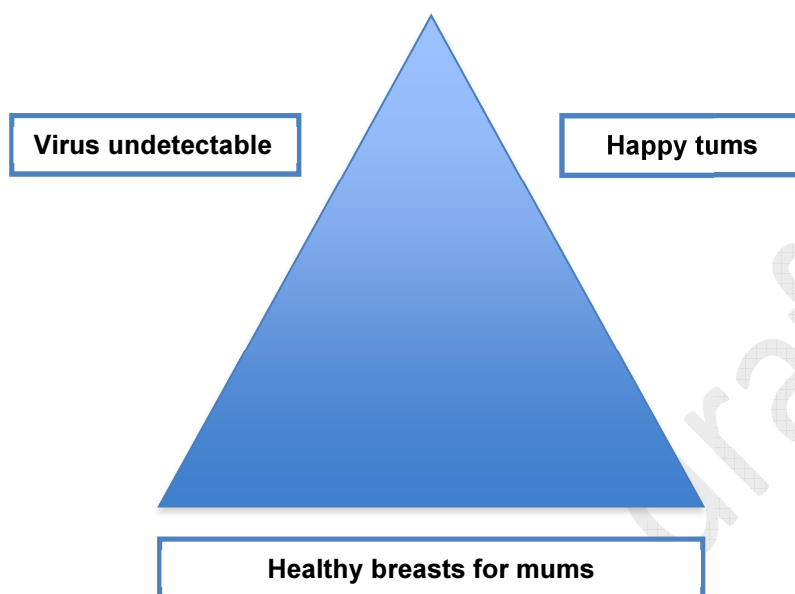
Virus undetectable

Happy tums

Healthy breasts for mums

Only breastfeed if your HIV is undetectable AND both you and your baby are free from tummy problems AND your breasts and nipples are healthy with no signs of infection.

- **If HIV virus becomes detectable in your blood**: Stop breastfeeding and start using formula milk. Do not use breast milk you have expressed and stored. Feed your baby using formula milk only until you have spoken with your HIV clinic.

- **If your baby has diarrhoea or vomiting:** Feed your baby with formula milk only. Keep feeding your baby using formula milk even after their tummy is healed.

- **If you have diarrhoea or vomiting, or your breasts have an injury or infection:** Stop breastfeeding and feed your baby with formula milk OR use breast milk that you expressed more than 2 days (48hrs) before your tummy or breast problem began. If your baby has formula milk while you are ill, continue feeding your baby formula milk only. If your baby did not receive formula milk you may return to breastfeeding two days (48hrs) after your breast problem is healed. If you had tummy problems you must contact your HIV clinic before breastfeeding.

If one side of the Safer Triangle breaks, stop breastfeeding.

Feeding your new baby

Information for women with HIV

The British HIV Association recommends that the safest way for a mother with HIV to feed her baby is with formula milk, as there is absolutely no risk of HIV transmission at all after birth (BHIVA 2017).

HIV health workers understand that HIV may not be the only thing you need to think about when feeding your new baby. We have put together information that will help you make an informed decision about feeding your baby. Whatever you decide, you will not be judged. Let your HIV care team know if you decide to breastfeed your baby. They can then work with you to help make this as safe as possible, even though it will still not be as safe as feeding your baby with formula.

The most important things you can do are to keep up with your medications and appointments, enjoy this time with your new baby, and get in touch if you have any questions or difficulties.

If you are considering breastfeeding your baby

- You need to have an undetectable viral load and be taking your anti-retroviral therapy treatment at the right time every day.
- If you breastfeed your baby, he or she should only have breastmilk and not formula or cow's milk too.
- There are times when the risk of passing HIV to your baby can increase. These include, if you have a detectable viral load, mastitis, cracked nipples, diarrhoea or vomiting or if your baby has diarrhoea or vomiting. **You should not breastfeed your baby at these times.** You will need to contact your HIV clinic for further advice on breastfeeding.
- The HIV team looking after you and your baby should know about your decision to breastfeed so that they can help you make it as safe as possible for your baby.
- Following the guidance above means you are following the plan for 'Safer Breastfeeding' and we will support you to breastfeed your baby.

Background

- If you formula feed your baby there is no risk of HIV infection after birth.
- The longer a baby is breast fed, the more likely he or she will be to get HIV.
- The research we have on HIV and breastfeeding comes from outside of the UK.
- There has been no research on HIV and breastfeeding in the UK

If 100 mothers with HIV…
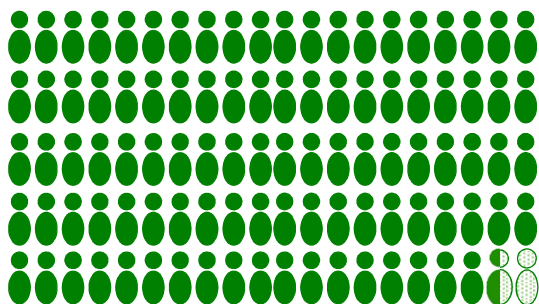
…breastfeed their babies for a year while having an undetectable viral load in the blood:

1–2 babies may become HIV positive
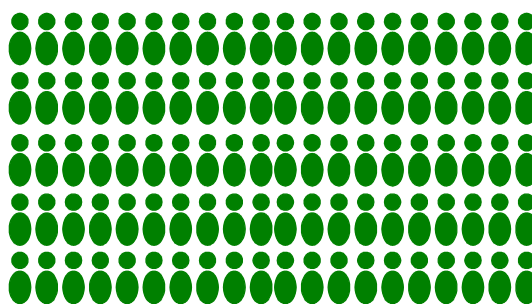
…formula feed their babies:

0 babies will become HIV positive

Is breast best for your baby?

Some mothers and babies find breastfeeding straightforward. For others it can be difficult. You might have read about benefits of breastfeeding for the mother and the baby. These benefits are real, but on balance, less important than the harm that HIV can do.

In resource poor areas (e.g. parts of Africa and Asia) it is safest for mothers with HIV to breastfeed their babies. This is because water may be unclean, there might not be ways to sterilize the baby bottles, and baby formula may not always be available or affordable. There is more risk that a formula fed baby in these areas will die from infections from dirty water or not having enough food, than a breastfed baby will die from HIV infection in the future.

In the UK, things are different. Your baby is unlikely to get an infection from the water used in formula feeding, but if you breastfeed, your baby might still get HIV.

Formula feeding is very common in the UK
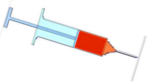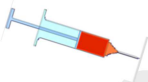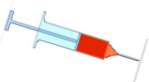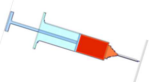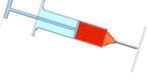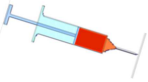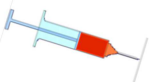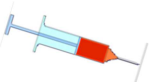
More than 8 out of 10 mothers in the UK are feeding their babies with formula milk by the time the baby is 3 months old. Once the baby is 6 months old, only 1 in 100 UK mothers are giving their baby breast milk only. If a mother is not breastfeeding in the UK, people will not think it is unusual and are unlikely to think it has anything to do with being HIV positive.

If you are formula feeding, having lots of eye contact and skin-to-skin contact with your baby will still give you and your baby a very close bond.

Appointments

You and your baby will have extra appointments and more blood tests if you decide to breastfeed. This is to make sure there is no HIV detected in your blood and to check your baby's health and make sure she or he remains HIV negative.

The number of blood tests and checks you and your baby will have depends on how you decide to feed your baby:

Timing of blood tests	Breastfeeding Mother	Breastfeeding Baby	Formula feeding Baby
At birth	💉	💉	💉
Every 4 weeks for as long as you are breast feeding	For example: Six blood tests if breastfeeding for 6 months 💉 1 month 💉 2 months 💉 3 months 💉 4 months 💉 5 months 💉 6 months	For example: Six blood tests if breastfeeding for 6 months 💉 1 month 💉 2 months 💉 3 months 💉 4 months 💉 5 months 💉 6 months	
6 weeks after birth			💉
12 weeks after birth			💉
4 weeks after you have stopped breast feeding		💉	
8 weeks after you have stopped breast feeding		💉	

Your medicines in your breast milk

Your HIV medication can get into your breast milk. How much will depend on what you are taking and how your body absorbs the drug.

Your HIV drugs will not usually hurt your baby. They will cause much less harm than if you stop taking your medications and the amount of HIV in your body increases.

Having a new baby can disrupt the best schedule. Make sure you are taking (adhering to) your HIV medicines every day at the correct time and getting your blood virus levels checked. Keeping the amount of virus in your blood undetectable will make it less likely the HIV will pass into your baby through breastfeeding.

There is a chance that if your baby gets passed HIV through breastfeeding the type of medicine you were taking may not work for your baby. This is important because children's HIV doctors won't have as many medicines to treat their HIV with in the future.

Only breast milk

'Exclusively breastfeeding' means your baby is receiving only breast milk, and no other food, drink or baby formula. Giving other foods and types of feeds, in addition to breastmilk, has been shown to double the risk for some babies of becoming infected with HIV. If you choose to breastfeed, you must breastfeed your baby *'exclusively'*. When you are ready to stop breastfeeding exclusively you can switch to formula milk if under 12 months, or cows milk if your baby is over 12 months of age.

Length of time

The shorter the length of time you breastfeed your baby, the less chance they will have of getting HIV. If you decide to breastfeed, it may be helpful to have an idea of when you will change to formula.

Money

It is important to make up your baby's bottle with the correct amount of water and formula for their age. That is how you will be certain they will be getting the right amount of vitamins and calories. You may need to spend about £250 to feed your baby for the first 6 months. From 6 months you will be introducing solid foods and starting to reduce the amount of formula you are giving your baby.

Formula and Bottle Feeding

You will need bottles and teats to bottle feed and a way to clean and sterilise them. You can use a bottle brush with a bottle steriliser (approx. £25), sterilizing chemicals (approx. £1.50 for 3 months) or boil the equipment in water for 10 minutes.

You may want to use a breast pump if you intend to breast-feed (approx. £15-150).

Financial support for formula feeding

Name of Support	What it Offers	You are entitled to this if…
Sure-Start Maternity Grant	A one-off payment of £500	…you are expecting your first child, are expecting twins or triplets, or you or your partner are receiving certain benefits.
Healthy Start vouchers	You can use these for food, milk and baby formula at supermarkets, chemists and corner shops	…you are on Income Support, Jobseeker's Allowance, receiving Child Tax Credit or are under 18 years old.
Your GP	May be able to provide baby formula	This will depend on your local area. Ask your GP about eligibility.
Body and Soul	May be able to provide baby formula	…you are a member of Body and Soul.
The Food Chain	Short term support with buying baby formula and groceries for people living with HIV in London	…you have been referred by your HIV clinic, midwife, peer supporter or HIV Support Organisation.

Other feeding options

In addition to formula feeding, you can also:

Express your milk and heat treat it

This will kill the HIV, but keep most of the nutrients in the breast milk. It is very time consuming and some mothers have found that it is not a very practical option.

To sufficiently heat treat your breast milk

1. Place 50–150ml milk in a large, clean covered glass jar (approximately 500ml).
2. Place the jar upright in a small pan of cold water.
3. The level of water in the pan should be two finger-widths above the level of the milk in the jar.
4. Place the pan on the stove and heat until the water reaches a rolling boil.
5. Remove the pan from the heat and remove the jar from the hot water.
6. Put the lid on the jar, and allow the milk to cool before feeding to the baby.

Donor Milk

Some hospital milk banks may be willing to supply you with donor milk. You will have to arrange and pay for this. http://www.ukamb.org/

We strongly suggest that you do not buy breast milk from the Internet. This is expensive and may not have

been checked properly for infections.

We strongly advise no one else breastfeeds your baby on your behalf.

Child Protection Concerns

If you are taking your treatment, have an undetectable viral load and are adhering to the rules of 'Safer Breastfeeding' we will support you to breastfeed your child.

If you are not taking your HIV treatment every day and are still breastfeeding, the risk of passing HIV on to your baby becomes much higher. This could put your baby at enough risk that Children and Family Services may need to be called to help keep the baby as safe as possible. We want to avoid ever having to do this and want to work with you to care for your baby in the safest way. We have worked with many mothers with HIV who have had to make the decision about how to feed their new baby.

Some women choose to breastfeed for the following reasons:

'I wanted to feel close to my baby'

'I know there are health benefits to breastfeeding'

'I breastfed my last baby and he is fine'

'Formula is too expensive'

'My mother in law keeps making me breastfeed'

'My husband does not know about my HIV and I do not want him to find out'

'I was told where I used to live that breastfeeding while taking treatment is safe'.

'Breast feeding is more convenient'

'My baby and I are going to a country where and I can't always get formula and do not know if the water is always clean'.

If you decide to formula feed, people may sometimes ask – or even pressure – you about why you are not breastfeeding.

Peer supporter M.M. (HIV+ 25yr) suggested these responses if someone asks why you are bottle feeding:

'I don't want to risk passing on HIV or my meds to my baby

'Breastfeeding just didn't work for us'.

'I am taking antibiotics'.

'He started off on formula so we just stuck with it'.

'The health visitor said she is doing great and to just keep doing what I am doing'.

'This means her Dad can help out more'.

'I was told skin-to-skin is just as good'.

'It's a personal choice'.

'I have inverted / painful nipples'.

'I had problems with breastfeeding previously'

'I prefer the privacy'

Whatever you decide, agree with your partner what you will say to friends and family – everyone is more likely to accept your reasons if they are always the same.

All new mothers need to make decisions about how they want to feed their baby. Having HIV just adds a few more things to think about.

This may be an easy or a complicated decision for you. You may know exactly what you want or you may have more things you want to know. Discuss these with your midwife, doctors, paediatric nurses and Mentor Mothers and peer supporters. Take time to make your decision. Do not to feel pressured by others.

If you feel you would like more support with making this decision you could consider talking to Mentor Mothers at Positively UK (Helen on 020 7713 0444 or email hrogers@positivelyuk.org) who would be very happy to talk things through with you.

Please talk to staff at the Family clinic here, we are all here for you and your new baby and will be happy to help you.

St Mary's Family Clinic Team, 2017

How do I make a comment about my visit?

We aim to provide the best possible service and staff will be happy to answer any of the questions you may have. If you have any **suggestions** or **comments** about your visit, please either speak to a member of staff or contact the patient advice and liaison service (**PALS**) on **020 3313 0088** (Charing Cross, Hammersmith and Queen Charlotte's & Chelsea hospitals), or **020 3312 7777** (St Mary's and Western Eye hospitals). You can also email PALS at pals@imperial.nhs.uk. The PALS team will listen to your concerns, suggestions or queries and is often able to help solve problems on your behalf.

Alternatively, you may wish to express your concerns in **writing** to:

The Chief Executive's Office
Imperial College Healthcare NHS Trust
Trust Headquarters
The Bays, South Wharf Road
London W2 1NY

Alternative formats

This leaflet can be provided on request in large print, as a sound recording, in Braille, or in alternative languages. Please contact the communications team on **020 3312 5592.**

Appendix 1: summary of the modified GRADE system (grades 1A–2D)

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 patients in most circumstances without reservation Clinicians should follow a strong recommendation unless there is a clear rationale for an alternative approach
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
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, and applies to most patients. Some of the evidence base supporting the recommendation is, however, of low quality
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 mainly on case studies and expert judgement
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 patients' or societal values
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 patients under some circumstances
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
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

Appendix 2: PICO questions

Search 1	Safety and efficacy of antiretrovirals in pregnancy
Study design	Systematic reviews (SRs), randomized control trials (RCTs), observational, risk, economic
Population	Women living with HIV
Intervention	Starting antiretroviral therapy during pregnancy
Comparator	None
Outcomes	Death, AIDS, non-AIDS co-morbidities, 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	Systematic reviews (SRs), randomized control trials (RCTs), observational, risk, economic
Population	HIV/HBV/HCV co-infected women
Intervention	Starting antiretroviral therapy during pregnancy
Comparator	None
Outcomes	Death, AIDS, non-AIDS co-morbidities, 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 breast feeding

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 MTCT 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	Systematic reviews (SRs), randomized control trials (RCTs), observational, risk, economic
Population	Women living with HIV
Intervention	Obstetric delivery and fetal monitoring
Comparator	None
Outcomes	Death, AIDS, non-AIDS co-morbidities, 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 CVS
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 (CVS) 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	Systematic reviews (SRs), randomized control trials (RCTs), observational, risk, economic
Population	HIV-exposed infants
Intervention	antiretroviral treatment and prophylaxis for neonates
Comparator	None
Outcomes	Death, AIDS, non-AIDS co-morbidities, 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	Systematic reviews (SRs), randomized control trials (RCTs), observational, risk, economic
Population	Women living with HIV
Intervention	Starting antiretroviral therapy during pregnancy

Comparator	None
Outcomes	Death, AIDS, non-AIDS co-morbidities, 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 3: literature search

Date of search: 9–16 November 2016

Databases searched from 1 July 2013 to November 2016

Abstracts searched from 2013 to November 2016

Search 1: Antiretrovirals

Search terms	ab(Antiretrovir*) AND (systematic review OR random* OR RCT OR observational OR cohort OR "case control" OR "case-control" OR risk OR economic OR cost) AND preg*
Databases	Embase Embase Alert MEDLINE
Limited by	Females, Humans Date: On or after 01 July 2013 Age group: 31 types searched (i.e. all age groups): adolescent, adolescent father, adolescent mother, adolescent parent, adult, aged , aged hospital patient, baby, boy, brain-damaged child , child, embryo, fetus, frail elderly, gifted child, girl, handicapped child , high-risk infant, hospitalized adolescent , hospitalized child, hospitalized infant, infant, juvenile, middle-aged, newborn, orphaned child, preschool child, school child, suckling, toddler, very elderly Document type: 18 types searched (i.e. not bibliography, biography, case study, commentary, correspondence, dictionary/glossary, editorial, interview, memoir/personal document, news): Article, book, book chapter, conference, conference paper, conference proceeding, correction/retraction, directory, feature, government & official document, instructional material/guideline, patent, reference document, report, review, speech/lecture, technical report, undefined Language: English
Results	*N*=650

Cochrane

Search 1: HIV and preg* and antiretrovir* in title/abstract/keywords; date between 2013 and 2016 (searched 9 November 2016)

Databases:	*N*
Cochrane reviews	7
Other reviews	7
Trials (from Cochrane)	142
Technology assessments	0
Economic evaluations	5

Conference

Conference	N
IAS Conference on HIV Pathogenesis and Treatment	289
International AIDS Conference	44
Conference on Retroviruses and Opportunistic Infections (CROI)	202
European AIDS Clinical Society (EACS)	5
International Congress on Drug Therapy in HIV Infection	11
British HIV Association Annual Conference	14
Children's HIV Association Conference (CHIVA)	1
International Workshop on HIV Paediatrics	19
International Conference on Antimicrobial Agents and Infectious Disease (ICAAC)	1

American Association for the Study of Liver Disease (AASLD)	0
European Association for the Study of the Liver (EASL)	1
International Workshop on HIV and Women	10

Search 2: Hepatitis co-infection

Search terms	(HIV OR "human immunodeficiency virus") AND preg* AND (hepatitis OR HBV OR HCV) AND (SR OR "systematic review" OR random OR RCT)
Databases	Embase Embase Alert MEDLINE
Limited by	Humans Date: On or after 01 July 2013 Document type: 18 types searched (i.e. not bibliography, biography, case study, commentary, correspondence, dictionary/glossary, editorial, interview, memoir/personal document, news): article, book, book chapter, conference, conference paper, conference proceeding, correction/retraction, directory, feature, government & official document, instructional material/guideline, patent, reference document, report, review, speech/lecture, technical report, undefined Language: English
Results	*N*=415

Cochrane

HIV and preg* and hepatitis in title/abstract/keywords; date between 2013 and 2016

Database	*N*
Cochrane reviews	3
Other reviews	0
Trials (from Cochrane)	15
Technology assessments	0
Economic evaluations	0

Conferences

Conference	*N*
IAS Conference on HIV Pathogenesis and Treatment	3
International AIDS Conference	1
Conference on Retroviruses and Opportunistic Infections (CROI)	3
European AIDS Clinical Society (EACS)	24
International Congress on Drug Therapy in HIV Infection	1
British HIV Association Annual Conference	1
Children's HIV Association Conference (CHIVA)	2
International Workshop on HIV Paediatrics	0
International Conference on Antimicrobial Agents and Infectious Disease (ICAAC)	4
American Association for the Study of Liver Disease (AASLD)	0
European Association for the Study of the Liver (EASL)	5
International Workshop on HIV and Women	1

Search 3: Fetal monitoring and obstetric issues

Search terms	(HIV OR "human immunodeficiency virus") AND preg* AND (SR OR "systematic review" OR random* OR RCT OR observational OR cohort OR "case control" OR "case-control" OR risk OR economic OR cost) AND (vaginal OR Caesarean OR Cesarean OR deliver* OR monitor* OR ECV OR "external cephalic version" OR induc* OR ventouse OR forceps OR instrument* OR episiotomy OR screen* OR CVS OR "chorionic villus sampling" OR amniocentesis OR rupture).
Databases	Embase Embase Alert

	MEDLINE
Limited by	Humans Date: After 01 July 2013 Document type: 18 types searched (i.e. not bibliography, biography, case study, commentary, correspondence, dictionary/glossary, editorial, interview, memoir/personal document, news): article, book, book chapter, conference, conference paper, conference proceeding, correction/retraction, directory, feature, government & official document, instructional material/guideline, patent, reference document, report, review, speech/lecture, technical report, undefined Language: English
Results	*N*=1652

Cochrane

HIV and preg* and deliver* in title/abstract/keywords; date between 2013 and 2016 (searched 10 November 2016)

Databases:	*N*
Cochrane reviews	8
Other reviews	1
Trials (from Cochrane)	108
Technology assessments	0
Economic evaluations	0

Search 3a.i: HIV and preg* and fetal and monitor* in title/abstract/keywords; date between 2013 and 2016 (searched 10 November 2016)
N=0

Search 3a.ii: HIV and preg* and induc* and (labor or labour) in title/abstract/keywords; date between 2013 and 2016 (searched 10 November 2016)
N=0

Search 3a.iii: HIV and preg* and (ECV or external cephalic version)
N=0

Search 3a.iv: HIV and preg* and episiotomy
N=0

Search 3b: HIV and preg and (instrument* or ventouse or forceps)*

Databases:	*N*
Cochrane reviews	2
Other reviews	0
Trials (from Cochrane)	1
Technology assessments	0
Economic evaluations	0

Search 3c: HIV and preg and (anomaly or CVS or "chorionic villus sampling" or amniocentesis)*

Databases:	N
Cochrane reviews	0
Other reviews	0
Trials (from Cochrane)	4
Technology assessments	0
Economic evaluations	0

Search 3d: HIV and preg and rupture*

Databases:	N
Cochrane reviews	0
Other reviews	0
Trials (from Cochrane)	3
Technology assessments	0

Economic evaluations	0

Conferences

Conference	N
IAS Conference on HIV Pathogenesis and Treatment	3
International AIDS Conference	1
Conference on Retroviruses and Opportunistic Infections (CROI)	0
European AIDS Clinical Society (EACS)	0
International Congress on Drug Therapy in HIV Infection	0
British HIV Association Annual Conference	0
Children's HIV Association Conference (CHIVA)	0
International Workshop on HIV Paediatrics	0
International Conference on Antimicrobial Agents and Infectious Disease (ICAAC)	0
American Association for the Study of Liver Disease (AASLD)	0
European Association for the Study of the Liver (EASL)	0
International Workshop on HIV and Women	4

Search 4: Neonatal issues

Search terms	(HIV OR "human immunodeficiency virus") AND (SR OR "systematic review" OR random* OR RCT OR observational OR cohort OR "case control" OR "case-control" OR risk OR economic OR cost) AND (prophyla* OR treat* OR intrapartum OR neonat* OR breast OR bottle OR formula OR feed* OR fed OR test*)
Databases	Embase Embase Alert MEDLINE
Limited by	Humans Date: After 01 July 2013 Age group: 6 types searched Baby, High-risk infant, Hospitalized infant, Infant, Newborn, Suckling Document type: 18 types searched (i.e. not bibliography, biography, case study, commentary, correspondence, dictionary/glossary, editorial, interview, memoir/personal document, news): article, book, book chapter, conference, conference paper, conference proceeding, correction/retraction, directory, feature, government & official document, instructional material/guideline, patent, reference document, report, review, speech/lecture, technical report, undefined Language: English
Results	*N*=1331

Cochrane

HIV and (infant or baby or neonate or newborn) and (treat* or prophyla*) in title/abstract/keywords; date between 2013 and 2016 (searched 10 November 2016)

Databases:	N
Cochrane reviews	13
Other reviews	1
Trials (from Cochrane)	190
Methods studies	0
Technology assessments	0
Economic evaluations	2

Search 4a: HIV and (infant or baby or neonate or newborn) and (breast or bottle or formula or feed* or fed) in title/abstract/keywords; date between 2013 and 2016 (searched 10 November 2016)

Databases:	N
Cochrane reviews	1
Other reviews	0
Trials (from Cochrane)	102
Methods studies	0
Technology assessments	0

Economic evaluations	2

Search 4b: HIV and (infant or newborn or neonate or baby) and (test or diagno*) in title/abstract/keywords; date between 2013 and 2016 (searched 10 November 2016)

Databases:	N
Cochrane reviews	6
Other reviews	1
Trials (from Cochrane)	135
Methods studies	0
Technology assessments	0
Economic evaluations	2

Conferences

Conference	N
IAS Conference on HIV Pathogenesis and Treatment	97
International AIDS Conference	1
Conference on Retroviruses and Opportunistic Infections (CROI)	34
European AIDS Clinical Society (EACS)	1
International Congress on Drug Therapy in HIV Infection	1
British HIV Association Annual Conference	2
Children's HIV Association Conference (CHIVA)	1
International Workshop on HIV Paediatrics	49
International Conference on Antimicrobial Agents and Infectious Disease ICAAC	0
American Association for the Study of Liver Disease (AASLD)	0
European Association for the Study of the Liver (EASL)	0
International Workshop on HIV and Women	4

Search 5: Investigations and monitoring in pregnancy

Search terms	(a) (HIV OR "human immunodeficiency virus") AND (SR OR "systematic review" OR random* OR RCT OR observational OR cohort OR "case control" OR "case-control" OR risk OR economic OR cost) AND preg* AND (test* OR monitor* or investigat* OR response OR toxic*) (b) (HIV OR "human immunodeficiency virus") AND (SR OR "systematic review" OR random* OR RCT OR observational OR cohort OR "case control" OR "case-control" OR risk OR economic OR cost) AND preg* AND (screen* OR treat* OR manage*) AND (infect* OR genital OR herpes OR syphilis OR chlamydia OR gonor* OR HPV OR wart OR STI OR "sexually transmitted").
Databases	Embase Embase Alert MEDLINE
Limited by	Humans Date: On or after 1 July 2013 Document type: 18 types searched (i.e. not bibliography, biography, case study, commentary, correspondence, dictionary/glossary, editorial, interview, memoir/personal document, news): article, book, book chapter, conference, conference paper, conference proceeding, correction/retraction, directory, feature, government & official document, instructional material/guideline, patent, reference document, report, review, speech/lecture, technical report, undefined Language: English
Results	(a) *N*=1801; (b) *N*=1705

Cochrane

Search 5a: HIV and preg* and (test* or monitor* or response or toxic* or investigat*) in title/abstract/keywords; date between 2013 and 2016 (searched 10 November 2016)

Databases:	N

Cochrane reviews	23
Other reviews	1
Trials (from Cochrane)	193
Methods studies	0
Technology assessments	0
Economic evaluations	3

Search 5b: HIV and preg* and (screen* or treat* or manage*) and (infect* or genital or herpes or syphilis or chlamydia or gonor* or HPV or wart or STI or "sexually transmitted") in title/abstract/keywords; date between 2013 and 2016 (searched 10 November 2016)

Databases	N
Cochrane reviews	24
Other reviews	2
Trials (from Cochrane)	176
Methods studies	0
Technology assessments	0
Economic evaluations	6

Conferences

Conference	N
IAS Conference on HIV Pathogenesis and Treatment	7
International AIDS Conference	1
Conference on Retroviruses and Opportunistic Infections (CROI)	0
European AIDS Clinical Society (EACS)	1
International Congress on Drug Therapy in HIV Infection	9
British HIV Association Annual Conference	2
Children's HIV Association Conference (CHIVA)	2
International Workshop on HIV Paediatrics	2
International Conference on Antimicrobial Agents and Infectious Disease (ICAAC)	3
American Association for the Study of Liver Disease (AASLD)	0
European Association for the Study of the Liver (EASL)	0
International Workshop on HIV and Women	4

Search 6: Elite controllers (HIV-positive people who maintain an undetectable HIV viral loads without the use of HIV drugs)

Search terms	HIV AND preg* and "elite control*"
Databases	Embase Embase Alert MEDLINE
Limited by	Females, Humans Date: After 01 July 2013 Document type: 18 types searched(i.e. not bibliography, biography, case study, commentary, correspondence, dictionary/glossary, editorial, interview, memoir/personal document, news): article, book, book chapter, conference, conference paper, conference proceeding, correction/retraction, directory, feature, government & official document, instructional material/guideline, patent, reference document, report, review, speech/lecture, technical report, undefined Language: English
Results	N=1

Cochrane

"elite control* and 2013 onwards

N=2 trials

Conferences

Conference	N
IAS Conference on HIV Pathogenesis and Treatment	0
International AIDS Conference	0
Conference on Retroviruses and Opportunistic Infections (CROI)	50
European AIDS Clinical Society (EACS)	0
International Congress on Drug Therapy in HIV Infection	0
British HIV Association Annual Conference	1
Children's HIV Association Conference (CHIVA)	0
International Workshop on HIV Paediatrics	0
International Conference on Antimicrobial Agents and Infectious Disease (ICAAC)	0
American Association for the Study of Liver Disease (AASLD)	0
European Association for the Study of the Liver (EASL)	0
International Workshop on HIV and Women	0

Search 7: Use of cabergoline

Search terms	HIV AND cabergoline
Databases	Embase Embase Alert MEDLINE
Limited by	Humans Date: After 01 July 2013 Document type: 18 types searched article, book, book chapter, conference, conference paper, conference proceeding, correction/retraction, directory, feature, government & official document, instructional material/guideline, patent, reference document, report, review, speech/lecture, technical report, undefined Language: English
Results	*N*=2

Cochrane

HIV and cabergoline and 2013 onwards

N=0

Conferences

Conference	N
IAS Conference on HIV Pathogenesis and Treatment	0
International AIDS Conference	0
Conference on Retroviruses and Opportunistic Infections (CROI)	0
European AIDS Clinical Society (EACS)	0
International Congress on Drug Therapy in HIV Infection	0
British HIV Association Annual Conference	0
Children's HIV Association Conference (CHIVA)	0
International Workshop on HIV Paediatrics	0
International Conference on Antimicrobial Agents and Infectious Disease (ICAAC)	0
American Association for the Study of Liver Disease (AASLD)	0
European Association for the Study of the Liver (EASL)	0
International Workshop on HIV and Women	0

Search 8: Postnatal depression and HIV

Search terms	HIV AND "postnatal depression"

Databases	Embase
	Embase Alert
	MEDLINE
Limited by	Humans
	Date: After 01 July 2013
	Document type: 18 types searched
	article, book, book chapter, conference, conference paper, conference proceeding, correction/retraction, directory, feature, government & official document, instructional material/guideline, patent, reference document, report, review, speech/lecture, technical report, undefined
	Language: English
Results	*N*=15

Cochrane

HIV AND (reten* OR enagage* OR remain* OR continu* OR default* OR discontinue* OR LTFU OR "loss to follow up" OR "lost to follow up") AND (post-partum OR "post partum" OR "after delivery" OR post-natal OR "post natal") and 2013 onwards
N=6 trials

Conferences

Conference	N
IAS Conference on HIV Pathogenesis and Treatment	1
International AIDS Conference	0
Conference on Retroviruses and Opportunistic Infections (CROI)	1
European AIDS Clinical Society (EACS)	0
International Congress on Drug Therapy in HIV Infection	0
British HIV Association Annual Conference	0
Children's HIV Association Conference (CHIVA)	0
International Workshop on HIV Paediatrics	0
International Conference on Antimicrobial Agents and Infectious Disease (ICAAC)	0
American Association for the Study of Liver Disease (AASLD)	0
European Association for the Study of the Liver (EASL)	0
International Workshop on HIV and Women	1

Search 9: Retention in care postpartum

Search terms	HIV AND (reten* OR enagage* OR remain* OR continu* OR default* OR discontinue* OR LTFU OR "loss to follow up" OR "lost to follow up") AND (post-partum OR "post partum" OR "after delivery" OR post-natal OR "post natal")
Databases	Embase
	Embase Alert
	MEDLINE
Limited by	Humans
	Date: After 01 July 2013
	Document type: 18 types searched
	article, book, book chapter, conference, conference paper, conference proceeding, correction/retraction, directory, feature, government & official document, instructional material/guideline, patent, reference document, report, review, speech/lecture, technical report, undefined
	Language: English
Results	*N*=239

Cochrane

HIV AND (reten* OR enagage* OR remain* OR continu* OR default* OR discontinue* OR LTFU OR "loss to follow up" OR "lost to follow up") AND (post-partum OR "post partum" OR "after delivery" OR post-natal OR "post natal") and 2013 onwards:
N=6 trials

Conferences

Conference	N
IAS Conference on HIV Pathogenesis and Treatment	3
International AIDS Conference	2
Conference on Retroviruses and Opportunistic Infections (CROI)	8
European AIDS Clinical Society (EACS)	5
International Congress on Drug Therapy in HIV Infection	1
British HIV Association Annual Conference	4
Children's HIV Association Conference (CHIVA)	0
International Workshop on HIV Paediatrics	9
International Conference on Antimicrobial Agents and Infectious Disease (ICAAC)	0
American Association for the Study of Liver Disease (AASLD)	0
European Association for the Study of the Liver (EASL)	5
International Workshop on HIV and Women	6

Search 10: Postpartum adherence and psychosocial support

Search terms	(a) HIV AND adhere* AND (post-partum OR "post partum" OR "after delivery" OR post-natal OR "post natal") (b) HIV AND support AND (post-partum OR "post partum" OR "after delivery" OR post-natal OR "post natal")Limits
Databases	Embase Embase Alert MEDLINE
Limited by	Humans Date: After 01 July 2013 Document type: 18 types searched article, book, book chapter, conference, conference paper, conference proceeding, correction/retraction, directory, feature, government & official document, instructional material/guideline, patent, reference document, report, review, speech/lecture, technical report, undefined Language: English
Results	*N*=29, *N*=92

Cochrane

10a: HIV AND adhere* AND (post-partum OR "post partum" OR "after delivery" OR post-natal OR "post natal") and 2013 onwards:
N=5 trials
10b: HIV AND support AND (post-partum OR "post partum" OR "after delivery" OR post-natal OR "post natal") and 2013 onwards:
N=3 trials

Conferences

Conference	N
IAS Conference on HIV Pathogenesis and Treatment	0
International AIDS Conference	2
Conference on Retroviruses and Opportunistic Infections (CROI)	5
European AIDS Clinical Society (EACS)	9
International Congress on Drug Therapy in HIV Infection	2
British HIV Association Annual Conference	4
Children's HIV Association Conference (CHIVA)	0
International Workshop on HIV Paediatrics	5
International Conference on Antimicrobial Agents and Infectious Disease (ICAAC)	0
American Association for the Study of Liver Disease (AASLD)	0
European Association for the Study of the Liver (EASL)	0
International Workshop on HIV and Women	4

Search 11: Clinical management of postpartum women

Search terms	HIV AND (treat* OR manage* OR therap* OR care) AND (post-partum OR "post partum" OR "after delivery" OR post-natal OR "post natal")
Databases	Embase Embase Alert MEDLINE
Limited by	Date: After 01 July 2013 Document type: 18 types searched article, book, book chapter, conference, conference paper, conference proceeding, correction/retraction, directory, feature, government & official document, instructional material/guideline, patent, reference document, report, review, speech/lecture, technical report, undefined Language: English
Results	*N*=211

Cochrane

HIV AND (treat* OR manage* OR therap* OR care) AND (post-partum OR "post partum" OR "after delivery" OR post-natal OR "post natal") and 2013 onwards;
N=23 trials

Conferences

Conference	N
IAS Conference on HIV Pathogenesis and Treatment	0
International AIDS Conference	1
Conference on Retroviruses and Opportunistic Infections (CROI)	18
European AIDS Clinical Society (EACS)	0
International Congress on Drug Therapy in HIV Infection	0
British HIV Association Annual Conference	1
Children's HIV Association Conference (CHIVA)	0
International Workshop on HIV Paediatrics	2
International Conference on Antimicrobial Agents and Infectious Disease (ICAAC)	0
American Association for the Study of Liver Disease (AASLD)	0
European Association for the Study of the Liver (EASL)	0
International Workshop on HIV and Women	0

Search 12: Bonding advice

Search terms	HIV AND bond* AND (infant OR neonate OR child OR baby)
Databases	Embase Embase Alert MEDLINE
Limited by	Humans Date: After 01 July 2013 Document type: 18 types searched article, book, book chapter, conference, conference paper, conference proceeding, correction/retraction, directory, feature, government & official document, instructional material/guideline, patent, reference document, report, review, speech/lecture, technical report, undefined Language: English
Results	*N*=48

Cochrane

HIV AND bond* AND (infant OR neonate OR child OR baby) and 2013 onwards;
N=1 trial

Conferences

Conference	N
IAS Conference on HIV Pathogenesis and Treatment	3
International AIDS Conference	0
Conference on Retroviruses and Opportunistic Infections (CROI)	0
European AIDS Clinical Society (EACS)	0
International Congress on Drug Therapy in HIV Infection	0
British HIV Association Annual Conference	0
Children's HIV Association Conference (CHIVA)	0
International Workshop on HIV Paediatrics	0
International Conference on Antimicrobial Agents and Infectious Disease (ICAAC)	0
American Association for the Study of Liver Disease (AASLD)	0
European Association for the Study of the Liver (EASL)	0
International Workshop on HIV and Women	0

Search 13: Multidisciplinary team

Search terms	HIV AND (multidisciplinary OR MDT) AND (preg* OR deliver* or postnatal OR post-natal OR birth OR "post partum" OR post-partum)
Databases	Embase Embase Alert MEDLINE
Limited by	Humans Date: After 01 July 2013 Document type: 18 types searched article, book, book chapter, conference, conference paper, conference proceeding, correction/retraction, directory, feature, government & official document, instructional material/guideline, patent, reference document, report, review, speech/lecture, technical report, undefined Language: English
Results	N=111

Cochrane

N=4 trials

Conferences

Conference	N
IAS Conference on HIV Pathogenesis and Treatment	24
International AIDS Conference	0
Conference on Retroviruses and Opportunistic Infections (CROI)	6
European AIDS Clinical Society (EACS)	0
International Congress on Drug Therapy in HIV Infection	0
British HIV Association Annual Conference	0
Children's HIV Association Conference (CHIVA)	0
International Workshop on HIV Paediatrics	0
International Conference on Antimicrobial Agents and Infectious Disease(ICAAC)	0
American Association for the Study of Liver Disease (AASLD)	0
European Association for the Study of the Liver (EASL)	0
International Workshop on HIV and Women	1