Appendix 1: PICO questions

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Appendix 2: Summary of the modified GRADE system

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

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

References

1. British HIV Association. *BHIVA Guideline Development Manual*. 28 January 2014. Available at: www.bhiva.org/GuidelineDevelopmentManual.aspx (accessed August 2015).

2. GRADE Working Group. Grading the quality of evidence and the strength of recommendations. Available at: www.gradeworkinggroup.org/intro.htm (accessed August 2015).

3. Guyatt GH, Oxman AD, Kunz R *et al.* Going from evidence to recommendations. *BMJ* 2008; **336**: 1049–1051.

Appendix 3: Drug dosing for infants

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

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