University College London Hospitals NHS
NHS Foundation Trust

Viral Hepatitis in Pregnancy

Clinical Guideline

Trust and Network-wide

Author(s)	**Dr Eleni Nastouli,** Consultant Virologist, University College London Hospitals **Dr Mike Jacobs**, Consultant in Infectious Diseases, Royal Free Hospital **Dr Andrew Millar**, Consultant Gastroenterologist, North Middlesex Hospital **Dr Dianne Irish**, Consultant Virologist, Royal Free Hospital **Dr Deepak Suri**, Consultant Hepatologist, Whittington
Owner/Sponsor	North Central London Viral Hepatitis Network (NCLVHN)
Review By Date	17.01.2014
Responsible Director	Dr Paul Glynne, Medical Director Medicine Board
Monitoring Committee	The authors on behalf of the NCLVHN
Target Audience	Clinical staff in Maternity, Neonatal Unit, Virology and Viral Hepatitis clinic
Related Trust Documents/Policies	N/A
Number of Pages and Appendices	13 pages including 2 Appendices
Equalities Impact Assessment	Low

UCL HOSPITALS

UCL Hospitals is an NHS Foundation Trust comprising: The Eastman Dental Hospital, The Heart Hospital, Hospital for Tropical Diseases, National Hospital for Neurology and Neurosurgery, The Royal London Hospital for Integrated Medicine and University College Hospital (incorporating the former Middlesex and Elizabeth Garrett Anderson Hospitals).

University College London Hospitals NHS
NHS Foundation Trust

Document control information

Version Number	01
Approved By *Delete as appropriate*	Clinical Guidelines Committee
Date Approved	17th January 2012
Publication Date	29th February 2012
Document Control Number	ExCPG/01/01
Title & version number / doc control number of document this replaces	N/A
Summary of significant changes	New - N/A

UCL HOSPITALS

UCL Hospitals is an NHS Foundation Trust comprising: The Eastman Dental Hospital, The Heart Hospital, Hospital for Tropical Diseases, National Hospital for Neurology and Neurosurgery, The Royal London Hospital for Integrated Medicine and University College Hospital (incorporating the former Middlesex and Elizabeth Garrett Anderson Hospitals).

Contents

Section			Page number
1.0	Summary		2
2.0	Introduction		2
3.0	Objectives		3
4.0	Scope		3
5.0	Definitions		3
6.0	Duties & Responsibilities		3
7.0	Development & Evidence Base		3
8.0	Consultation		3
9.0	Hepatitis B		4
	9.1	Antenatal testing	4
	9.2	Referral of women with HBV infection	4
	9.3	Laboratory investigations	4
	9.4	Management of labour	5
	9.7	Breastfeeding	7
	9.8	Family management	8
10.0	Hepatitis C		8
	10.1	Testing	8
	10.2	Delivery & breastfeeding	9
	10.3	Neonatal follow-up	9
11.0	Guidance Implementation		9
12.0	Monitoring compliance		10
13.0	References		10

Appendices

Appendix 1	12
Appendix 2	13

1.0 Summary

1.1 The guideline was developed following recommendations of a Sector-wide audit of management of pregnant women with HBV infection and their infants (2009 - 2010) and new recommendations from the Infectious Diseases Antenatal Screening Programme in 2011.

1.2 The key points:

HBV

Offer HBV screening to all women booking in at UCLH

Notification of all women that test positive by Virology

Prompt referral of all women that test positive within six weeks to the Viral Hepatitis Service

Management of HBV infection in pregnancy to be Consultant led especially with regards to antiviral treatment

Ensuring appropriate post exposure prophylaxis (vaccination +/- HBIG) is given to all infants

Ensure all infants are appropriately tested at the end of vaccination and appropriate referral is made if identified to be infected

Ensure advice for screening of the family is given

HCV

Offer screening for HCV infection to all women at risk

Prompt referral to the Viral Hepatitis Service of all women that are identified

Appropriate counselling regarding management of pregnancy, delivery and breastfeeding is given

Ensure infants are followed up and referral of those identified as infected is made

2 Introduction

Screening for viral hepatitis in pregnancy is part of the NHS Infectious Diseases in Pregnancy Screening Programme. The purpose of this document is to provide recommendations for the policies in place in the centres affiliated with the NCLVHN.

The teams within the hospital usually involved in the care of women with viral hepatitis in pregnancy are: Obstetrics (usually there is a dedicated midwife), Viral Hepatitis Services, Neonatology, Virology and Pharmacy. Although their individual role might differ between Trusts, policies and systems should be in place to ensure flow of information.

Clinical care for these women and their pregnancies should be provided by multidisciplinary approach with communication regarding follow up, testing, treatment and neonatal management and follow up as key factors for the success of the screening programme.

3 Objectives

3.1 The aim of the guideline is to act as guidance for all clinical staff involved in the management of women with viral hepatitis and their infants during pregnancy. The disciplines involved are: Maternity, Neonatal and Viral Hepatitis Services and Diagnostic Virology.

4 Scope

This document applies to:

4.1 All clinical staff involved in the care of pregnant women with viral hepatitis and their infants.

4.2 Pregnant women with viral hepatitis and their infants.

4.3 Maternity, Neonatal, Viral Hepatitis Services and Diagnostic Virology.

5 Definitions

HBV infection: chronic hepatitis B infection

HCV infection: chronic hepatitis C infection

HBV: Hepatitis B virus

HCV: Hepatitis C virus

HBIG: Hepatitis B Immunoglobulin

6 Duties & Responsibilities

6.1 The authors have co-ordinated the development of the guideline and will be responsible for monitoring implementation on behalf of the NCLVHN

6.2 The Consultants leading the implementation of the guideline at UCLH are: Dr Nastouli, Dr Whitten, Dr Sellwood, Dr Meek, with the significant contribution of the Specialist Midwife Jonathan Dominguez-Hernandez and the Antenatal Screening Coordinator Alison Fiddler.

7 Development & Evidence Base

See Section 13.0, references

8 Consultation

Contributors

North Middlesex Hospital

Royal Free Hospital:
Dr Anna Maria Geretti, Consultant Virologist
Dr Vivienne van Someren, Consultant Paediatrician

Anne Whitewright
Janet Catt, Lead Nurse in Viral Hepatitis

University College London Hospitals
Dr Melissa Whitten, Consultant Obstetrician
Jonathan Hernandez-Dominguez, Specialist Midwife
Dr Mark Sellwood, Consultant Neonatologist
Dr Judith Meek, Consultant Neonatologist
Dr Kate Ward, Consultant Virologist
Dr Mike Kidd, Consultant Virologist
Prof Deenan Pillay, Consultant Virologist

Whittington Hospital
Dr Deepak Suri, Consultant Hepatologist

Prof Geoff Dusheiko and Prof William Rosenberg reviewed the guideline.

9 Hepatitis B

The aim of antenatal screening for infection with hepatitis B virus (HBV) is twofold; a) to avoid mother-to-child transmission and b) to identify chronically infected women so that they can be followed up during and after pregnancy. For women found to have chronic HBV infection it is also an opportunity to advise testing of their extended family.

9.1 Antenatal testing

All pregnant women attending for booking should be offered **screening for HBV** infection. The benefits of testing should be explained. If declined, they should be offered re-screening at no later than 28 weeks by a senior member of the Antenatal Team. In case of late booking (after 24 weeks) the lab should be notified and an urgent result should be obtained. Women presenting in labour without booking blood results should be consented for testing and the on call Consultant Virologist/Microbiologist should be contacted to arrange this urgently.

9.2 Referral of women with HBV infection

All Hepatitis B surface antigen (HBsAg) positive women should be **referred to a Viral Hepatitis Service** for follow up during their pregnancy and afterward. An appointment should be offered within six weeks of the positive result or before 32 weeks gestational age (GA) whichever is sooner.

9.3 Laboratory Investigations

All pregnant women with HBV infection should have the following **further investigations** in order to:

9.3.1 Assess the HBV infection

Confirmatory HBV serology (Hepatitis B surface antigen, HBeAg and anti-Hbe).

HBV DNA should be performed preferably twice at least three months apart during pregnancy with one test at 28-32 weeks GA. This is in order to better assess the risk of mother infant transmission and inform mothers

of this risk and the opportunity for antiviral prophylaxis to prevent transmission to their infant.

9.3.2 Investigate liver disease

Full blood count, liver function tests including ALT, albumin, renal function, electrolytes, prothrombin time and APTT. (AFP is produced by the yolk sac and foetus and values are typically raised during pregnancy but may be reduced in infants with Downs syndrome. It should not be performed during pregnancy).

9.3.3 Test for blood-borne viral infections

HIV antibody, hepatitis C (HCV) antibody, hepatitis delta (HDV) antibody

9.4 Management of labour

Invasive procedures during labour and delivery (ie fetal scalp monitoring) should be avoided. Caesarean section may reduce the risk of transmission but this is not routinely advocated [7]

9.5 Neonatal Management

All infants born to HBsAg positive mothers should receive HBV vaccination according to the schedule recommended by the Department of Health (DoH) in the Green Book (HBV vaccine at a dose of 10µg at 0,1,2 and 12 months)

Additionally, HBIG (200 IU at a different site and within 24hrs after birth) should be administered when the risk of transmission is high; see table below

Hepatitis B status of mother	**Baby should receive**	
	Hepatitis B vaccine	**HBIG**
HBsAg positive and HBeAg positive	Yes	Yes
HBsAg positive, HBeAg negative, anti-HBe negative	Yes	Yes
HBsAg positive and HBeAg/eAb- not determined	Yes	Yes
Mother had acute hepatitis B during pregnancy	Yes	Yes
HBsAg positive and HBV DNA level equal or above $1x10^6$ IU/ml	Yes	Yes
HBsAg positive, HBeAg neg, anti-HBe positive And HBV DNA $<10^6$ IU/ml HBIG should also be considered if 1. there is a history of transmission in a previous pregnancy 2. babies weigh <1500g at birth	Yes	No

All infants, following the fourth dose of vaccination should be tested for HBsAg and anti-HBs

9.6 Antiviral treatment in pregnancy

Lamivudine, tenofovir or tenofovir plus emtricitabine and telbivudine have been used in pregnancy:

Tenofovir: potent, not associated with resistance, appears to be safe from data from Pregnancy Registries however extensive data lacking. FDA category B.

Lamivudine: extensively used, appears to be safe. Low genetic barrier to resistance. FDA category C.

Telbivudine: tested in clinical trials in Asia. Higher potency than lamivudine, relatively low genetic barrier to resistance. Not NICE approved (FDA category B)

Antiviral treatment in pregnancy should always be prescribed by a Consultant in the Viral Hepatitis Clinic.

9.6.1 **Women diagnosed before pregnancy** and not on antiviral treatment.

The likelihood of future pregnancy should be taken into account if starting antiviral therapy in women of child bearing age. Treatment of most young women planning a pregnancy can be deferred as many childbearing women with minimal liver disease may not require immediate antiviral therapy. Pegylated interferon alpha can be considered if indicated because of the possibility of a finite period of treatment; however conception should be avoided.

Alternatively for women requiring treatment, and who may (or may wish to) conceive while on treatment, Tenofovir may be the preferred treatment in view of the FDA classification (Category B) and experience in the first trimester of pregnancy in HIV and/or HBV positive women (Anti-retroviral pregnancy registry). However although clinical trials to interrupt transmission with lamivudine and telbivudine have been completed in pregnancy, no clinical trials with tenofovir in pregnancy have been done.

The principal indication to treat hepatitis B positive mothers throughout pregnancy should be the necessity for treatment of chronic hepatitis B in the mother. Women who become pregnant while on antiviral treatment should be referred urgently to their treating physician for further specialist management. If treatment was required for active hepatitis B, before pregnancy, it could be continued during and after pregnancy. However, the potential teratogenicity of nucleoside analogues and the potential risk of developmental defects in the infant must be clearly elucidated, and informed consent obtained. The antiretroviral pregnancy registry does not provide sufficient information regarding the *specific* nature of congenital abnormalities, and does not rule out development abnormalities such as an effect on ossification. (see breast feeding below)

Some women may choose to stop therapy once pregnant. Also, women on entecavir should be given the choice of a switch to tenofovir, as entecavir has not been studied in pregnancy and there is little registry data for this agent. The potential risks of stopping antiviral therapy

during pregnancy, particularly a severe hepatitis flare in pregnancy, should be discussed, and patients should be closely monitored.

9.6.2 **Women diagnosed during pregnancy** who require immediate treatment for their liver disease because of severe hepatitis B should be offered tenofovir. The same tenets as 5a apply. Tenofovir may be combined with lamivudine but this is seldom indicated in mono-infected women. Treatment will need to be continued in these patients post partum (see breast feeding below).

9.6.3 **Antiviral prophylaxis to prevent mother-infant transmission.** HBV vaccine and HBIG are effective in reducing most mother-infant transmission**.** A proportion of infants born to HBsAg mothers acquire hepatitis B despite prophylaxis. Estimates vary, but the risk is related to the presence of HBeAg and maternal viraemia: maternal concentrations of HBV DNA of greater than 10^8 copies/ml (or 2 x 10^7 IU/ml) confer a 10% or more risk of transmission despite HBIG and vaccination. Antiviral prophylaxis with tenofovir or lamivudine in the third trimester should be considered for women with HBV DNA >10^7 IU/ml. Women commencing antiviral **treatment to avoid transmission** should do so no later than 32 weeks. Short term lamivudine use is not thought to confer a high risk of resistance. However the potential teratogenicity of nucleoside analogues and the potential risk of developmental defects in the infant must be clearly elucidated, and informed consent obtained.

Therapy should be stopped at some early point post partum, perhaps after 4 weeks when the immunological perturbations of pregnancy may be less likely to exacerbate a potential flare in hepatitis B. Careful post treatment monitoring is required because of the risk of exacerbations.

9.6.4 **Women with a history of previous transmission** should be carefully assessed and counselled in the viral hepatitis clinic. Antiviral prophylaxis together with vaccination/HBIG for their babies should be discussed on the ground elucidated above.

9.7 Breastfeeding

HBsAg can be detected in breast milk, but breast feeding is not considered a contraindication in positive mothers. Women on antiviral treatment that want to breastfeed should be counselled as follows:

Women on tenofovir: “breastfeeding is not recommended” according to the drug label. A pharmacokinetic study in lactating rhesus macaques has shown that tenofovir is detected in the milk of the animals, but the peak concentrations (2 to 3 µM) were approximately 2 to 4% of those detected in serum. Recently tenofovir concentrations in breast milk of African mothers have been reported [8.] The median doses ingested via breast-feeding by a neonate weighing 3 kg are calculated to be 0.03% of the tenofovir dose proposed to prevent HIV transmission in neonates. Data already available for lamivudine suggest that the infant median daily doses received from breast milk corresponded to 2%, of the recommended infant daily doses [9].

Informed consent should be obtained and the risks and potential advantages explained. Women on lamivudine: Similar considerations as above apply.

9.8 Family Management

Screening of all **family members** for HBV infection should be strongly recommended and the GP should be advised accordingly.

10 Hepatitis C

10.1 Testing

Testing for infection with hepatitis C virus (HCV) is not part of the routine antenatal screening offered to women in the UK. However it is recommended that "high risk" populations should be targeted for screening. Obstetricians and midwives should therefore **offer testing** to the following women (www.cks.nhs.uk):

- women with unexplained abnormal liver function tests or jaundice
- women who are currently injecting drug users
- women who have injected drugs in the past even if only once
- women who are blood or organ recipients in the UK and who have received:
  - whole blood or organs prior to 1992
  - blood products prior to 1986
- women who are healthcare workers who have been accidentally exposed to blood where there is a risk of hepatitis C (ie needlesticks)
- women who have received medical, cosmetic or dental treatment (or any other invasive treatment or blood transfusion) in countries where hepatitis C is common and infection control maybe poor
- women who have had tattoos or body piercing where unsterilized equipment may have been used
- women that tested positive for HIV and/or HBV
- women that have or are currently snorting or smoking drugs (such as cocaine) particularly if they have shared straws or pipes
- if their partners are known to have chronic HCV infection
- women born in countries where HCV infection is endemic ie Bangladesh, Pakistan, India, Egypt, Japan, Eastern Europe, Sub-saharan Africa.

Women offered testing should have a pre-test discussion informing them about the benefits of testing.

The screening test is HCV antibody and if this is reactive, confirmation of this result in a separate sample is required. HCV RNA is also performed to confirm active, chronic infection. Women with chronic HCV infection should be **referred to a Viral Hepatitis Service**.

10.2 Delivery and breastfeeding

With regards to **the mode of delivery**, Caesarean section is not routinely recommended to avoid HCV transmission. It is however recommended when there is prolonged rupture of membranes (>6 hours) and for women co-infected with HIV.

Invasive procedures and monitoring (ie fetal scalp electrodes) during labour should be avoided.

Women monoinfected with HCV can **breastfeed** if they wish unless cracked nipples are present.

10.3 Neonatal follow up

The transmission risk is reported between 3-7%. The **neonatal follow up** consists of an HCV antibody test at 12 months. It is at the discretion of each Trust whether in addition HCV RNA is tested at birth and 3-4 months.

11 Guidance Implementation

11.1 Available via Insight

11.2 Presentation in Departmental meetings in Virology, Maternity, Neonatal Unit. Hepatology

11.3 Incorporate as teaching session in Departmental teaching programmes in all Departments involved (above)

12 Review, Monitoring & Compliance

Key process for which compliance or effectiveness is being monitored	Monitoring method (i.e. audit, report, on-going committee review, survey etc.)	Job title and department of person responsible for leading the monitoring	Frequency of the monitoring activity	Monitoring Committee responsible for receiving the monitoring report/audit results etc.	Committee responsible for ensuring that action plans are completed At UCLH
Management of women with viral hepatitis and their infants in pregnancy	Yearly audit and report	Dr Eleni Nastouli Consultant Virologist	One year after implementation And every two years after that	Authors on behalf of the NCLVHN	Dr Eleni Nastouli Dr Melissa Whitten Dr Mark Sellwood Dr Judith Meek Jonathan Dominguez-Hernandez Alison Fiddler

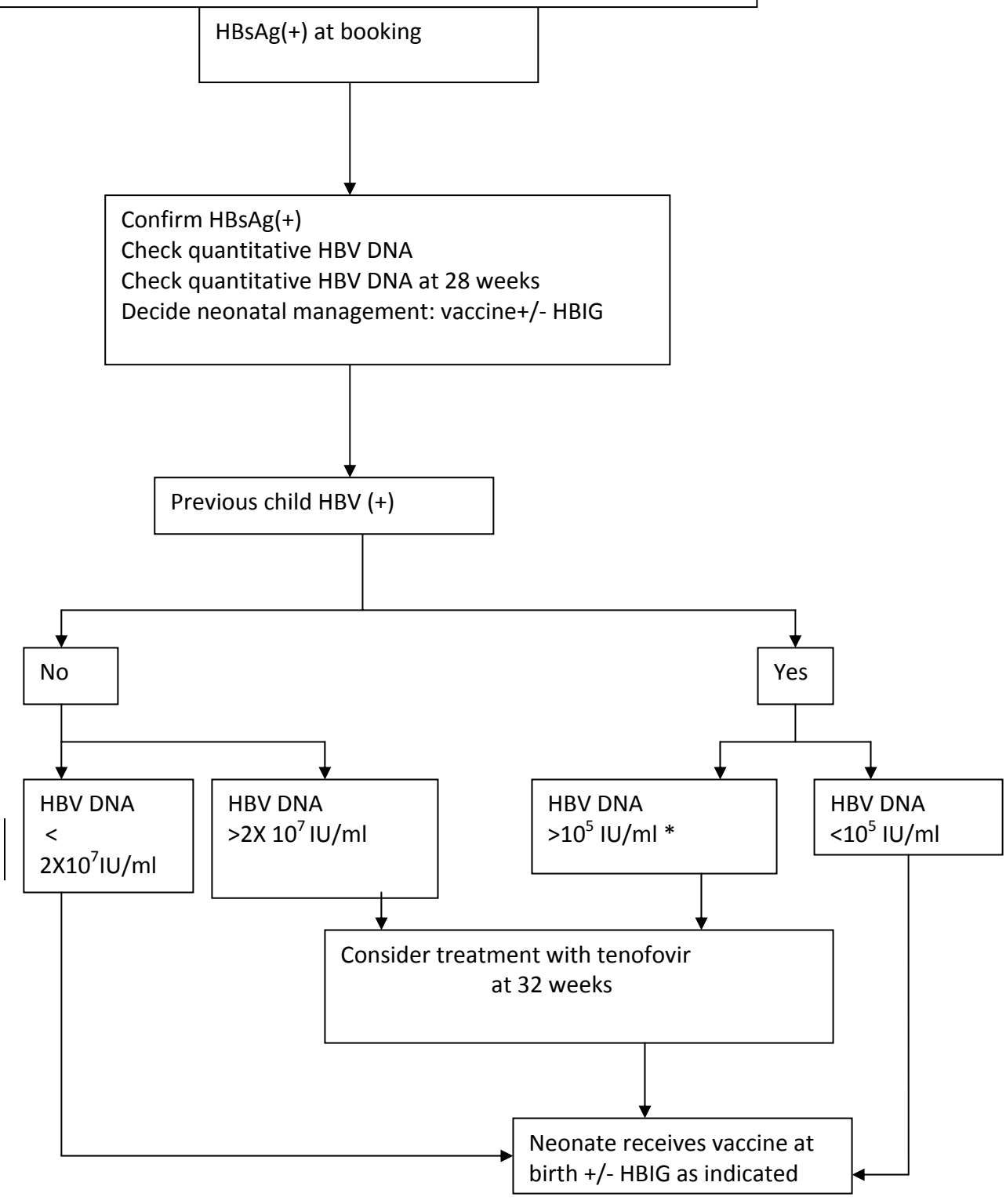
13 References

1. http://infectiousdiseases.screening.nhs.uk/standards
2. www.basl.org.uk BVHG consensus on management of HBV in pregnancy 2008
3. www.easl.eu Guideline for management of HBV infection
4. www.dh.gov.uk Green Book on Immunisation
5. Tran T. Management of hepatitis B in pregnancy: Weighing the options Cleve Clin J Med Vol 76 Supp 3 May 2009
6. Xu WM et al Lamivudine in late pregnancy to prevent perinatal transmission of hepatitis B virus infection J Viral Hepat 2008
7. Lee SD, Lo KJ, Tsai YT, Wu JC, Wu TC, Yang ZL et al. Role of caesarean section in prevention of mother-infant transmission of hepatitis B virus. Lancet 1988 October 8;2(8615):833-4.
8. Van Rompay KK, Hamilton M, Kearney B, Bischofberger N. Pharmacokinetics of tenofovir in breast milk of lactating rhesus macaques. Antimicrob Agents Chemother 2005 May;49(5):2093-4.

9. Benaboud S, Pruvost A, Coffie PA, Ekouevi DK, Urien S, Arrive E et al. Concentrations of tenofovir and emtricitabine in breast milk of HIV-1-infected women in Abidjan, Cote d'Ivoire, in the ANRS 12109 TEmAA Study, Step 2. Antimicrob Agents Chemother 2011 March;55(3):1315-7

14. Appendices

Appendix 1: Management of HBV infection in pregnancy



* Although there is no evidence to support antiviral treatment at this specific level of HBV DNA in these cases treatment should be considered and discussed at the Viral Hepatitis MDT

Adapted from Tran T et al 2009

Appendix 2: Management of the neonate (information available at the time of birth)

Hepatitis B status of mother	Baby should receive	
	HB vaccine	HBIG
HBsAg positive and HBeAg positive	Yes	Yes
HBsAg positive, HBeAg negative, anti-HBe negative	Yes	Yes
HBsAg positive and HBeAg/eAb not determined	Yes	Yes
Mother had acute hepatitis B during pregnancy	Yes	Yes
HBsAg positive, HBeAg neg, anti-HBe positive and HBV DNA $<1X10^6$ IU/ml	Yes	No
HBsAg positive and HBV DNA level equal or above $1x10^6$ IU/ml	Yes	Yes
Babies born < 1500g to HBV infected mothers regardless of HBeAg/eAb markers and HBV DNA level	Yes	Yes