National Institute for Health and Clinical Excellence

Hepatitis B Guideline
Guideline Consultation Comments Table
March 2013

Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
SH	Advisory Group on Hepatitis (AGH)	1	Full	General	General	This is a very impressive document with much valuable information.	Thank you for your comment.
SH	Advisory Group on Hepatitis (AGH)	2	Full	43	2	Should be more explicit that family members and other close contacts should be screened for HBV and discuss importance of vaccination (3 dose course) and relevance of testing for immunity following vaccination If IFN is advised, information should include the risks to the unborn in case of pregnancy during the treatment and the importance of pregnancy testing prior to starting therapy and offer contraceptive advice.	Thank you for your comment. Screening and vaccination are outside the scope of this guideline. The guideline cross refers to the NICE Public Health Guideline 43; Hepatitis B and C: ways to promote and offer testing to people at increased risk of infection. This clinical guideline should be used in conjunction with the public health guideline. The following footnote has been added to recommendation 41: "Avoid use of peginterferon alfa-2a in pregnancy unless the potential benefit outweighs risk. Women of childbearing potential must use effective contraception throughout therapy".
SH	Advisory Group on Hepatitis (AGH)	3	Full	46	7	Consider adding: Screen other children in the family	Thank you for your comment. The guideline cross refers to the NICE Public Health Guideline 43; Hepatitis B and C: ways to promote and offer testing to people at increased risk of infection. This

							clinical guideline should be used in conjunction with the public health guideline.
SH	Advisory Group on Hepatitis (AGH)	4	Full	46	19	Include in baseline tests anti-HBc IgG as well as IgM	Thank you for your comment. This test is not relevant for people who are HBsAg positive.
SH	Advisory Group on Hepatitis (AGH)	5	Full	46	26	Children with chronic HBV should be managed by a paediatric hepatologist/specialist with interest in hepatology in a specialist centre with the paediatric MDT trained to manage and support children with HBV and their families	Thank you for your comment. There are very few centres currently available and therefore it would not be practical to make such a recommendation. We have recommended that children are seen by paediatric specialists.
SH	Advisory Group on Hepatitis (AGH)	6	Full	46	28	Consider adding • The referring health professional should include the child's HBV vaccination schedule with dates when applicable. • Include information of parents and siblings to ascertain transmission route	Thank you for your comment. Whether infection of a new-born occurs as a result of no vaccination or inadequate vaccination has no significance in terms of further action as regard treatment of the infant.
SH	Advisory Group on Hepatitis (AGH)	7	Full	46	31	A comment needs to be included about the confounding effect of high ALT values on fibroscan readings. The document correctly lists fat and other confounders but inflammation (detected by a raised ALT) is well recognised as a confounder and should be included.	Thank you for your comment. We have added to the linking evidence to recommendations section. The GDG felt that this issue would be covered by the training recommendation. The linking evidence to recommendation table now says, "All non-invasive tests are surrogate tests that do not directly measure fibrosis. Therefore they are influenced by other factors including the level of liver inflammation and fatty infiltration. Although the evidence on the effect of

							ALT on test accuracy was inconsistent, the GDG noted that raised ALT levels may due to causes other than chronic hepatitis B. The GDG anticipated that this would be part of the awareness training offered in the recommendation." The GDG decided to differentiate between an active CHB and an inactive CHB infection, in which the ALT elevation is due to some other chronic liver disease, by adding an HBV DNA requirement to the transient elastography recommendation for cirrhosis. The GDG noted that patients with raised ALT levels due to other factors, who had a TE score between 6 and 10 kPa, would be offered a biopsy and other causes would be distinguished.
SH	Advisory Group on Hepatitis (AGH)	8	Full	47	27	ALT levels, in paediatrics, are age and gender specific. The levels quoted may be within normal range. It may be better to state ALT above the normal level.	Thank you for your comment. The primary evidence for the variation of ALT levels by age and gender is weak and future studies are unlikely due to the ethical constraints of taking blood samples from healthy children. Most children without liver disease have ALT levels in single figures or low teens. This is a research priority, but it is valid to challenge current 'received wisdom' and in the absence of better data we should stand by the realignment of paediatric values in keeping with thresholds for young adults.
SH	Advisory Group on Hepatitis (AGH)	9	Full	47	34	No clear description of management of the patient with low level ALT/HBV DNA and significant fibrosis on a liver biopsy. The management of patients where the serology	Thank you for your comment. The GDG therefore decided to differentiate between an active CHB and an inactive CHB infection, in which the ALT elevation is

						is not matched by the liver biopsy findings is challenging and recommendations would be useful	due to some other chronic liver disease, by adding an HBV DNA requirement to the transient elastography recommendation for cirrhosis. They also recommended fairly frequent monitoring of these people with high TE levels, but low levels of viraemia, for example every 12-24 weeks, at the discretion of the clinician. If HBV DNA levels became detectable on any one occasion, the patient would be offered antiviral treatment. Therefore the monitoring recommendation 75 was also changed.
SH	Advisory Group on Hepatitis (AGH)	10	Full	48	10	Liver biopsy is not a requirement before initiating treatment. Treatment decisions in children are based on ALT levels and HBV DNA levels. No paediatric hepatologist would insist on demonstrating fibrosis before considering treatment. Selection of children with abnormal ALT has been accepted as an entry criteria for clinical trials because these children are more likely to respond.	Thank you for your comment. We accept that not every child/young person requires a biopsy prior to starting treatment. However in young people arriving for example as migrants from endemic regions with high viral loads and active transaminitis, it will be unclear how long they have been in an immune-reactive phase of infection and they may have advance fibrosis. Perhaps more importantly, the liver biopsy may reveal other pathologies and save the need for embarking on antiviral treatment. Recommendation 25 has been amended to read ‘consider’ rather than ‘offer’.
SH	Advisory Group on Hepatitis (AGH)	11	Full	49	50	There is no evidence to base the recommendation that children should be treated with 48 weeks pegylated interferon, nor to start with an antiviral if no response to pegylated interferon. Clinical trials are now in progress to evaluate the efficacy of this treatment	Thank you for your comment. These recommendations were based on GDG consensus as noted in the linking evidence to recommendations section.

SH	Advisory Group on Hepatitis (AGH)	12	Full	50	22	It is not clear how the threshold of 10^7 log10 IU/ml was selected. The studies cited in the analysis mostly used between 10^6 and 10^7 copies/ml as threshold. When translated to IU/ml this equates to between 200,000 to 2,000,000 IU/ml. Hence, a threshold of HBV DNA > 106 IU/ml would be closer to where the evidence came from. In addition, the Green Book recommendation for HBIG for the baby also uses HBV DNA > 10^6 IU/ml as a criterion. This will make the management algorithm less complicated in that HBV DNA > 10^6 IU/ml in the pregnant woman is considered as a higher risk category triggering both antiviral for the mother during the third trimester and HBIG for the baby at birth.	Thank you for your comment. The GDG did not examine studies on different vaccination strategies. The comment that the Green Book recommends Hepatitis B immune globulin (HBIG) for the baby whose mothers had HBV viraemia over 10^6IU/ml is not inconsistent with this guidance. This guidance refers to the treatment of mothers with viraemia over 10^7IU/ml. The former is to guide prophylaxis for the babies, the latter is about relating the risk of transmission with the level of viraemia in the mothers and offering the mothers the additional strategy which would reduce their viral load and reduce the risk of transmission. There are few long term follow up studies to prove safety in the babies, other than those in HIV treated women, the safety margin of using 10^7 makes sure that only the mothers at greatest risk of infecting their babies are offered treatment. The level of 10^6Iu/ml for the addition of HBIG to the prophylaxis for the babies was an arbitrary level based on best evidence at the time. There are no studies of treatment in the mothers which include data on babies at risk given vaccine alone; all use vaccine plus immune globulin, so there is no data to support the discontinuation of the use of HBIG.
SH	Advisory Group on Hepatitis (AGH)	13	Full	51	6	This recommendation seems to assume that anti-HBc is the screening test before starting immunosuppression therapy. Using anti-HBc alone as a screening test in this	Thank you for your comment. We have amended recommendation 68 to include people who are HBsAg and/or anti-HBc positive.

						patient population is not safe as there are many examples of individuals who do not mount anti-HBc response despite being HBsAg positive. This could be related to the underlying disease such as HIV or haematological malignancy. The guidelines should instead state that both HBsAg and anti-HBc should be screened before starting immunospuppresion therapy. Individuals tested positive for either or both of these two HBV markers should be further tested for HBV DNA level and ALT. It is not clear what the use of anti-HBs is in this context, as the subsequent management algorithm does not use the anti-HBs information at all. If a laboratory result does not affect management, it should not be listed as a requirement in the guidelines.	
SH	Advisory Group on Hepatitis (AGH)	14	Full	51	13	The studies cited in the analysis offered prophylaxis to HBsAg positive individuals regardless of their HBV DNA level. The threshold of HBV DNA < 2000 IU/ml is based on the criterion for defining inactive HBV infection in the otherwise normal population and it is not certain if this is applicable to a patient group who is being immunosuppressed. The guidelines would be much simpler if it simply stated that “In people who are HBsAg positive, offer prophylaxis with entecavir or tenofovir disoproxil”. The role for lamivudine is limited unless the patient has undetectable viral load and the duration of immunosuppression is < 6 months.	Thank you for your comment. The recommendations do not use the 2000 IU/ml level to determine whether prophylaxis should be given. Instead it is used to estimate a DNA level at which it is more likely to be cost effective to use lamivudine rather than entecavir or tenofovir. The GDG felt that if the DNA level was less than 2000 IU/ml and immunosuppression was likely to last less than 6 months then lamivudine would be the most cost effective drug.

SH	Advisory Group on Hepatitis (AGH)	15	Full	51	25	A similar argument as above. HBV DNA threshold of 2000 IU/ml may not be applicable to this patient group. Instead, detectable or undetectable viral load should be used. Prophylaxis should be offered to anyone under this category who has a detectable viral load. Those whose HBV DNA are undetectable at baseline should be monitored monthly and premptively treated if HBV DNA became positive.	Thank you for your comment. The recommendations do not use the 2000 IU/ml level to determine whether prophylaxis should be given. Instead it is used to estimate a DNA level at which it is more likely to be cost effective to use lamivudine rather than entecavir or tenofovir. The GDG felt that if the DNA level was less than 2000 IU/ml and immunosuppression was likely to last less than 6 months then lamivudine would be the most cost effective drug.
SH	Advisory Group on Hepatitis (AGH)	16	Full	52	16	There is no rationale for testing ALT in children every 12 weeks, especially those in the immune tolerant phase do not require 3 monthly follow up. Follow up with repeat blood tests every 6-12 months is appropriate. We need to consider that these are well children and they are not keen to take time off school or provide explanation about non-attendance to their school teacher.	Thank you for your comment. We have amended recommendation 77 to read as follows: Monitor ALT levels every 24 weeks in children and young people with HBeAg positive disease who have normal ALT levels (less than 30 IU/ml for males and less than 19 IU/ml for females) and no evidence of significant fibrosis (METAVIR stage less than F2 or Ishak stage less than 3)..
SH	Advisory Group on Hepatitis (AGH)	17	Full	52	22	Children in the immune clearance phase should be reviewed every 12 weeks or more frequently to monitor their LFTs and disease progression.	Thank you for your comment. We have amended recommendations 77 and 79 to reflect this: 77. Monitor ALT levels every 24 weeks in children and young people with HBeAg positive disease who have normal ALT levels (less than 30 IU/ml for males and less than 19 IU/ml for females) and no evidence of significant fibrosis (METAVIR stage less than F2 or Ishak stage less than 3)

							79. Review every 12 weeks children and young people with HBeAg-negative disease who have abnormal ALT (greater than or equal to 30 IU/ml for males and greater than or equal to 19 IU/ml for females) and HBV DNA greater than 2000 IU/ml.
SH	Advisory Group on Hepatitis (AGH)	18	Full	52	26	Pegylated Interferon – monitoring schedule in children differs to that in adults. Children require close monitoring at 0, 2, 4 and every 4 weeks whilst on pegylated interferon.	Thank you for your comment. We have added in a recommendation (80) to address this that reads: Review injection technique and adverse effects weekly during the first month of treatment in people taking peginterferon alfa-2a.
SH	Advisory Group on Hepatitis (AGH)	19	Full	52	25	Monitoring of weight and height in children on PEG-IFN is essential and needs to be included, especially children during puberty. In general, interferon should be avoided during puberty because of the detrimental effect on growth and nutrition	Thank you for your comment. We agree and have amended recommendation 81 to reflect this: Monitor full blood count, liver function (including bilirubin, albumin and ALT), renal function (including urea and electrolyte levels) and thyroid function (and in children, weight and height) before starting peginterferon alfa-2a and 2, 4, 12, 24, 36 and 48 weeks after starting treatment to detect adverse effects. The risk:benefit ratio for treating during puberty needs careful evaluation that takes into account educational and family constraints and the potential detrimental effects on growth and nutrition.
SH	Advisory Group on	20	Full	52	25	Children who require PEG-IFN therapy	Thank you for your comment. We agree

	Hepatitis (AGH)					should be appropriately addressed for the timing e.g. not during puberty, their year of important exams, carer's commitments. Consideration will need to be given to the need for proper preparation especially the need for play therapy due to anxiety, training preparation and psychological preparation in case of non response to treatment. This also includes when and how to inform school when some parents do not want to disclose their child's diagnosis to the school.	with your comment and have amended recommendation 81 to reflect this. Monitor full blood count, liver function (including bilirubin, albumin and ALT), renal function (including urea and electrolyte levels) and thyroid function (and in children, weight and height) before starting peginterferon alfa-2a and 2, 4, 12, 24, 36 and 48 weeks after starting treatment to detect adverse effects.
SH	Advisory Group on Hepatitis (AGH)	21	Full	52	31	It is understandable why HBV DNA and HBeAg status should be monitored as these are treatment endpoints. HBV DNA level change also serves as a futility rule for interferon therapy. However, the role of HBsAg quantitation is not clear. There are accumulating evidences for the use of quantitative HBsAg, but the management algorithm as it stands in this guidelines does not require the knowledge of HBsAg level. HBsAg positive or negative is clearly a treatment endpoint and needs to be monitored, but a qualitative test will give this outcome. With the quantitative test being more expensive and not widely available, the guideline writing group should consider whether the recommendation of routine monitoring of HBsAg level is justifiable. If this is to be included, the guidelines should indicate how the results should be used.	Thank you for your comment. We have revised the review on the use of HBsAg in stopping rules for people on peginterferon, and included three additional studies identified during consultation. The revised review is in chapter 12 of the full guideline. The GDG recognised that a first-line recommendation of peg interferon should be accompanied by accurate stopping rules appropriate to that therapy. This was particularly important in view of the known adverse events of peginterferon. On the other hand, the GDG wished to maximise the opportunity of achieving immune control and adopted fairly conservative stopping rules that include HBsAg and HBV DNA at 24 weeks. Recommendations 83 and 84 have been modified accordingly.
SH	Advisory Group on Hepatitis (AGH)	22	Full	53	4	In paediatrics, children and particularly young children should be monitored every 3 months when on treatment for side effects	Thank you for your comment. We have added in a recommendation (80) to address this that reads:

						and compliance.	Review injection technique and adverse effects weekly during the first month of treatment in people taking peginterferon alfa-2a.
SH	Advisory Group on Hepatitis (AGH)	23	Full	53	11	HBV DNA monitoring in Children on lamivudine for more than 48 weeks should be considered to detect viral breakthrough due to resistance	Thank you for your comment. Recommendation 87 also applies to children.
SH	Advisory Group on Hepatitis (AGH)	24	Full	53	13	3 monthly review for children on Tenovofir for monitoring of side effects.	Thank you for your comment. The recommendation has been amended to monitor 4 weeks after starting treatment and then every 3 months to detect adverse effects when cessation of treatment or dose reduction would be indicated.
SH	Advisory Group on Hepatitis (AGH)	25	Full	53	13	Children who developed rash while on the treatment will need a review by a paediatric dermatologist and consider discontinuation of Tenovofir if the rash is moderate or severe	Thank you for your comment. Rash is a very uncommon adverse event in children receiving tenofovir. Clinicians prescribing tenofovir should be familiar with managing adverse events. A paediatric dermatologist's opinion may be sought in unusual clinical presentations.
SH	Advisory Group on Hepatitis (AGH)	26	Full	53	32	Very few children (except those with fulminant hepatitis) develop decompensated disease	Thank you for your comment which is noted. More information about this are now added to the 4th linking evidence to recommendations table in chapter 12 of the full guideline.
SH	Advisory Group on Hepatitis (AGH)	27	Full	59		Assessment of liver disease in children does not include liver biopsy in all cases.	Thank you for your comment.
SH	Advisory Group on Hepatitis (AGH)	28	Full	59		The treatment scheme suggested for children and young people is not based on any evidence	Thank you for your comment. We accept that not every child/young person requires a biopsy prior to starting treatment. However in young people arriving for example as migrants from endemic

							regions with high viral loads and active transaminitis, it will be unclear how long they have been in an immune-reactive phase of infection and they may have advance fibrosis. Perhaps more importantly, the liver biopsy may reveal other pathologies and save the need for embarking on antiviral treatment. Recommendation 25 has been amended to read 'consider' rather than 'offer' to reflect the strength of evidence.
SH	Association of Clinical Biochemistry	1	NICE	25	20	Would it be possible to include more information and guidance on the dynamics of tenofovir in reducing viral load. Maybe in appendix.	Thank you for your comment. This is outside the scope of a NICE guideline. For information on viral dynamics under treatment we would suggest you refer to the primary literature.
SH	Association of Clinical Biochemistry	2	NICE	26	1	Suggest stating a date in pregnancy e.g. 28/40 to start treatment. Other published guidance i.e. EASL 2012 and British Viral Hepatitis Group 2008 recommends use of tenofovir when viral load exceeds $>10^6$ IU/ml not $>10^7$ IU/ml – why the difference? Although primary non response is not often observed with tenofovir, would it not be advisable to monitor HBV DNA levels at term to check for compliance in addition to 2 months post treatment start. Suggest needs to be more information or comment made on the safety of tenofovir therapy during breast feeding. Also should these babies be recorded in database as tenofovir is a level B drug.	Thank you for your comment. The GDG considered that threshold of mother's viraemia higher than 10^7IU/ml makes sure that only the mothers at greatest risk of infecting their babies are offered antiviral treatment**.** In the linking evidence to recommendations table, the GDG have commented that women are safe to continue breast feeding whilst on treatment.
SH	Association of Clinical Biochemistry	3	NICE	27	2	Recommend that those that are delta positive are screened with quantitative RNA	Thank you for your comment. Recommendation 1.5.46 has been

						assay. State in more detail when these patients should be re-tested and what levels of RNA are significant.	amended to address this: "Consider stopping treatment if there is no HDV RNA decline after 6 months to 1 year of treatment. Otherwise, continue treatment and re-evaluate treatment response annually".
SH	Betsi Cadwaldr University Health Board	1	Full	527	17	 Betsi Cadwaldr comments.docx **12.2.2** **Review question: When and how frequently should surveillance testing be offered to detect early hepatocellular carcinoma in people with chronic hepatitis B?** 1. There is currently a lack of consensus around the clinical effectiveness of surveillance for hepatocellular carcinoma in people with chronic liver disease. Consideration of how often this surveillance should be offered, if it is ineffective, appears to be the wrong question to be asking in a process of improving clinical practice. 2. Surveillance of those with chronic liver diseases for HCC is widely practiced and through guidance issued by hepatologist associations in the United States, Europe and the UK has become..the de facto standard of care.. (Heuman & Habib, 2012). This appears	Thank you for your comment. When formulating the review question, the GDG took into consideration their knowledge of the evidence from two randomised trials on surveillance compared with no surveillance, and their experience, and noted that surveillance (together with appropriate treatment) led to reductions in mortality. With this background, they were interested to know the timing of surveillance testing. We agree that the recommendations appear to rely on ultrasound and alpha fetoprotein being accurate tests for hepatocellular carcinoma. If the evidence were only concerned with diagnosis of small lesions, then this would be an important consideration. However, the evidence reviewed is not solely concerned with diagnostic test accuracy in that it compares the effects of different frequencies of monitoring, with survival as an important outcome. If the tests were inaccurate they would be unlikely to discriminate between different frequencies of surveillance in predicting survival.

						to have been relied upon in the proposed clinical guideline with Line 13 page 527 noting the tests are "commonly used", however widespread use does not automatically equate to effective provision. 3. Effectiveness in this context relates to test performance - making the distinction between neoplastic nodules and nodular regeneration/macronodular in cirrhosis can be extremely difficult, and is widely noted in the literature as limiting the effectiveness of this screening. The presence of fibrosis, fatty infiltration and body habitus can also increase the difficulties in accurately detecting nodules/lesions. It is estimated that between 85% (Patel et al, 2012) and 99.5% (Gannon et al, 2009) of HCC occur against a background of cirrhosis indicating this complicating factor is significant. The examination is operator-dependent (Braillon, 2011) and demands highly trained operators and dedicated equipment and ultimately, on an ongoing basis, 'requires' a critical volume of assessments to maintain proficiency. This dependency is acknowledged in the proposed guideline a combination of ultrasound with AFP estimation is suggested as the 'solution' to this, yet the American Association for the Study of Liver Disease (AASLD, 2010) notes that AFP determination lacks adequate sensitivity and	We have revised the linking evidence to recommendations section as follows, placing greater emphasis on survival outcomes: "The GDG also took into consideration further information in the Trinchet 2011 RCT regarding very small HCC lesions: these were sometimes difficult to identify (for example, in the presence of fibrosis and fatty infiltration) and did not always develop into more advanced cancers. The GDG therefore placed more reliance on the effect of frequency on mortality in determining appropriate surveillance times. For this reason, they did not wish to recommend a periodicity of less than 6 months, because they thought that the increased incidence of "HCC" at shorter times, with its preponderance of lesions less than 10mm, could be unreliable. However, the GDG considered that a 6 month period was appropriate and decided that the very low quality evidence - showing a significant effect on mortality of 6 versus 12 monthly surveillance - was consistent with their experience and with the potential for increased mortality at even shorter times in the RCT studies. They were of the opinion that development of HCC lesions from very small to untreatable could occur in 12 months and they wanted to avoid this possibility by recommending a 6 month surveillance frequency. Finally, the guideline does not make recommendations for the subsequent

						specificity for effective surveillance, and consequently do not recommend this mode for surveillance. 4. Additionally, when comparing sonography results to explanted liver pathological results Bennett et al, 2002 detected 75% of large (>5cm diameter) carcinomas, but only 13.6% of lesions with diameters between 1-2cm, albeit as part of a small series. Their conclusion was that i. ..sonography was not sensitive enough for the detection of hepatocellular carcinoma..in patients with a cirrhotic liver.. (Bennett et al, 2002)	management of detected HCC lesions, but it is likely that further monitoring/testing would take place before treatment." We also note that the recommendations are for people at high risk of HCC and not everyone with CHB should undergo surveillance. This would be expected to reduce the risk of false positives and ensuing invasive tests and psychological burden.

						5. Current detection rates may well be above this if only because of technological advances. 6. Further, Bolondi et al, 2001 noted that ..surveillance discloses a large number of nodules of uncertain malignant potential.. and in the 2011 RCT comparing periodicities for screening as referenced in the proposed guidelines (Trinchet, et al, 2011) nearly half of all lesions detected were indeterminate or had disappeared at the end of the trial and just 34.4% were HCC. Additionally just 19% of the nodules <10mm detected were confirmed as HCC. Overall, in the 1278 patients enrolled in this solid randomised study more indeterminate lesions were detected than HCC, and just 1/5th of small nodules were identified as HCC, leaving 81% of nodules detected as not HCC.	

						These points highlight the potential for over diagnosis with these findings being very likely to lead to further tests, as well as psychological burden for the patient. 7. The National Cancer Institute (US Department of Health and Human Services) updated its position on screening for HCC on 25th January 2012. Its PDQ® (Physician Data Query) information summary about liver (hepatocellular) cancer states the summary of benefits succinctly - "Based on fair evidence, screening would not result in a decrease in mortality from hepatocellular cancer". Adding that this might also result in (rare) side effects. (NCI, 2012). 8. There is potential psychological harm from the testing and potential over diagnosis. In circumstances where such harms exist the burden of proof customarily falls on those advocating action (screening in this case) (Kelley, 2011). Without this proof inaction (not screening, in this case) should be the recommended practice. 9. Recommendations 90 and 91 concerned with	

						performing/considering screening are made on evidence from studies about periodicities, not more appropriate studies comparing outcomes for those screened and not screened. This latter evidence should be considered in full and the recommendations revised accordingly. **References** AASLD (American Association for the Study of Liver Disease), 2010 Practice Guideline - Management of Hepatocellular Carcinoma: An Update Accessed at: http://www.aasld.org/practiceguidelines/Documents/Bookmarked%20Practice%20Guidelines/HCCUpdate2010.pdf Last Accessed: 24th September 2012 Bennett GL, Krinsky GA, Abitbol RJ, Kim SY, Theise ND, Teperman LW. Sonographic detection of hepatocellular carcinoma and dysplastic nodules in cirrhosis: correlation of pretransplantation sonography and liver explant pathology in 200 patients. American Journal of Roentgenol. 2002 Jul; 179(1):75-80.	

						Bolondi L, Sofia S, Siringo S, Gaiani S, Casali A, Zironi G, Piscaglia F, et al. (2001) Surveillance programme of cirrhotic patients for early diagnosis and treatment of hepatocellular carcinoma: a cost effectiveness analysis. Gut 2001; 48:251–259. Braillon, A., 2011. Surveillance for hepatocellular carcinoma, Annals of Internal Medicine, 155 (4), 274-275 Gannon, C. J., Izzo, F., Aloia, T. A., Pignata, S., Nasti, G., Vallone, P., Orlando, R., Scordino, F., & Curley, S. A., 2009. Can hepatocellular cancer screening increase the proportion of long-term survivors?, Hepato-Gastroenterology, 56 (93), 1152-1156 Heuman, DM & Habib, A (2012) Which Patients with Chronic Liver Disease Should i screen for HCC? Accessed at: http://www.healio.com/gastroenterology/liver-biliary-disorders Last Accessed: 20th June 2012 Kelley, M (2011) Surveillance for hepatocellular carcinoma Annals of Internal Medicine; 155(4):274 Lederle, F and Pocha, C (2012)	

						Screening for Liver Cancer: The Rush to Judgment Annals of Internal Medicine 156(5):387 National Cancer Institute Liver (Hepatocellular) Cancer Screening (PDQ®) Accessed at: http://www.cancer.gov/cancertopics/pdq/screening/hepatocellular/HealthProfessional/page1/AllPages Last Accessed: 11th September 2012 Patel, M., Shariff, M. I., Ladep, N. G., Thillainayagam, A. V., Thomas, H. C., Khan, S. A., & Taylor-Robinson, S. D., 2012. Hepatocellular carcinoma: diagnostics and screening. Journal of Evaluation in Clinical Practice, 18 (2), 335-342 Trinchet, JC et al, 2011 Ultrasonographic Surveillance of Hepatocellular Carcinoma in Cirrhosis: A Randomized Trial Comparing 3- and 6-Month Periodicities Hepatology, Vol. 54, No. 6, 2011	
SH	Bristol Myers Squibb	1	Full	14	19	'*Where recommendations have been made for the use of drugs outside their licensed indications ('off-label use'), these drugs are*	Thank you for your comment. This guideline recommends some drugs

						marked with a footnote in the recommendations.' NICE clinical guidelines should not recommend the use of drugs outside their licensed indications. Regulatory authorities would have granted a license for these drugs if there was a substantial evidence basis to do so, and/or if the manufacturer had submitted to the licensing process. In the absence of a regulatory license such recommendations are contrary to the NHS's commitment to innovation as outlined in 'Innovation Health and Wealth' (http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/documents/digitalasset/dh_134597.pdf) from December 2011. Furthermore such recommendations are contrary to the Government's life sciences strategy, as outlined in 'Strategy for UK Life Sciences' (https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/32457/11-1429-strategy-for-uk-life-sciences.pdf), which aims to establish the UK as the global-hub for life sciences. Thus, NICE recommending the off-label use of drugs proactively counteracts both Government and NHS strategy. We therefore ask that throughout the document any recommendation of PEG IFN in children, and multiple references to Truvada (tenofovir plus emtricitabin), be withdrawn.	for indications for which they do not have a UK marketing authorisation at the date of publication, if there is good evidence to support that use. Where recommendations have been made for the use of drugs outside their licensed indications ('off-label use'), these drugs are marked with a footnote in the recommendations. We have removed all references to Truvada from the document.

SH	Bristol Myers Squibb	2	Full	49	2	Universal recommendation for PEG-IFN as a first line choice in both HBeAg positive and HBeAg negative patients does not take into account the limitations, imposed by well defined pre-treatment predictors of response. (Buti M et al [2012] EASL Clinical Practice Guidelines: Management of chronic hepatitis B virus infection Journal of Hepatology 2012 vol. 57 167–185) (Pegasys SmPC; http://www.medicines.org.uk/EMC/medicine/10081) There are multiple clinical trials proving the efficacy and safety of PEG-IFN alpha2b (ViraferonPeg) in HBV which are not discussed in this guidance. While off-label in the UK this product is indicated for HBV elsewhere.	Thank you for your comment. The GDG recommended peg-IFNa as first line treatment for both HBeAg positive and negative patients taking into account the clinical and cost effectiveness of all antiviral drugs reviewed. The economic model showed that a strategy with a first line treatment with peg-IFN was cost-effective in the base case. We also conducted sensitivity analyses to take into account predictors of response such as increased ALT and genotype. When the baseline rate of e antigen seroconversion was increased up to 25% to consider the cases where patients have increased ALT or when different genotypes were considered in the analysis, results did not change overall and PegIFN was still the most cost-effective initial treatment. Therefore we concluded that even when predictors were accounted for, PegIFN was likely to be the most cost-effective initial treatment. Peg-IFN a-2b was not included in the network meta-analysis as it didn't connect in the network. There was only one trial (Chan 2005) that included peg a-2b in the sequence of peg for 4 weeks followed by combination of peg a-2b +LAM for 24 weeks followed by LAM monotherapy (28w) which was not included in the NMA as the GDG considered it was not part of the current clinical practice.
SH	Bristol Myers Squibb	3	Full	49	6	When comparing clinical efficacy of ETV &	Thank you for your comment. We agree

						TDF using MTC methodologies it is important to account for baseline viral load and different definitions of response in pivotal clinical trials. (Mealing et al; ISPOR 2012; Abstract #40303) & (Diva et al. ISPOR 2009; Poster PMC39) Entecavir (ETV) is approved as a first-line treatment (Buti M et al [2012] EASL Clinical Practice Guidelines: Management of chronic hepatitis B virus infection Journal of Hepatology 2012 vol. 57 167–185) and (NICE guidance TA 153 http://publications.nice.org.uk/entecavir-for-the-treatment-of-chronic-hepatitis-b-ta153). The new study REALIST (Mete B et al, Poster 337 (control ID: 1422588) AASLD 2012) directly compares ETV and TDF in a predominantly HbeAg positive Turkish population, and concludes a superior eAg seroconversion rate for ETV. This reinforces the point that in HBeAg positive patients ETV should be positioned at least equal to TDF.	that baseline viral load could introduce bias in the estimates of effect that is the reason we performed a sensitivity analysis as part of the network meta-analysis. Three studies were identified in the model with high baseline HBV DNA levels and final results were not affected by excluding these studies. We also agree that different definitions of responses can introduce bias that is why we have preselected specific outcomes for the four networks of the Network Meta-Analysis. The selection of antiviral treatments in the recommendations was based on a clinical and cost-effectiveness analysis and on GDG clinical expert opinion. REALIST study was not part of the evidence reviewed as it was an observational study and did not match our protocol.
SH	Bristol Myers Squibb	4	Full	49	20	ETV should be mentioned first alphabetically (no linguistic or methodological reason for Tenofovir (TDF) to be mentioned first)	Thank you for your comment. This change has been made.

SH	Bristol Myers Squibb	5	Full	49	22	Switching slow / partial responders to alternative nucleotide / nucleoside agent is not justified based on clinical evidence and EASL guidance 2012. (Bang J et al; *Digestive & Liver Disease 2013*; http://dx.doi.org/10.1016/j.dld.2012.12.013) (Buti M et al [2012] EASL Clinical Practice Guidelines: Management of chronic hepatitis B virus infection Journal of Hepatology 2012 vol. 57 167–185)	Thank you for your comment. There were no randomised trials comparing continuation of entecavir versus entecavir switched to tenofovir; or comparing tenofovir continuation versus tenofovir switched to entecavir, in HBeAg negative patients who had already received peg interferon as first line therapy. The Bang 2013 paper was published after the guideline reviewing period had ended, but was not a randomised trial. In the absence of direct RCT evidence, the GDG considered a decision model of the sequences described above; the sequences modelled only allowed a switch to a nucleos(t)ide with a different resistance profile, to avoid cross resistance. The EASL guideline states that the optimal management of patients with a partial response on entecavir or tenofovir is currently debatable. However, the GDG thought it would be better for the patient in the longer term to switch drugs than to persist with the same drug that was only achieving a partial response at best. The model calculates resistance rates for the first drug and uses risk ratios from the trials (network meta-analysis), in order to estimate the cost effectiveness of the different sequences.
SH	Bristol Myers Squibb	6	Full	50	10	The term advanced cirrhosis does not sufficiently quantify the disease state and is open to misinterpretation. It should state “liver decompensation”.	Thank you for your comment. This change has been made.

SH	Bristol Myers Squibb	7	Full	50	14	*Since VIREAD (tenofovir disoproxil fumarate) was approved on October 26, 2001, FDA have become aware of a potential renal safety signal with VIREAD (tenofovir disoproxil fumarate) in their review of the safety data from clinical trial GS-US-174-0108. A higher proportion of VIREAD (tenofovir disoproxil fumarate) exposed subjects with decompensated disease experienced an increase in serum creatinine ≥ 0.5 mg/dL over baseline, and a creatinine clearance < 50 mL/min. However, trial GS-US-174-0108 was too small to allow adequate evaluation of these events. Therefore, based on appropriate scientific data, FDA has determined that manufacturer is required to conduct a prospective 5-year pre-OLT (orthotopic liver transplant) registry study to collect and analyze data regarding renal function in patients with chronic hepatitis B and decompensated liver disease treated with VIREAD (tenofovir disoproxil fumarate) and a comparator group taking another nucleoside analogue, such as entecavir.* (FDA letter to Gilead: NDA 021356/S-034 (reference ID 2844152) October 1st 2010). http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2010/021356s034ltr.pdf Similar safety issues have been raised by Gory et al (Poster 702 (control ID: 1424607) AASLD 2012).	Thank you for your comment. We have amended recommendation 61 to read as follows: Offer entecavir as first-line treatment in people with decompensated liver disease if there is no previous exposure to lamivudine. Offer tenofovir to people with previous exposure to lamivudine. Reduce the dose of tenofovir disoproxil in people with renal impairment, in line with the guidance in the BNF.

						Further to being selected as a comparator by the FDA, ETV has recently become the first EASL recommended antiviral with label confirmed efficacy and safety in liver transplantation patients. Ref: 109 poster and ETV SPC Therefore ETV could be considered the standard of care in decompensated HBV patients.	
SH	Bristol Myers Squibb	8	Full	50	14	ETV should be stated as first-line treatment for patients with decompensated liver disease – as demonstrated by its licence, clinical trial data, real life data, and most recently the AWMSG approval – ahead of TDF approval (AWMSG Final Appraisal Recommendation Advice No: 0212 – February 2012). This is also supported by the following study Liaw Y-F et al, Hepatology 2011; 54(1): 91-100.	Thank you for your comment. The GDG recommended tenofovir as first line treatment for people with decompensated liver disease based on the results from clinical and cost-effectiveness analysis. Entecavir was recommended as alternative to tenofovir for those with high risk of renal or bone toxicity. The study by Liaw et al (2011) was included in the clinical review and its results were taking into consideration in the clinical and cost effectiveness analysis. The GDG considered that tenofovir may further supress viral HBV DNA compared to entecavir and is less prone to resistance mutations.
SH	Bristol Myers Squibb	9	Full	53	4	ETV does not require renal monitoring after baseline assessment. In contrast, TDF requires monthly renal monitoring for the first 12 months of treatment, and every 3 months thereafter. Indeed, the TDF SmPC has recently been updated (December 2012) to reflect the renal toxicity related to treatment in HBV. http://www.medicines.org.uk/emc/medicine/	Thank you for your comment. The cost of monitoring patients who receive TDF was already included in our model and therefore results are already reflective of this additional cost. This is discussed in the health economic model in appendix I, section I.2.3.10.

						9008	
SH	Bristol Myers Squibb	10	Full	54	25	Renal monitoring costs (test and follow-up (approximate composite cost for first year £1,057 and each subsequent year £672)) in addition to the cost of TDF need to be taken into account when initiating TDF treatment. Furthermore, renal monitoring although always a key requirement within the TDF SmPC since launch was updated recently (19th Dec 2012) to include hepatitis B specific data (section 4.8) http://www.medicines.org.uk/emc/medicine/9008)	Thank you for your comment. The cost of monitoring patients who receive TDF was already included in our model and therefore results are already reflective of this additional cost. More information can be found in appendix I.
SH	Bristol Myers Squibb	11	Full	56	Flow chart	ETV should be included as a first-line option of HbeAg positive, and mentioned first (alphabetically) for HbeAg negative patients. See Point 3 Above.	Thank you for your comment. Results from the clinical and cost effectiveness analysis of antiviral treatments showed that pegylated interferon is the most cost effective first line treatment for HBeAg positive people. In the NMA, entecavir was found to have a very low probability of being the best treatment of achieving undetectable HBV DNA and HBeAg seroconversion for HBeAg positive people.
SH	Bristol Myers Squibb	12	Full	58	Flow chart	We question the level of evidence for recommending TDF in pregnancy (this is off label and supported with minimal evidence). Data show that TDF human birth defect rate is substantially higher than in ETV. (Brown R et al. Tenofovir Disoproxil Fumarate-Containing Regimens in Pregnancy: Report from the Antiretroviral Pregnancy Registry. 60th Annual AASLD	Thank you for your comment. This recommendation was based on GDG expert opinion. The GDG considered that Tenofovir is a drug that is highly potent, has a high barrier to resistance and the risk of toxicity is low so would be permissible for use in pregnancy as used in the HIV field. However, the GDG agreed that further data on the long term use of tenofovir in pregnant women is

						Meeting. October 31-November 3. Boston, MA. Poster #407) DHHS guidelines express concerns of potential renal bone toxicity in foetus. '*Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States'* http://aidsinfo.nih.gov/guidelines	required and made a research recommendation.
SH	Bristol Myers Squibb	13	Full	155	4	Evidence is emerging regarding the positive effects of ETV on the disease progression endpoints recommended by NICE, such as: *decompensation* (Lampertico et al; Poster 366 Control ID: 1418022 AASLD 2012); *HCC prevalence* (Hosaka T et al Poster 356 Control ID 1419064: AASLD 2012 and Hosaka T et al Hepatology. 2012 Dec 5. doi: 10.1002/hep.26180. [Epub ahead of print]); *HCC progression* (Urata Y at al.; Effects of antiviral therapy on long-term outcome after liver resection for hepatitis B virus-related hepatocellular carcinoma; J Hepatobiliary Pancreat Sci (2012) 19:685–696 DOI 10.1007/s00534-011-0489-z) & (Chen et al Poster 404 Control ID: 1422006 AASLD 2012); and graft protection from re-infection (Perillo et al 2012 EASL Poster.); *Liver related mortality* (Wong et al;	Thank you for your comment. The proposed studies were not included in the review of evidence as either they were not randomized trials or their population didn't match our pre-specified protocol.

						Hepatology; DOI: 10.1002/hep.26301 Kumada T et al; Journal of Hepatology; Volume 58, Issue 3, March 2013, Pages 427–433 Xie F et al. (2013) Effects of Nucleoside Analogue on Patients with Chronic Hepatitis B-Associated Liver Failure: Meta-Analysis. PLoS ONE 8(1): e54773. doi:10.1371/journal.pone.0054773	
SH	Bristol Myers Squibb	13	Full	155	4	Lin B et al. (2012) *Entecavir improves the outcome of acute-on-chronic liver failure due to the acute exacerbation of chronic hepatitis B;* Hepatol Int: *DOI 10.1007/s12072-012-9415-y* As compelling evidence of this quality is only available for ETV and not available for any other EASL and NICE recommended antiviral, we request these data be recognised as fundamental to the successful long term treatment of Hepatitis B patients. Furthermore we suggest NICE consider elevating their recommendation for the line of use of ETV in HbeAg positive, HBeAg negative and (especially) decompensated patients.	Thank you for your comment. This study by Lin et al (2013) is not a RCT and is not eligible for inclusion in the evidence base.
SH	Bristol Myers Squibb	14	Full	General	General	The document does not currently reflect the need for patient choice when deciding on treatment as outlined in the nhs patient choice framework. (NHS Website; http://www.nhs.uk/choiceintheNHS/Yourcho	Thank you for your comment. The GDG have developed specific recommendations recognizing the patient informed choice before starting treatment (recommendations 1, 15, 24, 31, 51, 62 in full guideline). In addition NICE guidance

						ices/allaboutchoice/Pages/Allaboutchoice.aspx)	on the components of good patient experience in adult NHS services (NICE clinical guidance 138) has been cross referred to in this guideline. Finally, the GDG has recognized individual patient preference after discussion with clinicians about the benefits and harms of each antiviral drug in the linking evidence to recommendations section of the recommendations for the antiviral treatments.
SH	British Association for Adoption and Fostering	1	Full	General	General	This response is being submitted on behalf of the BAAF Health Group, which is also a special interest group of the Royal College of Paediatrics and Child Health (RCPCH). The Health Group was formed to support health professionals working with children in the care system, through training, the provision of practice guidance and lobbying to promote the health of these children. With over 500 members UK-wide, an elected Health Group Advisory Committee with representation from community paediatricians working as medical advisers for looked after children and adoption panels, specialist nurses for looked after children, psychologists and psychiatrists, the Health Group has considerable expertise and a wide sphere of influence. Our area of concern is the particularly vulnerable group comprised of looked after and adopted children and young people.	Thank you for your comment. Looked after children are covered by the guideline. We note your concern.
SH	British Association for Adoption and Fostering	2	NICE	General	General	While we appreciate the recommendation to follow guidelines in 'Seeking consent: working with children' noted on line 16 of	Thank you for your comment. The GDG consider the management and treatment of looked after children would not differ.

						page 7, we nevertheless strongly recommend that a comment be made here about the complexity of obtaining informed consent for looked after children. Practitioners who are unaccustomed to working with this group of children need reminding about the importance of obtaining consent from the child with capacity to consent, or an adult with parental responsibility. In our experience, health professionals who do not routinely work with looked after children often do not understand the complexity of obtaining consent in this vulnerable group of children, and may err in seeking consent from foster carers who do not have parental responsibility. For example, this is relevant to sections: Page 20, paragraph 1.3.9 Page 24, paragraph 1.5.28	Reference has been made to the Looked After children guideline which addresses the needs of this group.
SH	British Association for Adoption and Fostering	3	NICE	26	10	With reference to HBV immunisation, it is essential to alert practitioners that sometimes immunisation of neonates is required as an emergency procedure in situations where infected women have received minimal or no prenatal care, and present/are diagnosed at or shortly after delivery.	Thank you for your comment. Immunisation is outside the scope of the guideline.
SH	British Association for Adoption and Fostering	4	NICE	General	General	It may be challenging and stressful for anyone, but especially children to cope with a chronic disease requiring repeated medical appointments, blood tests and treatments, and this is particularly the case for looked after children. It would be helpful to at least acknowledge additional needs for ongoing support, sperhaps in the section on	Thank you for your comment. The GDG consider the management and treatment of looked after children would not differ. Reference has been made to the Looked After children guideline which addresses the needs of this group**.** The patient centred care section is standard text within all NICE guidance and your

						page 7 on Patient centred care.	comments have been passed on.
SH	British Association for Sexual Health and HIV (BASHH)	1	Full	25	11	Sexual health services are screening high risk individuals including men who have sex with men, commercial sex workers and HIV antibody positive individuals for hepatitis B. They offer an effective area to perform pre-therapeutic tests for individuals diagnosed within the service. However funding of the service through the GU tariff should take account of the costs of this assessment. Sexual health services are ideally placed to provide partner notification, screening and vaccination (see below). This section on pre-therapeutic tests should include assessment by history taking. All adults should have a comprehensive sexual and drug and alcohol history taken to inform risk reduction strategies.	Thank you for your comment. The guideline cross refers to the NICE Public Health Guideline 43; Hepatitis B and C: ways to promote and offer testing to people at increased risk of infection. This clinical guideline should be used in conjunction with the public health guideline. The GDG consider history taking to be standard medical practice which would not be included in the guideline.
SH	British Association for Sexual Health and HIV (BASHH)	2	Full	43	14	We welcome the routine offer of HIV testing for individuals diagnosed with hepatitis B. It would be useful to have a short explanation of the rationale for this recommendation including • Increased risk of other blood borne viruses • Benefit of diagnosing HIV early • The critical need to avoid suboptimal nucleoside reverse transcriptase therapy in HIV positive individuals We emphasise that not only should HBsAg+ individuals be tested for HIV at baseline but also that HIV testing should be REPEATED prior to initiation of nucleoside	Thank you for your comment. The tests recommended by the GDG were those thought to be standard prior to initiating treatment and are used in current practice. We have added in a recommendation to cover retesting – recommendation 32 states “Re-assess the person’s risk of exposure to HIV before starting treatment and offer repeat testing if necessary”. Recommendation 52 states the same should be done for children and young people.

						therapy in those at risk. HIV testing should be repeated DURING therapy at appropriate intervals*. *annually or more frequently if clinical symptoms are suggestive of seroconversion or ongoing high risk exposure (UK National Guidelines for HIV testing 2008. www.bashh.org)	
SH	British Association for Sexual Health and HIV (BASHH)	3	Full	63	1	What are the information needs of patients with CHB and their carers? • Understanding how CHB will impact on their daily activities • Not only need to be aware of modes of transmission but also information about the risks of transmission and strategies to reduce risk including vaccination of partners, use of condoms and reducing number of sexual partners • Issues relating to possible criminalisation should be discussed • Understanding the short term / long term potential health problems • How to discuss potential referral for vaccination if appropriate for carers • Access to professional support groups / information e.g. http://www.hepb.org.uk/ • Understand treatment / side effects • Be aware of modes of transmission	Thank you for your comment. Some aspects listed such as transmission, vaccination and criminalisation are outside the scope of the guideline. The patient information recommendation covers planning, lifestyle issues, treatment options and long term goals as well as recommending offering a personalised care plan to people with chronic hepatitis B or family members or carers.
SH	British Association for Sexual Health and HIV (BASHH)	4	Full	54	24	We note the comments on tenofovir safety and the cost-effectiveness of safety monitoring. We support these comments	Thank you for your comment.

						and echo that the same applies to the use of tenofovir to treat HIV.	
SH	British Association for Sexual Health and HIV (BASHH)	5	Full	371	9	A short explanation as to why there are specific issues with HIV co-infection (eg 1st paragraph) and why this is not covered by the guidance should be included. It would be helpful if the British HIV Association hepatitis guidelines were referenced.	Thank you for your comment. HIV is outside the scope of the guideline.
SH	British Association for Sexual Health and HIV (BASHH)	6	Full	43	8	Should include hepatitis A testing with a view to vaccination if non-immune, given the high rate of severe hepatitis in patient who get acute hepatitis A on top of chronic liver disease from other causes (such as HBV)	Thank you for your comment. Vaccination is outside the scope of the guideline. We agree that Hepatitis A should be tested for and have added lgG anti-HAV to the list of tests in recommendation 6.
SH	British Association for Sexual Health and HIV (BASHH)	7	Full	45	24	Should include hepatitis A testing with a view to vaccination if non-immune, given the high rate of severe hepatitis in patient who get acute hepatitis A on top of chronic liver disease from other causes (such as HBV)	Thank you for your comment. Vaccination is outside the scope of the guideline. We agree that Hepatitis A should be tested for and have added lgG anti-HAV to the list of tests in recommendation 6.
SH	British Association for Sexual Health and HIV (BASHH)	8	Full	50	26	It is not clear why they recommend continuing antivirals after delivery if the mother otherwise does not need treatment. Page 50, recommendation 62. (and page 447) Why stop tenofovir 4-12 weeks after delivery in HBV+ women? Why not stop at delivery?	Thank you for your comment. The continuation of antivirals after delivery is related to post-partum flares in hepatitis B. The GDG considered a possible benefit in treating beyond 4 weeks to provide additional protection for the mother.
SH	British Association for Sexual Health and HIV (BASHH)	9	Full	51	2	If there is no risk of transmission to the baby through breastfeeding, why recommend continuing to treat whilst breast feeding?	Thank you for your comment. The GDG considered that continuation of treatment while mothers breast feeding is not about risk of transmission through breast feeding, but to avoid the risk of 'post partum' flares of HBV activity.
SH	British Association for Sexual Health and HIV	10	Full	General	General	CRUCIAL: Partner notification and vaccinating sexual partners and drug-using	Thank you for your comment. Screening and vaccination are outside the scope of

	(BASHH)					partners The guideline does not cover the need to make a risk assessment following comprehensive sexual and drug use history taking. All partners should be invited in for screening and vaccination. The only mention of vaccination is in relation to mother to child transmission. The term 'partner notification' – an integral part of managing any sexually transmissible infection – do not appear in the guideline at all! We acknowledge that the guideline specifically excludes vaccination and primary prevention but we would consider at least a short paragraph on screening and vaccinating contacts as an integral part of the care of individuals with CHB – we could argue that vaccinating in this setting is more secondary than primary prevention? The role of specialist clinics in managing sexual and/or family contacts should be highlighted.	this guideline. The guideline cross refers to the NICE Public Health Guidance 43; Hepatitis B and C: ways to promote and offer testing to people at increased risk of infection. This clinical guideline should be used in conjunction with the public health guidance. All guidance will be linked together in the pathway.
SH	British HIV Association (BHIVA)	1	Full	1	1	BHIVA comment: An emphasis on HIV testing both at diagnosis and pre-initiation of treatment, if different	Thank you for your comment. The guideline recommends HIV testing be arranged for adults who are hepatitis B surface antigen positive (recommendations 6 in full guideline). We have added in a recommendation to cover retesting – recommendation 32 states "Re-assess the person's risk of exposure to HIV before starting treatment and offer repeat testing if necessary". Recommendation 52 states the same should be done for children and young people.
SH	British HIV Association	2	Full	43	7	5 Guideline summary	Thank you for your comment. Vaccination

	(BHIVA)			and Page 45	Line 24	1 Assessment and referral BHIVA comment: Should include hepatitis A testing with a view to vaccination if non-immune, given the high rate of severe hepatitis in patient who get acute hepatitis A on top of chronic liver disease from other causes (such as HBV)	is outside the scope of the guideline. We agree that Hepatitis A should be tested for and have added lgG anti-HAV to the list of tests in recommendation 6.
SH	British HIV Association (BHIVA)	3	Full	50 and Page 447	26 First line (not numbered) – paragraph heading "Other considerations"	Recommendation 62 BHIVA comment: BHIVA agrees with the guideline	Thank you for your comment.
SH	British HIV Association (BHIVA)	4	Full	51 and Page 447	2 Last paragraph (line not numbere	Recommendation 64 BHIVA comment: BHIVA agrees with the guideline	Thank you for your comment.

					d)		
SH	British Infection Association	1	Full	426		NICE recommends short-term antiviral Rx if the viral load of the pregnant woman is > 10^7 IU/ml. Evidence to support this is unclear. I think 10^6 IU/ml is a better threshold as it also matches the Green Book criterion for HBIG, making it a uniform category of high risk women.	Thank you for your comment. The GDG considered that threshold of mother's viraemia higher than 10^7IU/ml makes sure that only the mothers at greatest risk of infecting their babies are offered antiviral treatment. This decision was made based on consensus of the group and their knowledge of the published literature.
SH	British Liver Trust	1	Full	General	General	In general the British Liver Trust welcome these guidelines as a step in the right direction for the management of hepatitis b. The wording is however written from a clinical perspective, and does not focus enough on the patient perspective.	Thank you for your comment. NICE will produce a number of versions of this guideline, including 'information for the public' which is written using suitable language for people without specialist medical knowledge
SH	British Liver Trust	2	Full	16	6	Information should be provided to a recognised standard i.e Information Standard or Crystal Mark approved to ensure that the patient, family and carers have clear access to information to take away with them.	Thank you for your comment. We agree information provided should be of the highest standard.
SH	British Liver Trust	3	Full	19	9	Throughout the whole document there is mention of Transient Elastography, and while we welcome the fact that patients have a non invasive procedure rather than biopsy when necessary, not all hospitals have a 'Fibroscan' and therefore not all patients will have access to this technology.	Thank you for your comment. Fibroscan is increasingly available in some centres and access may require the patient to travel to a centre as an interim arrangement before fibroscans are more generally available.
SH	British Liver Trust	4	Full	26	24	Patients who are eligible should be offered appropriate viral hepatitis treatment which should include Protease Inhibitors or any emerging technologies approved for use, of which there may be many in the future.	Thank you for your comment. Protease Inhibitors are outside the scope for this guideline. For your information, the NICE Technology Appraisals programme looks at significant new technologies that emerge.

SH	British Medical Association	1	NICE	17	9 -18	We are concerned at the number of tests required in general practice before referral. As the tests are likely to be required infrequently, these will be both difficult for GPs to remember and expensive for them to commission. It is also possible that GPs will be accused of, or penalised for, requesting these tests too often. We would suggest that NICE recommends that all pathology laboratories will carry out these tests by allowing an online form requesting 'further Hepatitis B blood tests' to be ticked.	Thank you for your suggestion, we will pass on to NICE Implementation team.
SH	British Medical Association	2	NICE	17	19 -20	We are particularly concerned about the need for general practitioners to arrange a test "for surveillance for hepatocellular carcinoma (HCC), including hepatic ultrasound and alpha-fetoprotein testing" before referral. This seems inappropriate for primary care, which does not have systems set up to reliably achieve this level of testing, and should more properly be done in a secondary care setting.	Thank you for your comment. The GDG agreed that arranging a test for hepatocellular carcinoma (HCC) including ultrasound was appropriate within primary care and this is currently done in some areas.
SH	British Medical Association	3	NICE	29 -32		We are also concerned that it is not specified where either the continued monitoring of patients undergoing treatment or the regular surveillance for hepatocellular carcinoma should be carried out. The guideline must specify that this work should be carried out in a secondary care setting.	Thank you for your comment. This work would be carried out in a secondary care setting. There is no suggestion in the guideline that on-going surveillance would be carried out in primary care. All HBsAg positive patients are recommended to be referred to and followed up in secondary care.
SH	British Medical Association	4	NICE	Gene ral	Gen eral	We are concerned that there appears to have been no input or representation from primary care during the drafting of this guideline. Given that the recommendations will impact on general practice, a GP	Thank you for your comment. The GDG included a GP, Dr Alan Mitchell.

						representative should have been part of the initial drafting.	
SH	British Society of Gastroenterology - Liver Section Committee	1	Full	General	General	The document is a very, very long and careful review of most aspects of chronic hepatitis B virus infection and delineates carefully which aspects of hepatitis B aren't covered. The recommendations are of value to those in primary care and to both secondary and tertiary referral centres. Whilst I think most hepatologists in the field would agree with much or most of this document there are areas that are out of step with current practice in some centres and the recommendation to offer Tenofovir to all hepatitis B positive mothers with a certain level of viraemia, which appears rational, is not yet supported by clinical evidence. More specific point-by-point responses to the recommendations in the document are below.	Thank you for your comment. The recommendation to offer tenofovir to all hepatitis B mothers with HBV DNA>10^7 log10 IU/ml in the third trimester was based only on GDG clinical expert opinion. No studies were identified to compare other nucleos(t)ide analogues other than lamivudine and telbivudine which are not currently in use in clinical practice. The GDG considered that tenofovir which is a highly potent drug would be permissible for use during pregnancy and that preventing cases of CHB transmission is of paramount importance. The GDG have drawn on the indirect evidence on the use of tenofovir in the HIV population, which they agree is applicable to women with hepatitis B. This has been made clearer in the linking evidence to recommendations section of the guideline. However, the GDG agreed that studies needed to assess the long term effects of tenofovir in pregnancy.
SH	British Society of Gastroenterology - Liver Section Committee	2	Full	45 -46	Recs 5 and 9	The blood tests recommended at initial diagnosis of hepatitis B virus infection should include acknowledgement that a low white cell count and a low platelet count can be excellent indicators of underlying liver disease and should be included in the assessment and my own preference is that it should be part of the initial referral letter to secondary or tertiary care. For those in primary care, who in my view should be referring all such patients on, a low white	Thank you for your comment. It is not the view of the GDG that these tests would be carried out routinely. The GDG agreed that a history and clinical examination would be a usual part of the consultation with the patient. This is standard practice and does not require highlighting in the recommendations.

						cell count and platelet count would be a further reason to encourage prompt referral. At the same time I believe that patients should be screened for the commoner metabolic diseases such as haemochromatosis and alpha-1-anti-trypsin deficiency as these can be important co-factors in progressive liver injury. More importantly, an accurate history of alcohol consumption and a body mass index should be included as these are much more common associations of chronic hepatitis B virus infection. Patients with hepatitis B infection are just as likely to suffer from non-alcohol-related fatty liver disease or alcohol-related fatty liver disease and in many cases the hepatitis B may be the secondary event. Screening for these four disorders becomes even more important in view of the document, which steers away from routine liver biopsy and which is pronounced throughout the document. My own view in addition is that we perhaps need to state the obvious and that taking a history and a formal clinical examination is seen as an essential part of assessing any patient with hepatitis B virus infection. This may seem pedantic but much of the document is in that sort of detail but doesn't mention clinical history and clinical examination in identifying those patients with more advanced disease at first referral.	
SH	British Society of Gastroenterology - Liver Section	3	Full	47 -48	Recs 15 -19	The area of elastography is contentious and it doesn't come across in the document that not all hepatologists, nor indeed all	Thank you for your comment. The GDG agree that there may be a subgroup of patients with raised ALT due

	Committee					gastroenterologists with an interest in hepatology, are fully behind the notion of routine elastography for patients with liver disease. There is no doubt that elastography helps identify patients at extremes so that those who are healthy and those who have advanced disease can be identified readily. The recommendations indeed recognise this by indicating that those with intermediate values should undergo staging liver biopsy but that patients at either extreme do not necessarily need to undergo liver biopsy. An alternative view is that a patient with little fibrosis or inflammation in relation to chronic hepatitis B virus infection will have no symptoms, will have a normal clinical examination, normal liver ultrasound, normal liver function tests and in those patients elastography probably adds nothing to the identification of the patients with benign disease. In my view at this stage elastography may provide further confidence for the physician and patient but cannot be regarded as an essential part of care. For patients with more advanced disease avoidance of liver biopsy because elastography has revealed fibrosis may cause problems. If for example a patient has non-alcohol-related fatty liver disease or alcohol-related liver disease which is causing abnormal liver function tests and also happens to be hepatitis B virus carrier the focus will be on treating the hepatitis B. A biopsy at this stage might show that alcohol-related and non-alcohol related fatty	to non-alcohol-related fatty liver disease or alcohol-related liver disease and who are also hepatitis B virus carriers; there is a risk that these patients could be treated inappropriately for hepatitis B because of the lack of contradictory evidence from a biopsy. The GDG therefore decided to differentiate between an active CHB and an inactive CHB infection, in which the ALT elevation is due to some other chronic liver disease, by adding an HBV DNA requirement to the transient elastography recommendation for cirrhosis. In the case of active CHB, the HBV DNA will be detectable and in the inactive group the HBV DNA will be undetectable; the GDG set the threshold at the detectable/undetectable level on any one occasion, rather than at 2000 IU/ml on two consecutive occasions, because they considered it likely that the majority with high TE would have cirrhosis due to CHB, and that it was important to start people with cirrhosis on antiviral treatment as soon as possible. The GDG considered that people with fatty-liver disease and alcohol-related liver disease might be at risk of complications following liver biopsy and so did not wish to recommend a biopsy for these people. Instead they recommended fairly frequent monitoring of people with high TE levels, for example every 12-24 weeks, at the discretion of the clinician. If HBV DNA levels became detectable on any one occasion, the

						liver disease are causing peri-sinusoidal fibrosis and that hepatitis B is a secondary event.	patient would be offered antiviral treatment. Therefore the monitoring recommendation 75 was also changed.
SH	British Society of Gastroenterology - Liver Section Committee	3	Full	47 -48	Recs 15 -19	Treating the hepatitis B without a biopsy at this stage would mean that the wrong disease was being treated and whilst reducing the influence of hepatitis B as an important co-factor the patient would be left with the impression that the disease was being managed but would find out later that the wrong disease was being managed. I think all of us recognise that liver biopsy is inconvenient and uncomfortable and does have morbidity and occasional mortality but I still believe that an accurate diagnosis of patients with intermediate and advanced fibrosis is important. Many hepatologists will feel the same. The emphasis on elastography should also take into the account that MR elastography, which is likely to be more reliable, is not very far away and will be introduced in some tertiary centres in the near future. The authors do not really discuss ultrasound at all in assessing patients with liver disease which is perhaps surprising as it is a routine part of every hepatologists armamentarium and I think many radiologists would also be surprised that there is so little emphasis on this in the clinical management. Perhaps that is because ultrasound has not been assessed formally in patients with hepatitis B virus infection as it is now part of the established process whereas elastography is a	

						newcomer to the scene.	
SH	British Society of Gastroenterology - Liver Section Committee	4	Full	45	Rec 5	The report suggests that at referral an ultrasound should be organised as part of the screening programme. Screening doesn't get much of a mention thereafter in the document and I suspect there are reasons for this, which include contrary advice from NICE about the value of screening in liver disease in general for hepatocellular carcinoma. I think it is reasonable to accept that there are strong widely accepted guidelines on screening for liver cancer in patients with hepatitis B and that we should follow those criteria. The implication of the document (I may have interpreted this incorrectly) is that screening should be introduced at first identification of hepatitis B and the implication then is that it could be done or organised by the primary care physician. We shouldn't be screening all patients and this is giving the wrong message about the risk of HCC. Screening should be focussed on those at high risk of HCC and in my view should be organised through secondary or tertiary care where specific individuals are targeted towards screening because they have the appropriate expertise and turnover. In my view a stronger recommendation about screening should be included in the document. This is covered in section 5 and in section 10, there is a suggestion that we should be screening children for HCC. I really don't know that this is justified and whether it would cause more anxiety than it	Thank you for your comment. Recommending an ultrasound in the pre referral tests for ruling out HCC at the stage when a patient is first found to have CHBV infection, is considered by the consensus of the GDG to be appropriate for both adults and children and reflects good practice. The GDG were in agreement that the initial tests should be carried out within primary care in order that all the necessary information was available when referred to a specialist, and this would be beneficial to the patient and reduce the number of hospital appointments. In a subsequent section, we deal with further screening for HCC.

						resolves.	
SH	British Society of Gastroenterology - Liver Section Committee	5	Full	50	Recs 63-64	Perhaps one of the most difficult areas for managing hepatitis B is in pregnancy and during breast-feeding. A number of different message are delivered by different specialities and unfortunately we do not always sing from the same hymn sheet. I think it would be advantageous if there was a stronger message from NICE. It appears that with respect to breast-feeding the advice is coming from the wrong angle. There is no evidence at all that breast-feeding is dangerous and that point should be made strongly. The observation that *post-exposure* vaccination of babies is effective needs to be emphasised. It would also, I think, be advisable if in the same section there was clear advice on the wisdom or otherwise of proceeding to Caesarean section which is undertaken in some hospitals - in my view incorrectly - in mothers who are hepatitis B positive to reduce the risk of transmission of the virus. This is a practice that is decreasing but still present. In addition I think it would be useful to emphasise in this document that just because a baby has been vaccinated, perhaps with vaccine and perhaps also with hepatitis B immunoglobulin does not mean that the baby is immune. Certainly a number of mothers that I deal with are left under the impression that all is well at this stage and post vaccination testing of babies needs to be emphasised in the document to identify children who escape protection	Thank you for your comment. We agree that the point on safety of breast-feeding is important that is why the GDG included a recommendation to advice women that there is no risk of transmitting HBV to their babies through breastfeeding if guidance on child immunization has been followed and that they may continue antiviral treatment. Continuation of treatment while mothers breast feeding is not about risk of transmission through breast feeding, but to avoid the risk of 'post partum' flares of HBV activity. This recommendation was based on GDG clinical expert opinion as no available evidence on lactating mothers with CHB was found. Recommendation 66 follows guidance on best practice guidance for hepatitis B antenatal screening and newborn immunization programme, Green book and NICE guidance 43 and 21.

						offered at birth. There is no doubt in my mind that services have improved considerably over the past three or four years but there are still gaps and misconceptions and a lot of the patients that I see are not fully informed about the longer term risks.	
SH	British Society of Gastroenterology - Liver Section Committee	6	Full	50	Rec 60	On the same theme the use of Tenofovir in the last trimester of pregnancy appears to be rational especially when targeted at mothers who have a high viral load. However I haven't seen data in this document that support this change in practice. When I deal with a pregnant patient in my clinic and discuss anti viral therapy in pregnancy there are a number of questions that are asked repeatedly and mothers need to be well informed. Before recommending Tenofovir in such strong terms as in this current document it is important to be able to be able answer questions such as: 1. What precise benefit in terms of risk reduction does Tenofovir add? 2. What is the precise viral load at which therapy should be introduced? 3. What happens to HBV replication in the third trimester of pregnancy if patients are not given anti viral therapy? 4. How many foetuses have been exposed to Tenofovir and can we	Thank you for your comment. Please see below for the responses to your queries: 1. We do not know the precise benefit; there are no studies to answer this question. 2. In pregnancy the precise viral load at which therapy should be introduced is 10^7 copies/ml. 3. It remains the same. 4. A large number of foetuses have been exposed to tenofovir – more information can be found in the antiviral register. 5. A rebound will occur with or without the course of tenofovir. The GDG have drawn on the indirect evidence on the use of tenofovir in the HIV population, which they agree is applicable to women with hepatitis B. This has been made clearer in the linking evidence to recommendations section of the guideline. However the GDG agree that further data on the long term use of

						honestly say that this is safe for the foetus as well as for the mother? 5. For those patients who are being given a transient course of Tenofovir what is the precise risk of rebound hepatitis?	tenofovir is needed.
SH	British Society of Gastroenterology - Liver Section Committee	6	Full	50	Rec 60	In my view many mothers will not accept therapy for hepatitis B under these circumstances unless there are precise answers to the questions above, which mothers ask frequently in clinic. The worldwide exposure to drugs such as Lamivudine and Adefovir is much greater currently than for Tenofovir and it would be useful if Gilead was to allow us to see all the data that are available on maternal use of Tenofovir and for clinical trials to continue until such time as there are clear answers to the questions above. I think another point to make in the document at this stage is that it is exceptional for a hepatitis B infected mother to become pregnant in the presence of significant liver disease. In my view the statement on the use of Tenofovir in pregnancy is too dogmatic for the evidence base.	Thank you for your comment.
SH	British Society of Gastroenterology - Liver Section Committee	7	Full	49	Rec 39 And 45	Another important issue managing patients with hepatitis B virus infection is when treatment is being discussed. I have long been in favour of more frequent use of Interferon Alpha and I have no strong objections to the conclusions that Interferon	Thank you for your comment. The GDG considered patients' informed choice to be important and this is reflected in recommendations 1, 15, 24, 31, 51, 62 in the full guideline. Individual patient preference is also acknowledged as a

						Alpha should be first line therapy for a significant number of adult patients who are being offered antiviral therapy. However I think the recommendations are very dogmatic and could be softened. Patients are quite capable of making a decision between a defined course of Interferon Alpha and a long-term course of oral therapy. I would have thought the majority of patients would chose the former and get it over with. But because of the side effects associated with Interferon many actually elect for the latter. I think the decision to use Interferon Alpha therapy in many cases has to be one that is discussed with the patient where oral therapies are offered as a good alternative and we must make allowance for social factors, professional issues, planning families etc. The clearance of HBe antigen and the clearance of HBsAg was one reason to push Interferon Alpha in the past but this is observed increasingly with long-term oral therapies.	factor influencing the choice of antiviral treatment and noted in the other considerations section of the linking evidence to recommendations table for the above recommendations. The recommendation on adefovir has been modified to allow patients to have the choice of continuing on adefovir if it is working well, or of switching if it is not. The recommendation now says, "People currently receiving adefovir dipivoxil should be offered the option to switch to a different treatment. Offer tenofovir disoproxil or entecavir depending on previous antiviral exposure…" The recommendation on telbivudine already gave the option of continuation. For any other drugs, the use of the verb 'offer' in the treatment recommendations takes account of patient choice, in the light of patient information, as described above.
SH	British Society of Gastroenterology - Liver Section Committee	7	Full	49	Rec 39 And 45	The authors also suggest that some patients could switch therapy if they are felt to be on sub optimal therapy based on the current evidence. This strikes me as nonsense. If a patient is well on a safe combination of drugs with normal liver function tests and remains HBV DNA negative I would be keen to do nothing until such time as a change was mandated by clinical status. There is no evidence that	

						we should change treatment in patients who are stable with controlled HBV replication.	
SH	British Society of Gastroenterology - Liver Section Committee	8	Full	52	Recon monitoring patients not on treatment	It needs to be stated who should undertake this – a long-term commitment.	Thank you for your comment. This will be determined according to local resources and/or circumstance.
SH	British Society of Gastroenterology - Liver Section Committee	9	Full	General	General	My next point is certainly a minority view. With the way the drugs were developed a large number of patients were started initially on Lamivudine and then when Adefovir became available this was added often when resistance to Lamivudine was observed or because of the concerns of monotherapy with lamivudine. There are many patients who are managed well on Lamivudine and Adefovir with good long-term control, low breakthrough rates and a low incidence of progressive liver injury. Gilead changed the prices of Tenofovir and Adefovir such that the price of Tenofovir fell and the price of Adefovir rose. I don't know quite when Adefovir will come off patent but I think it is around about now, if this date hasn't already passed. This would change the economic arguments based on the use	Thank you for your comment. The combination treatment of lamivudine plus adefovir was included as a comparator for all the networks of network meta-analysis. For both outcomes in the network meta analyses (NMA) (undetectable HBV DNA and HBeAg seroconversion), tenofovir had the highest probability of being the best treatment whereas the combination treatment of lamivudine plus adefovir came very low in the ranking of all treatments. We are aware that a change in the cost of drugs may change the outcome of our economic model. However, we have to make recommendations based on the costs applicable at the time of the guideline publication. Any reduction in costs will be taken into account when the guideline is next updated.

						of monotherapy with Tenofovir. If Adefovir was available generically the cost could drop considerably which would be an enormous saving for the health service if it was used in combination with Lamivudine as an alternative to Tenofovir. This is particularly true because of the prolonged nature of therapy with these agents. This doesn't mean that Tenofovir wouldn't be used with this approach, simply that Tenofovir could be held in reserve for occasions when Adefovir and Lamivudine was no longer effective. The use of Adefovir has received very little attention in this document and the combination of Adefovir with Lamivudine again hasn't been addressed in any detail. This is something that has evolved in clinical practice and not have subjected to comparative clinical trial. Another issue which I think needs to be expanded is the duration of therapy with oral therapy and whether the goal is HBsAg clearance or control of HBV replication. The first solid evidence regarding loss of HBsAg that I have been aware of was presented at the American Association of Liver Disease meeting in Boston recently and may be regarded as too preliminary for this document. However it is important to state that oral therapy is long term and it might be wise to recommend some areas at which oral therapy *might* be curtailed. The long term nature of oral therapy needs to be emphasised so that patients and	Regarding the duration of oral therapy and the potential for treatment for life: the recommendations cover the points made, but we agree they could be better linked. There are two main criteria for stopping oral antiviral treatment: following HBeAg seroconversion (recommendation 90); and following HBsAg seroconversion and undetectable HBV DNA (recommendation 91). People who achieve HBeAg seroconversion are then monitored every 6 months (recommendation 92) and if DNA levels and ALT become too high, then antiviral treatment should be offered in line with recommendations 27 and 28. People who achieve HBsAg seroconversion can be discharged if they are anti-HBs positive on 2 consecutive tests (recommendation 93). Otherwise they are monitored annually for HBsAg. Recommendation 31 advises the health care professional to discuss with the patient, treatment options, adverse effects and long-term prognosis before starting treatment. Recommendation 1 covers patient information on treatment options and contraindications based on the patient's circumstances, short- and long-term treatment goals, causes of treatment failure, including non-adherence to

						practitioners can make a realistic decision to consider the use of Interferon Alpha at an earlier stage and to be made aware that therapy could be for many, many years and that therapy has to be unbroken during that period without causing risk. The document is a little light on the fact that some patients simply don't tolerate oral therapies and whether this is due to genuine side effects or anxiety about taking therapy long term I am not sure but this point doesn't come across readily in the document. The need to assess compliance and resistance in cases unresponsive to oral therapy also needs expansion.	prescribed medicines, and options for re-treatment and risks of treatment, including adverse effects and drug resistance. The GDG has also produced a new recommendation for a personalised care plan. We have added linking phrases to the various linking evidence to recommendations sections, e.g. in the monitoring/stopping rules linking evidence to recommendations table: "The GDG was mindful that stopping rules should be considered in conjunction with patient information on the different types of treatment for CHB, including awareness of the potential for short term (one-off) treatment with peg interferon versus potential for lifetime treatment with nucleo(t)sides, and side effects of drugs including resistance, and with reference to the patient's personalised care plan (Chapter 6)". We anticipate that the links between sections will be more apparent in the NICE pathway and in implementation strategies.
SH	BSPGHAN	1	Full	Recommendations	General	There are no specific comments within the recommendations with regard to children and young people. Most paediatric hepatologists would agree that in the absence of proven effective therapy, children should be treated with anti-viral therapy only in clinical trials,	Thank you for your comment. The GDG agree that in the absence of proven effective therapy, children and young people should ideally be treated with anti-viral therapy only in clinical trials, except for compassionate use or clinical need. Their recommendation for children is that

						except for compassionate use	antiviral drugs could be considered, but, in the footnote to the recommendation, they state that each of the antiviral drugs did not have UK marketing authorisation for use in children and that the prescriber should follow relevant professional guidance, taking full responsibility for the decision. The GDG felt that the professional guidance and good practice would ensure appropriate treatment of children.
SH	BSPGHAN	2	full	46	19	Include in baseline tests anti-HBc IgG as well as IgM	Thank you for your comment. This test is not relevant for people who are HBsAg positive.
SH	BSPGHAN	3	full	46	26 no 11	Children with chronic HBV should be managed by a paediatric hepatologist/specialist with interest in hepatology in a specialist centre with the paediatric MDT trained to manage and support children with HBV and their families	Thank you for your comment. We have recommended that children are seen by paediatric specialists. There are very few centres currently available and therefore it would not be practical to make such a recommendation.
SH	BSPGHAN	4	Full	46	28 no 12	Consider adding • The referring health professional should include the child's HBV vaccination schedule with dates when applicable. • Include information of parents and siblings to ascertain transmission route	Thank you for your comment. Whether infection of a new-born occurs as a result of no vaccination or inadequate vaccination has no significance in terms of further action as regard treatment of the infant.
SH	BSPGHAN	5	full	47	27 no 24	ALT levels, in paediatrics, are age and gender specific. The levels quoted may be within normal range. It may be better to state ALT above the normal level.	Thank you for your comment. The primary sources of data are thin and confounded by ethical constraints of taking blood samples from healthy children. Most children without liver disease run

							transaminases in single figures or low teens. This is a research priority, but it is valid to challenge current 'received wisdom' and in the absence of better data we should stand by the realignment of paediatric values in keeping with thresholds for young adults.
SH	BSPGHAN	6	full	48	10 no 29	Liver biopsy is not a requirement before initiating treatment. Treatment decisions in children are based on ALT levels and HBV DNA levels. No paediatric hepatologist would insist on demonstrating fibrosis before considering treatment. Selection of children with abnormal ALT has been accepted as an entry criteria for clinical trials because these children are more likely to respond	Thank you for your comment. We accept that not every child/young person requires a biopsy prior to starting treatment. However in young people arriving for example as migrants from endemic regions with high viral loads and active transaminitis, it will be unclear how long they have been in an immune-reactive phase of infection and they may have advance fibrosis. Perhaps more importantly, the liver biopsy may reveal other pathologies and save the need for embarking on antiviral treatment. Recommendation 25 has been amended to read 'consider' rather than 'offer'.
SH	BSPGHAN	7	full	49	50	There is no evidence to base the recommendation that children should be treated with 48 weeks pegylated interferon, nor to start with an antiviral if no response to pegylated interferon. Clinical trials are now in progress to evaluate the efficacy of this treatment	Thank you for your comment. These recommendations were based on GDG consensus as noted in the linking evidence to recommendations section.
SH	BSPGHAN	8	full	46	7 no 8	Consider adding: Screen other children in the family	Thank you for your comment. The guideline cross refers to the NICE Public Health Guideline 43; Hepatitis B and C: ways to promote and offer testing to people at increased risk of infection. This clinical guideline should be used in conjunction with the public health

							guideline.
SH	BSPGHAN	9	Full	52	16 no 72	There is no rationale for testing ALT in children every 12 weeks, especially those in the immune tolerant phase do not require 3 monthly follow up. Follow up with repeat blood tests every 6-12 months is appropriate. We need to consider that these are well children and they are not keen to take time off school or provide explanation about non-attendance to their school teacher.	Thank you for your comment. We have amended recommendation 77 to read as follows: Monitor ALT levels every 24 weeks in children and young people with HBeAg positive disease who have normal ALT levels (less than 30 IU/ml for males and less than 19 IU/ml for females) and no evidence of significant fibrosis (METAVIR stage less than F2 or Ishak stage less than 3).
SH	BSPGHAN	10	full	52	22 No 74	Children in the immune clearance phase should be reviewed every 12 weeks or more frequently to monitor their LFTs and disease progression	Thank you for your comment. We have amended Recommendations 77 and 79 to reflect this: 77. Monitor ALT levels every 24 weeks in children and young people with HBeAg positive disease who have normal ALT levels (less than 30 IU/ml for males and less than 19 IU/ml for females) and no evidence of significant fibrosis (METAVIR stage less than F2 or Ishak stage less than 3) 79. Review every 12 weeks children and young people with HBeAg-negative disease who have abnormal ALT (greater than or equal to 30 IU/ml for males and greater than or equal to 19 IU/ml for females) and HBV DNA greater than 2000 IU/ml.
SH	BSPGHAN	11	full	52	26	Pegylated Interferon – monitoring schedule in children differs to that in adults. Children	Thank you for your comment. We have added in a recommendation (80) to

					no 75	require close monitoring at 0, 2, 4 and every 4 weeks whilst on pegylated interferon	address this that reads: Review injection technique and adverse effects weekly during the first month of treatment in people taking peginterferon alfa-2a.
SH	BSPGHAN	12	full	52		Monitoring of weight and height in children on PEG-IFN is essential and needs to be included, especially children during puberty. In general, interferon should be avoided during puberty because of the detrimental effect on growth and nutrition	Thank you for your comment. We agree with your comment and have amended recommendation 81 to reflect this. Monitor full blood count, liver function (including bilirubin, albumin and ALT), renal function (including urea and electrolyte levels) and thyroid function (and in children, weight and height) before starting peginterferon alfa-2a and 2, 4, 12, 24, 36 and 48 weeks after starting treatment to detect adverse effects.
SH	BSPGHAN	13	Full	52		Children who require PEG-IFN therapy should be appropriately addressed for the timing e.g. not during puberty, their year of important exams, carer's commitments. Consideration will need to be given to the need for proper preparation especially the need for play therapy due to anxiety, training preparation and psychological preparation in case of non response to treatment. This also includes when and how to inform school when some parents do not want to disclose their child's diagnosis to the school	Thank you for your comment. We agree that this consideration is important. This is standard paediatric practice and does not need to be included in the guideline.
SH	BSPGHAN	14	Full	53	4 79 and 80	It is very important that antiviral treatment is considered in treatment centres equipped with adequate resources to monitor clinical and psychosocial need of the child. These	Thank you for your comment. We agree with your comment but very few centres are available currently. This is reflected in recommendation 12 in the full guideline.

						should include paediatric multi disciplinary team and specialists (preferably paediatric Hepatologist) with viral hepatitis case load of about > 20 children per year. The team should be the main carers and shared cared with the local consultant or GP. The child should not be shunted from one centre to another.	
SH	BSPGHAN	15	full	59	Algo rithm	Assessment of liver disease in children does not include liver biopsy in all cases. The treatment scheme suggested for children and young people is not based on any evidence	Thank you for your comment. We accept that not every child/young person requires a biopsy prior to starting treatment. However in young people arriving for example as migrants from endemic regions with high viral loads and active transaminitis, it will be unclear how long they have been in an immune-reactive phase of infection and they may have advanced fibrosis. Perhaps more importantly, the liver biopsy may reveal other pathologies and save the need for embarking on antiviral treatment. Recommendation 25 has been amended to read 'consider' rather than 'offer' to reflect the strength of evidence.
SH	BSPGHAN	16	Full			In paediatrics, children and particularly young children should be monitored every 3 months when on treatment for side effects and compliance. HBV DNA monitoring in Children on lamivudine for more than 48 weeks should be considered to detect viral breakthrough due to resistance 3 monthly review for children on Tenovofir for monitoring of side effects. Children who developed rash while on the treatment will need a review by a paediatric	Thank you for your comment. We have added in a recommendation (80) to address this that reads: Review injection technique and adverse effects weekly during the first month of treatment in people taking peginterferon alfa-2a**.** Thank you for your comment. Rash is a very uncommon adverse event in children receiving tenofovir. Clinicians prescribing

						dermatologist and consider discontinuation of Tenovofir if the rash is moderate or severe Very few children (except those with fulminant hepatitis) develop decompensated disease Patients' Information : Should be more explicit that family members and other close contacts should be screened for HBV and discuss importance of vaccination (3 dose course) and relevance of testing for immunity following vaccination If IFN is advised ,information should include the risks to the unborn in case of pregnancy during the treatment and the importance of pregnancy testing prior to starting therapy and offer contraceptive advice.	tenofovir should be familiar with managing adverse events. A paediatric dermatologist's opinion may be sought in unusual clinical presentations. Thank you for your comment. We agree and have added a footnote to recommendation 41 in stating the following "avoid use of peginterferon alfa-2a in pregnancy unless the potential benefit outweighs risk. Women of childbearing potential must use effective contraception throughout therapy."
SH	BSPGHAN	16	Full	53	88	The study below: Boxall E, Sira J, Standish RA, Sleight E,	Thank you for your comment. All the proposed studies were not included in the evidence reviews as they

						Adeodu O, Dhillon A P, Scheur P J, Kelly D 2004. The natural history of hepatitis B in perinatally infected carriers. States : 35 liver biopsies were performed in children with active virus replication (HBeAg or HBV DNA positive). Results found only weak correlation between histological evidence of hepatitis and ALT and AST levels. The response to interferon alone was better in children with genotype A compared to D (50% and 36%), but prednisolone priming improved the response so that there was no difference between genotypes A and D (66.7% and 70%). Boxall E, Sira J, Kaskar S, Workman J, Kelly D.Does genotype predict response to treatment in children infected with hepatitis B perinatally? J Med Virol. 2012 Oct;84(10):1535-40. doi: 10.1002/jmv.23308. Small study which demonstrated the efficacy of interferon on delayed seroconversion Boxall EH, Sira J, Ballard AL, Davies P, Kelly DA. Long term follow up of hepatitis B carrier children treated with Interferon and Prednisolone. J Med Virol 2006; 78: 888-895. Consider treating mothers with eAg positivity or previous vaccination failure or known vaccine escape mutation. Consider adding autoantibodies	didn't match our prespecified protocols.

						References	
SH	BSPGHAN	16	Full			Paganelli M, Stephenne X, Sokal K. Chronic Hepatitis B in Children and adolescents. J Hepatol October 2012; 57(4):885-896 Barbara A, Haber MD, Joan M et al. Recommendations for screening, Monitoring, and Referral of Pediatric Chronic Hepatitis B. Pediatrics, 2009;124:e1007-1013 Sokal EM, Conjeevaram HS, Roberts EA, Alvarez F, Bern EM, Goyens P, et al. Interferon alfa therapy for chronic hepatitis B in children: a multinational randomized controlled trial. Gastroenterology. 1998;114:988–995 Zoulim F, Locarnini S. Hepatitis B Virus Resistance to Nucleos(t)ide Analogues. Gastroenterology. 2009 November 137(5); 1593-1608.	We reviewed the study by Sokal et al (1998) and its results were taken into consideration for the recommendations on antiviral treatments for children. The other proposed studies were reviews or expert guidelines and they didn't meet the inclusion criteria of our prespecified protocols.
NICE	CCP Comissioning team	1	NICE	18		Recommendation 1.2.5 – It's not clear whether the GP waits for the results of the test or they refer without the tests. Please can this be clarified.	Thank you for your comment. The recommendation states that the results of the initial tests should be included with the referral.
NICE	CCP Comissioning team	2	NICE	22		Recommendation 1.5.12 – We are in discussion with the TA team about whether this can be presented as a guideline recommendation i.e. 'Do not offer'.	Thank you for your comment.
NICE	CCP Commissioning team	3	NICE	22		Recommendation 1.5.12 – What happens if you are currently receiving Adefovir	Thank you for your comment. This is covered by recommendation

						dipivoxil? Should it be stopped or should you keep receiving it?	1.5.14.
NICE	CCP Commissioning team	4	NICE	22		Recommendation 1.5.34 – Please can you clarify the reason for referring to the BNF in the recommendation. The SPC covers renal impairment and dosage and we would usually highlight any special cautions or contrainidications in a footnote rather than referring to the BNF.	Thank you for your comment. The recommendation has been amended to refer to the summary of product characteristics rather than the BNF.
NICE	CCP Commissioning team	5	NICE	16	6	Recommendation 1.1.1 - Should monitoring also be mentioned here?	Thank you for your comment. “Monitoring” has been added to the recommendation.
NICE	CCP Commissioning team	6	Full	Algorithms		Algorithms – Please can you consider the presentation of the algorithms. The algorithms usually include the recommendation wording and are distinguishable from the NICE pathway presentation.	Thank you for your comment. We have considered your comment and have amended the algorithms.
SH	Department of Health	1	NICE	General	General	No comment	N/A
SH	Gilead Sciences	1	Full	48	17	As per the updated 2012 EASL Clinical Practice Guidelines (CPG), many patients can benefit from pegylated interferon (Peg-IFN) treatment but this is not suitable for all patients, especially HBeAg negative patients. *“Currently, there are two different treatment strategies for both HBeAg-positive and HBeAg-negative CHB patients: treatment of finite duration with (PEG-IFN) or a Nucleos(t)ide Analogue (NA) and long-term*	Thank you for your comment. The guideline is not inconsistent with the 2012 European Association of the study of the liver Clinical Practice Guidelines by recommending both types of antiviral treatment. However, after clinical and cost effectiveness analysis of all antiviral treatments reviewed, the GDG recommended pegylated interferon as first line treatment and tenofovir or entecavir as second line for HBeAg negative people.

						treatment with NAs". http://www.easl.eu/assets/application/files/ef520780b91cf4f_file.pdf. Gilead Sciences suggests that both treatment strategies should be reflected in the final NICE guidelines.	
SH	Gilead Sciences	2	Full	49	10	The 2012 EASL Clinical Practice Guidelines state that *"The optimal management of patients with partial virological response under entecavir or tenofovir is currently debatable. In such patients with a partial virological response at week 48, the HBV DNA levels at week 48 and their kinetics must be taken into account. Patients with declining serum HBV DNA levels may continue treatment with the same agent (entecavir or tenofovir) given the rise in rates of virological response over time and the very low risk of resistance with long-term monotherapy with both these agents".* Gilead Sciences suggests that this treatment strategy be updated in line with the clinical evidence noted in the 2012	Thank you for your comment. The recommendations of this guideline are not inconsistent with statement of 2012 European Association of the study of the liver Clinical Practice Guidelines. The GDG recommends that for those taking tenofovir who have detectable HBV DNA at 48 weeks of treatment (partial responders); tenofovir should be continued with adding lamivudine (if no resistance history) or entecavir (if lamivudine resistance present). Recommendation 90 has been amended.

						EASL CPG.	
SH	Gilead Sciences	3	Full	49	22	As per comment 2	
SH	Gilead Sciences	4	Full	49	18	The 2012 EASL CPG state that *"* The goal of therapy for CHB is to improve quality of life and survival by preventing progression of the disease to cirrhosis, decompensated cirrhosis, end-stage liver disease, HCC and death. This goal can be achieved if HBV replication can be suppressed in a sustained manner. Then, the accompanying reduction in histological activity of CHB lessens the risk of cirrhosis and decreases the risk of HCC, particularly in non-cirrhotic patients (B1)." In light of the recently published 5 year data on tenofovir and histological regression in CHB patients, we feel that tenofovir should be considered as an alternative treatment alongside Peg-IFN in HBeAg negative patients. Regression of cirrhosis during treatment with tenofovir disoproxil fumarate for chronic hepatitis B: a 5-year open-label follow-up study. Patrick Marcellin et al. Lancet 2013_381_468-75	Thank you for your comment. The GDG agrees with this statement and this was considered when they assessed the relative values of different outcomes when making the recommendations on antiviral treatments. Pegylated interferon in HBeAg negative people came as the most cost effective treatment followed by tenofovir.
SH	Gilead Sciences	5	Full	50	15	The 2012 EASL CPG state that "*NAs are cleared by the kidneys, and appropriate dosing adjustments are recommended for patients with creatinine clearance <50 ml/min (A1). Therefore, all*	Thank you for your comment. This recommendation is reflected in the monitoring recommendations (chapter 12 of full guideline).

						patients starting NA therapy should be tested for serum creatinine levels and estimated creatinine clearance before treatment (A1). In addition, the baseline renal risk should be assessed for all patients". As a result, Gilead Sciences suggests that this recommendation should be reflected in the final NICE guidelines.	
SH	Gilead Sciences	6	Full	53	13	Viread has recently been granted an adolescent/ paediatric licence and as such, the final NICE document should be updated to include this. http://www.medicines.org.uk/EMC/searchresults.aspx?term=viread&searchtype=QuickSearch Please note the Viread Prescribing Information (PI) dated Dec 2012. Indication: Treatment of CHB in adolescents 12 to <18 years of age with compensated liver disease and evidence of immune active disease.	Thank you this has been noted and the guideline has been updated with this information.
SH	Gilead Sciences	7	Full	124	11	With regards to the economic modelling noted in this document, Gilead Sciences would like to challenge the scientific validity of grouping tenofovir and adefovir. The Guideline Development Group (GDG) have incorrectly assumed HBeAg negative patients coming off treatment with tenofovir have a higher annual rate of sero-reversion	Thank you for your comment. We have performed a sensitivity analysis where the probability of seroreversion and viral re-activation with tenofovir is assumed to be the same as with entecavir/lamivudine. The analysis shows that results are not sensitive to this change and the strategy Peg IFN > TDF > TDF+LAM is still the most cost-effective in this scenario. We

						than HBeAg negative patients coming off entecavir. • No data are available for tenofovir, therefore the GDG assumes the results will be the same as for adefovir (but gives no justification for such an assumption); • Although annual rates of seroreversion for adefovir were only 8%, the GDG have decided to take an arbitrary figure of 25% because 'the high rate of durability may be related to the long duration of treatment' • Although 23% and 30% of patients on entecavir seroreverted in the cited trials, the GDG have arbitrarily used a lower figure of 20%. .	acknowledge the possible limitations in our approach and we have added this discussion to the 'limitations' paragraph in the model write-up (Appendix I – section I.4.2). The GDG consider grouping tenofovir and adefovir a reasonable assumption based on the fact that these two drugs target the same molecular site and are known to have similar effectiveness. This is explained in Appendix I – paragraph I.2.1.2. In Table 45 of Appendix I, we explain that although in the study HBeAg seroconversion was maintained in 92% of patients, the GDG considered this figure to be biased by the long duration of treatment in the study; therefore using experts opinion, it was assumed that the relapse rates were less than those reported, with durability of treatment at around 75%. We believe that using experts' opinion to validate the data to be used in the model is appropriate. We would like to point out that tenofovir was the most cost-effective second line treatment and that by using seroreversion data which do not favour tenofovir makes our conclusions on its cost-effectiveness even more robust. Therefore by changing those data, overall results would not change. .
SH	Gilead Sciences	7	Full	124	11	Gilead Sciences suggests that in the final	Thank you for your comment. We

						NICE document, both adefovir and tenofovir are not grouped together in any cost-effectiveness models based on the fact that the molecules are distinct whilst being in the same class with differential safety profiles (tenofovir having less renal adverse events than adefovir) and efficacy (tenofovir having superior suppression rates, superior s-Ag loss and e-sero-conversion rates) and tenofovir also having a zero resistance rate at one year, maintained to 6 years with adefovir having a 25% resistance rate at one year. http://www.easl.eu/assets/application/files/ef520780b91cf4f_file.pdf. Tenofovir disoproxil fumarate versus adefovir dipivoxil for chronic hepatitis B. Patrick Marcellin et al. New England Journal of Medicine 2009; 359(23):2442-55.	acknowledge the possible limitations in our approach and we have added this discussion to the 'limitations' paragraph in the model write-up (Appendix I – section I.4.2). The GDG consider grouping tenofovir and adefovir a reasonable assumption based on the fact that these two drugs target the same molecular site and are known to have similar effectiveness. This is explained in Appendix I – paragraph I.2.1.2. In Table 45 of Appendix I, we explain that although in the study HBeAg seroconversion was maintained in 92% of patients, the GDG considered this figure to be biased by the long duration of treatment in the study; therefore using experts opinion, it was assumed that the relapse rates were less than those reported, with durability of treatment at around 75%. We believe that using experts' opinion to validate the data to be used in the model is appropriate as sometimes data from studies need to be scrutinised and modified. We would like to point out that tenofovir was the most cost-effective second line treatment and that by using seroreversion data which do not favour tenofovir makes our conclusions on its cost-effectiveness even more robust. Therefore by changing those data, overall results would not change. We have however performed a sensitivity

							analysis where the probability of seroreversion and viral re-activation with tenofovir is assumed to be the same as with entecavir/lamivudine. The analysis shows that results are not sensitive to this change and the strategy Peg IFN > TDF > TDF+LAM is still the most cost-effective in this scenario.
SH	Gilead Sciences	8	Full	124	11	As stated in the 2009 NICE TA173 "The Committee was satisfied that the effectiveness of tenofovir disoproxil was at least comparable to that of other currently recommended options, notably entecavir, and that the acquisition cost of tenofovir disoproxil was lower. Therefore the Committee concluded that tenofovir disoproxil is a cost-effective option for the treatment of HBeAg-positive and HBeAg-negative chronic hepatitis B." Furthermore, a systematic review of cost-effectiveness, found tenofovir more cost-effective when compared to entecavir. (Buti et al. PharmacoEconomics, 2013). Gilead Sciences suggests that TA-173 supports the cost-effectiveness of tenofovir compared to other options (including entecavir) and this should be addressed in the final guidelines.	Thank you for your comment. Both entecavir and tenofovir were recommended in TA153 and TA173 respectively. Our guideline has looked again at the evidence on these drugs and based on the results of our original model, in the guideline we have recommended tenofovir for HBeAg positive people as second line, while we have recommended entecavir only as an alternative if tenofovir is not tolerated or contraindicated. Therefore these recommendations are in agreement with your view. Based on the clinical and economic data, the GDG did not feel they could recommend tenofovir over entecavir for HBeAg negative people as the clinical data in this population showed an increased efficacy of entecavir, therefore in this population entecavir is unlikely to be dominated by tenofovir. We estimated the incremental cost-effectiveness of strategies with entecavir compared to strategies with tenofovir in the model and we saw there was high uncertainty in the results and either tenofovir or entecavir

							could be cost-effective. For this reason, the GDG did not recommend one intervention over the other. The paper by Buti et al was a systematic review which was published after our cut-off date for retrieving evidence but it should include all the papers that we had already identified in our systematic search. Some papers may have been excluded according to our criteria used for quality assessing economic analyses.
SH	Public Health Medicine Environmental Group	1	Full	45	1	Patient information should include the reasons why household and sexual contacts should be followed up as detailed in the DH Green Book on Immunisation at https://www.wp.dh.gov.uk/immunisation/files/2012/07/chap-18.pdf. This is frequently forgotten or ignored by clinicians. This section should contain a cross reference to previous NICE guidance recommending contact tracing at http://guidance.nice.org.uk/PH43	Thank you for your comment. The guideline does cross refer to the NICE Public Health Guideline 43; Hepatitis B and C: ways to promote and offer testing to people at increased risk of infection. This clinical guideline should be used in conjunction with the public health guideline.
SH	Public Health Medicine Environmental Group	2	Full	45	24	Following on from the above; although chronic hepatitis is not notifiable as a disease the causative agent is a notifiable organism. Part of assessment and referral should include identification of contacts requiring screening.	Thank you for your comment. The guideline cross refers to the NICE Public Health Guideline 43; Hepatitis B and C: ways to promote and offer testing to people at increased risk of infection which refers to screening. This clinical guideline should be used in conjunction with the public health guideline.
SH	Public Health Medicine Environmental Group	3	Full	46	7	The requirement to refer all pregnant women to a specialist and undertake viral	Thank you for your comment. The GDG considered that given that HBV

						load testing to inform treatment is a substantial change from current practice. Many are not referred until after the baby is delivered. At present viral load testing is variable depending upon the centre which has implications for laboratory workloads and costs (which do not seem to be included in the economic analyses). There is no assessment of the impact on the requirement for HBIG for babies born to mothers with high viral loads, nor advice on modification of this requirement.	immunoprophylaxis is over 90% successful and the introduction of treatment for the mothers will further reduce that risk for the baby would justify the cost of viral load testing at pregnancy.
SH	Public Health Medicine Environmental Group	4	Full	75		(no line number on this page) We welcome the recommendation to refer all patients with HbsAg to a specialist. There have long been inequalities of access where many clinicians refer those with hepatitis C, but not B, not realising that treatment is available and desirable	Thank you for your comment.
SH	Public Health Medicine Environmental Group	5	Full	General	General	It would be helpful for the non-specialist reading this document to have a paragraph describing the natural history of hepatitis B and when the various phases (immune tolerant, immune reaction etc) occur during the course of the disease, to put the discussion of the various drug combinations in context.	Thank you for your comment. The introduction has been amended.
SH	Public Health Medicine Environmental Group	6	Full	143	4	Should it read ".was conducted in 228 HBeAg mixed.."	Thank you for your comment. This change has been made.
SH	Public Health Medicine Environmental Group	7	Full	General	General	It would have been useful to have a virologist and a public health representative on the working group	Thank you for your comment. The GDG did include a virologist, Dr Elizabeth Boxall. The GDG did not include a public health representative; however the technical team were in dialogue with the developers of the public health guideline throughout.

SH	RCN		NICE	General	General	No comment	N/A
SH	Roche Products Ltd	1	NICE	6	3	This sentence only makes reference to NA therapy treatment outcomes and requires further explanation. We recommend throughout the document, that any statements regarding the goals of therapy should clearly differentiate between NA long term therapy to achieve continuous viral suppression and finite Peginterferon alfa-2a therapy to achieve off-treatment sustained immune control and HBsAg loss, the optimum treatment endpoint (as defined in the EASL HBV Clinical Guidelines, 2012) and the closest to clinical cure (Brunetto et al; Hepatology, 2009), respectively. To this point we suggest the guidance recommends to achieve the ultimate endpoint of therapy (HBsAg loss) first with the initial treatment choice, and this treatment strategy should be defined early in the guidance.	Thank you for your suggestion. The introduction to the guideline has been amended.
SH	Roche Products Ltd	2	NICE	13	11	We recommend that a mechanism is put in place to ensure the routine practice of screening of all HBsAg-positive patients at least once for Hepatitis delta, as we understand this is not currently the case in England and Wales in many treatment centres.	Thank you for your comment. Screening is outside of the scope of the guideline.
SH	Roche Products Ltd	3	NICE	13	26	We recommend that a mechanism be put in place to ensure that second-line treatments are only considered once peginterferon alfa-2a therapy has failed, to help reduce the wide variation in HBV prescribing. Data from Lau et al, 2005 & 2006 demonstrates that rates of HBeAg seroconversion actually	Thank you for your comment. Recommendation 1.5.18 has been amended.

						increases post-treatment following 48 week duration of Peginterferon alfa-2a. This state of off treatment sustained immune control can lead to a proportion of patients achieving off treatment HBsAg loss. Therefore, we recommend in patients that receive a full 48 week course of Peginterferon alfa-2a, that guidance on initiating NA therapy as a second-line intervention should only be considered at least 1 year post-treatment, or if HBV DNA or ALT increase. This strategy provides increased potential for off-treatment sustained immune control, and may enable more patients to be treatment free for the remainder of their lives.	
SH	Roche Products Ltd	4	NICE	14	6	As with line 4 we recommend a mechanism is put in place to ensure that second line treatments are only considered once Peginterferon alfa-2a therapy has failed, to help reduce the wide variation in HBV prescribing and to reduce the rate of patients initiated on lifelong NA therapy.	Thank you for your comment. Recommendation 1.5.18 has been amended.
SH	Roche Products Ltd	5	NICE	16	17	Prior to initiating treatment information surrounding the optimum treatment goals of the different classes of available interventions should be given to patients. This should include the short term goal of a chance of achieving off treatment sustained immune control and the potential of achieving the closest to clinical cure (HBsAg loss) with finite duration Peginterferon alfa-2a vs. the long term goal of lifelong viral suppression with NA therapy.	Thank you for your comment. The GDG made a recommendation to discuss the different treatment options with patients before starting treatment. A further recommendation on patient information includes providing information to patients about the different treatment options, including short and long term treatment goals.
SH	Roche Products Ltd	6	NICE	23	8	We recommend that HBsAg levels are	Thank you for your comment. We have

						measured as a marker of treatment response in this patient group. There's a large body of evidence which shows that HBsAg quantification at week 12 or 24 is a good predictor of response/no response to Peginterferon alfa-2a. For example, the phase III trial of PegInterferon alfa-2a showed that HBsAg <1,500 IU/mL at week 12 identified 57% and 11% of patients with post-treatment HBeAg seroconversion and HBsAg clearance, respectively (Piratvisuth, et al. Hepatol Int, 2011).These data were subsequently confirmed in the NEPTUNE study, where week 12 HBsAg <1,500 IU/mL identified 58% and 10% of patients with post-treatment HBeAg seroconversion and HBsAg clearance, respectively. This study also showed that any patient with HBsAg titres >20,000 IU/mL at week 12 or 24 had 0% chance (ie, 100% negative predictive value, NPV) of HBeAg seroconversion or HBsAg loss at 6 months post–treatment (Liaw, et al. Hepatology 2011). Additionally, a pooled analysis of Peginterferon alfa data from three large randomised studies showed that HBsAg levels >20,000 IU/mL at week 12 or 24 was associated with a 100% NPV for HBsAg loss , with the advantage of week 24 that it is genotype-independent (Sonneveld, et al. AASLD 2012 [Abstract 23]). We recommend that the Response Guided Therapy rule for HBeAg-positive patients should therefore read 'Stop peginterferon alfa-2a 12 or 24 weeks after starting treatment if HBsAg level is >20,000 IU/mL, and offer second-	revised the review on the use of HBsAg in stopping rules for people on peginterferon, and included three additional studies. We note that some of the studies you mention were published after our cut-off date and have not been included. The revised review is in chapter 12 of the full guideline. The GDG recognised that a first-line recommendation of peg interferon should be accompanied by accurate stopping rules appropriate to that therapy. This was particularly important in view of the known adverse events of peginterferon. On the other hand, the GDG wished to maximise the opportunity of achieving immune control and adopted fairly conservative stopping rules that include HBsAg and HBV DNA at 24 weeks. Recommendations 1.5.24 and 1.5.33 have been modified accordingly.

						line treatment in line with recommendations'. This would align with the recent EASL HBV guidelines which recommend to consider stopping Peginterferon therapy in patients with HBsAg titre levels >20,000 IU/mL at week 12.	
SH	Roche Products Ltd	7	NICE	23	13	We recommend that patients who do not achieve HBeAg seroconversion after first-line treatment with Peginterferon alfa-2a should not receive NA therapy for at least one year following EOT (as per comment 9) due to the chance of post-treatment HBeAg seroconversion, with the exception of patients experiencing a relapse or patients that at week 48 are clear non responders.	Thank you for your comment. We recognise that patients may have an off-treatment response following a course of peg interferon therapy. The GDG did not wish to recommend a particular prolonged period off-treatment for patients who had not seroconverted, but left the recommendation open to clinician discretion. We have amended recommendation 1.5.18 to read as follows: "Offer tenofovir disoproxil as second line treatment to people who do not undergo HBeAg seroconversion or those who relapse following first line treatment with peginterferon alfa-2a".
SH	Roche Products Ltd	8	NICE	23	22	We recommend that NA therapy is not stopped following HBeAg seroconversion and 12 months of consolidation NA therapy. Anecdotally there are few UK clinicians that have confidence in this strategy due to the poor durability of off treatment response following NA therapy. We recommend that this guidance should read the same as 1.5.21 for patients with well-compensated cirrhosis. This will help guide a patients decision when considering the appropriate	Thank you for your comment. Recommendation 1.5.27 states that clinicians should consider stopping NA therapy. If NA therapy is stopped, the monitoring recommendations 1.67 and 1.68 come into play, such that if any of HBeAg, anti-HBe, HBV DNA levels and liver function change adversely, the patient can be restarted on NA therapy.

						treatment option for themselves and questions any NA treatment cost effectiveness models.	
SH	Roche Products Ltd	9	NICE	21	23	It is perceived that most patients suitable for treatment would automatically be treated with Nucleos(t)ide Analogue (NA) therapy, even though the last NICE MTA recommended that Peginterferon alfa-2a should be the first line treatment option. We suggest that little consideration for the long-term prospects of patients on lifelong therapy or the economic burden to the NHS has been taken into account, with a growing pool of patients undergoing a lifelong treatment strategy. We recognise the date of the last literature search compiled as part of this review and would like to make the panel aware of the following cost-effectiveness data (Iannazzo et al. AASLD 2012 Abstract 911]) that adds further evidence supporting the use of Peginterferon alfa-2a as the preferred first-line treatment option. We understand that this paper will be published prior to final publication of this guidance and request for it to be taken into consideration.	Thank you for your comment. Our guideline does recommend peginterferon alfa-2a as the first line treatment for people who are either HBeAg negative or HBeAg positive with compensated liver disease. Further recommendations in the guideline clarify this. Regarding the study by Iannazzo et al, we have not included economic studies that were published only in abstract form. However, we have checked the conclusions of this study which are in agreement with the findings of our original economic model and with the guideline recommendations as peginterferon alfa-2a is recommended as the first-line treatment for people with HBeAg negative chronic hepatitis B.
SH	Roche Products Ltd	10	NICE	24	4	As with HBeAg-positive patients, we recommend the use of HBsAg quantification levels at week 12 or 24 as a predictor of post treatment response to peginterferon alfa-2a therapy in HBeAg-negative patients. This is based on the phase III trial data which showed that ≥10% HBsAg decline at week 12 or 24 was associated with HBV DNA suppression (<2,000 IU/mL) in 43–47% and 36–42% of	Thank you for your comment. We have revised the review on the use of HBsAg in stopping rules for people on peginterferon, and included three additional studies. The revised review is in chapter 12 of the full guideline. The GDG recognised that a first-line recommendation of peg interferon should be accompanied by accurate stopping rules appropriate to that therapy. This

						patients at 1 year and 5 years post-treatment, respectively (Marcellin, et al. Hepatol Int 2012). Additionally, ≥10% HBsAg decline at week 12 or 24 was associated with HBsAg loss in 9% and 22–23% of patients at 1 year and 5 years post-treatment. Therefore, we propose the implementation of a <10% HBsAg decline stopping rule for HBeAg-negative genotype non-D patients. For HBeAg-negative genotype D patients, the validated PARC rule showed that no HBsAg decline and HBV DNA decline <2 log at week 12 was associated with 95% NPV (Rijckborst, et al. Hepatology 2012). Therefore, we recommend using this rule at week 12 to determine the probability of post-treatment sustained immune control with Peginterferon alfa-2a therapy in HBeAg-negative genotype D patients (where genotype testing is available) and to determine which patients should stop therapy and which ones should continue until week 48. The EASL 2012 guidelines have recognised the concept of stopping treatment in HBeAg-negative patients, in particular those with genotype D, treated with Peginterferon alfa-2a who fail to achieve any decline in serum HBsAg levels and ≥2 log IU/mL HBV DNA decline.	was particularly important in view of the known adverse events of peginterferon. On the other hand, the GDG wished to maximise the opportunity of achieving immune control and adopted fairly conservative stopping rules that include HBsAg and HBV DNA at 24 weeks. Recommendations 1.5.24 and 1.5.33 have been modified accordingly. The GDG was not confident that there was an effect of genotype D in the combination stopping rule, even though the odds ratio was not significant for the non-D genotype patients and was significant for the D genotype patients; this difference was as likely to be due to sample size issues as an effect of genotype. In addition, the GDG had not recommended genotype testing to determine initial treatment because the cost effectiveness analysis showed no effect of genotype in HBeAg positive patients and a marginal difference for genotype A in HBeAg negative patients. For the latter, there was considerable uncertainty in the probabilistic sensitivity analysis. Therefore the recommendations for monitoring and stopping treatment apply for all HBV genotypes.
SH	Roche Products Ltd	11	NICE	24	7	We suggest a review of the recommendation of when to consider the initiation of NA therapy as a second-line treatment in patients who did not achieve sustained immune control following a finite course of treatment with Peginterferon alfa-	The GDG had already taken into account the 24 week off-treatment response of peg interferon in the cost effectiveness analysis. Their view was that there was insufficient high quality evidence in the Marcellin 2012 study to show that patients

						2a. Marcellin et al, 2012 demonstrated that patients who achieve >10% decline of HBsAg levels at week 12 of therapy from baseline, had the best chance of achieving off-treatment sustained immune control, a state identified when a patients HBV DNA remains beneath 10,000 copies/mL (2,000 IU/mL). This low level of virus is such that the current draft recommendations do not advocate treatment initiation unless virus is raised above this level along with a raised ALT. The proposed draft guidance would advocate initiating any of these Sustained Immune Control patients with detectable HBV DNA on a course of potentially lifelong NA therapy. This would be unwarranted as 40% of these Immune Control patients would go on to achieve HBsAg loss 5 years post-treatment thanks to their 48 course of Peginterferon alfa-2a, as demonstrated by Marcellin et al, 2012. This study establishes the durability of the off treatment immune control state and therefore suggests that the second-line intervention may only be required if there is a flare in ALT or if HBV DNA rises to >10,000 copies/mL. This strategy would allow for more patients to remain free of potentially lifelong NA therapy and adds a further layer of cost-effectiveness to the Peginterferon alfa-2a first-line treatment strategy.	who had detectable levels of HBV DNA at the end of treatment would go on to achieve HBsAg clearance at a later date following a period off treatment. The GDG noted that the 40% cited referred to patients who had a greater than 10% decline in HBsAg at 12 weeks as well as detectable HBV DNA at 1 year. The GDG did not wish to recommend a particular prolonged period off-treatment for patients who had detectable HBV DNA, but left the recommendation open to clinician discretion.
SH	Roche Products Ltd	12	NICE	24	13	The durability of off-treatment response with NA therapy is known to be questionable and chances of HBsAg loss/ seroconversion is rarely seen with this treatment choice (same chance of	Thank you for your comment. We agree that evidence shows that HBsAg loss/seroconversion is rare for NAs and, where reported, there is low quality evidence of no clinically important

						spontaneous clearance of HBsAg). Zoutendijk et al, 2011 suggest that it would require over 35 years of NA therapy to achieve HBsAg loss. We would therefore recommend this point is deleted.	difference between NAs and placebo. However, the GDG formulated the recommendation partly to cover the rare instances when HBsAg seroconversion does occur and partly to have symmetry with the HBeAg positive population. If NA therapy is stopped, the monitoring recommendation 1.6.8 comes into play, so that patients with HBsAg seroconversion are monitored annually for HBsAg and anti-HBs; if these change, patients can be restarted on NA therapy.
SH	Roche Products Ltd	13	NICE	30	15	We would recommend that there is clearer guidance given around the specific markers of treatment response using HBsAg quantification in line with our other comments already made around response guided therapy in HBV.	Thank you for your comment. We have revised the review on the use of HBsAg in stopping rules for people on peginterferon, and included three additional studies. Recommendations 1.5.24 and 1.5.32 have been modified accordingly and now include HBsAg as well as HBV DNA**.**
SH	Roche Products Ltd	14	NICE	32	24	Due to the volume of HBV therapies that have been NICE approved, thousands of patients in the UK are managed on NA therapy with little hope of treatment cessation. We pose the question as to what guidance may be given for NA-pre-treated patients? A recent abstract presented at AASLD 2012 by Ning et al suggested that HBeAg positive patients, managed on lifelong NA therapy may be suitable candidates to be switched to Peginterferon alfa-2a to achieve off-treatment sustained response. We recommend that the concept of switching patients from potential lifelong therapy to Peginterferon alfa-2a be considered in the future research	Thank you for your comment. We agree that this would be an interesting study. However, we note that there is a trial registered with clinicaltrials.gov (NCT01769833) that is due to start in May 2013 which has the same objective. A research recommendation has not been made as this study is already underway.

						recommendations, with guidance as to the potential value of this strategy to patients.	
SH	Roche Products Ltd	15	NICE	37	13	Peginterferon alfa-2a recently received a paediatric licence update for the treatment of Hepatitis C which is currently being reviewed through the MTA process (Hepatitis C (children and young people) Peginterferon alfa 2a and Ribavirin [ID373])	Thank you for your comment.
SH	Royal College of Anaesthetists	1	NICE	General	General	No comment	N/A
SH	Royal College of Obstetricians and Gynaecologists	1	Full	General	General	Very good document summarising this complex subject The hard work by GDG is to be commended.	Thank you for your comment.
SH	Royal College of Obstetricians and Gynaecologists	2	Full	14	3	..when treatment should be started in people without cirrhosis remains a topic of debate'' reads better as " Appropriate time of commencement of treatment remains a topic of debate"	Thank you for your suggestion, this has been changed.
SH	Royal College of Obstetricians and Gynaecologists	3	Full	43	18	surveillance for hepatocellular carcinoma (HCC0, minor typo: surveillance for hepatocellular carcinoma (HCC)	Thank you for your comment. This has been amended.
SH	Royal College of Obstetricians and Gynaecologists	4	Full	60	21	'It is known there are cultural misconceptions of CHB' reads better as 'It is known that there are...'	Thank you for your comment. This has been amended.
SH	Royal College of Obstetricians and Gynaecologists	5	Full	73	Recomm 8	'Receiving' spelt incorrectly	Thank you for your comment. This has been corrected.
SH	Royal College of Obstetricians and Gynaecologists	6	Full	426	9	The earlier the time of infection, the risk of the infection becoming persistent is higher' reads better as " the earlier the time of infection, the higher is the risk of infection becoming persistent"	Thank you for your comment. This has been amended.
SH	Royal College of Obstetricians and	7	Full	73	Recomm	States 'refer women who are HBsAg positive to a hepatologist... within 6 weeks	Thank you for your comment. The recommendation advises that pregnant

	Gynaecologists				8	of receiving the screening test result and to allow treatment in the third trimester'. Do you mean make the referral within 6 weeks, or the woman should be seen by the hepatologist within 6 weeks? please clarify.	women should be seen within 6 weeks of the screening test result.
SH	Royal College of Obstetricians and Gynaecologists	8	Full	73	Recomm 8	There is already an existing recommendation (which is applied as a “non-cancer KPI” requiring that such patients are seen more quickly than this. This KPI acts to skew clinical priorities, any relaxation of this existing needless standard would be welcomed by those working in the field.	Thank you for your comment.
SH	Royal College of Obstetricians and Gynaecologists	9	Full	426		In the section that specifically applies to pregnancy (11.3, page 426), there is much discussion about the clinical and cost-effectiveness of anti-viral therapy to reduce the risk of vertical transmission from mother to infant. The GDG identified 5 studies to include in the review (2 rcts and 3 prospective open-label studies). 3 of these compared lamivudine versus no therapy, and the other 2 telbivudine versus no therapy. The quality of the evidence ranges from ‘very low’ to ‘moderate’ (but mostly very low). There are no data specifically looking at tenofovir and hep b transmission in pregnancy (though I understand that there is considerable experience of its use in women with HIV in pregnancy). It is concerning that the guideline is recommending that clinicians offer tenofovir to women with high levels of hbv in the 3rd trimester when there is no evidence to support its use in this situation. How is the recommendation justified? There is also no	Thank you for your comment. The recommendation on antiviral treatment for pregnant women was based on GDG expert clinical opinion. The GDG noted that tenofovir carries a lower teratogenic risk, has a higher barrier to resistance and evidence on people who are not pregnant showed to be more effective than lamivudine. The GDG have drawn on the indirect evidence on the use of tenofovir in the HIV population, which they agree is applicable to women with hepatitis B. This has been made clearer in the linking evidence to recommendations section of the guideline.

						economic evidence to support its use - instead the developers say "the increased cost of tenofovir would likely be outweighed by the increase in quality of life associated with its use".	
SH	Royal College of Obstetricians and Gynaecologists	10	Full	General	General	How large is the pool of women to which this section applies? Cases that would fulfil their criteria “very high viraemias defined as >10^7IU/ml” appear to be very rare in UK practice.	Thank you for your comment. This is very rare. Our evidence was from Yu 2012 and Han 2011 which used this cut-off. Xu 2009 used 1000mEq/ml which is 8.3log10 IU/ml. Therefore any recommendation for a lower viraemia would not be supported by evidence. The European Association for the study of the liver guideline has reduced it slightly to 10^6 – 10^7.
SH	Royal College of Obstetricians and Gynaecologists	11	Full	General	General	It is disappointing that the GDG has lost both of its lay members and that there seem to be no other members of the GDG that can readily provide the patient perspective or advocate for patients (with the possible exception of a nurse consultant). Is there a good reason why there is no lay representation?	Thank you for your comment. The GDG included a total of 3 lay members, 2 of which were members of the GDG for the majority of the development phase.
SH	Royal College of Obstetricians and Gynaecologists	12	Full	General	General	The GDG consider Caesarean Section as a possible outcome of antiviral therapy but there seems to be no consideration of CS as an intervention to reduce the risk of vertical transmission. Is this correct? It is acknowledged that for the relatively low risk women (not women “with very high viraemias defined as >10^7IU/ml”) the evidence is that post-exposure prophylaxis is very effective and that CS as an intervention in this context is not necessary. Are the GDG able to say that delivery by CS has no benefit even in cases of women “with very high viraemias defined as	Thank you for your comment. The question was set up to review the evidence on the clinical and cost-effectiveness of antiviral treatments to reduce the risk of vertical transmission from mother to child. Caesarean section was reported as an adverse event outcome. Caesarean section was not reviewed in this guideline as a type of intervention to reduce the risk of vertical transmission.

						>10^7IU/ml"?	
SH	Royal College of Obstetricians and Gynaecologists	13	Full	General	General	A member of our committee comments 'As an obstetrician working in a relatively high-prevalence unit for nearly twenty years where I have had sole obstetric responsibility for all Hep-B +ve mothers, I am unaware of any to date "with very high viraemias defined as >10^7IU/ml". How common are such cases and accordingly how important is this topic?	Thank you for your comment. This is very rare. Our evidence was from Yu 2012 and Han 2011 which used this cut-off. Xu 2009 used 1000mEq/ml which is 8.3log10 IU/ml. Therefore any recommendation for a lower viraemia would not be supported by evidence. The European Association of the study of the liver guidance has reduced it slightly to 10^6 – 10^7.
SH	Royal College of Obstetricians and Gynaecologists	14	Full	Recommendations in 11.3.6		Suggest that antiviral treatment only be discussed in women in who treatment might be applicable ie a small minority.	Thank you for your comment. We agree with your suggestion.
SH	Royal College of Obstetricians and Gynaecologists	15	Full	Recommendations		Is it still pertinent to refer to the Green Book concerning vaccinations?	Thank you for your comment. The Green Book remains the most appropriate reference for immunisation of the babies along with the Best Practice Guidance document which is also referred to.
SH	Royal College of Paediatrics and Child Health	1	Full	69	7.2	We think that the hepatitis B and C treatments are, like the various paediatric cancer protocols, an example of how systematic cohort management has steadily improved results with better use of existing treatments, new treatments and better patient selection. In order for trainees to be immersed in the selection, treatment and follow-up of patients it is necessary for them to be treated in sufficient numbers, which is in any case the optimum for scientific reasons. We would therefore argue that while in section 7.2.2 it is recommended that liver	Thank you for your comment. We have recommended that children are seen by paediatric specialists, the GDG do not believe it is a practical option to only offer treatment within specialist paediatric centres.

						centres, infectious disease centres and some gastro centres could be involved with treatment, only centres treating 20 paediatric patients per year can provide sufficient exposure for training purposes. In effect this means that HBV treatment should take place in the 3 paediatric liver centres.	
SH	Royal College of Paediatrics and Child Health	2	NICE	General	General	More consideration needs to be given to the suggested referral pathway (especially for children) and the on-going management of children who are HBSAg positive. We fully accept that they may well require the skills and attention of a Paediatric Gastro-Hepatologist for the specialist input and procedures such as liver biopsy and that they will require on-going expert monitoring but we strongly feel that for many families the delivery of the care that they require could be delivered in a much more distributed way with a network of Generalists with a special interest closely allied to their local tertiary specialists and centres. Thus to summarise we feel that the location of the individual parts of the care pathway needs to be much more carefully considered so that 'tertiary' drift does not adversely affect the travel costs and burden of care that families endure. Much of the care could be delivered by local services with careful and close networking arrangements. *We understand that comment one and*	Thank you for your comment. The delivery of services for children would be determined locally and is not specified in this guideline.

						comment two conflict. However, these are the views of a generalist and tertiary specialist; both are valid points and not mutually exclusive.	
SH	Royal College of Paediatrics and Child Health	3	Full	5	47 -48	The guidelines for liver biopsy and for treatment do not seem to make sense. If the advice is to treat all children with abnormal ALT as implied, then why do a biopsy, as the trigger for biopsy is higher (i.e. HBV DNA >2000 AND abnormal LFT).	Thank you for your comment. We agree that some clarification is needed. The GDG's view is that not every child/young person requires a biopsy before starting treatment, particularly not children/young people that have been followed from the immune tolerant phase through to immune clearance, and in these people treatment can be initiated on the basis of continuing viremia in the presence of abnormal ALT. However in some young people, for example those arriving as migrants from endemic regions and presenting with high viral loads and active transaminitis, it will be unclear how long they have been in an immune-reactive phase of infection and they may have advanced fibrosis. In addition, the liver biopsy may reveal other pathologies and save the need for embarking on antiviral treatment. Therefore, a liver biopsy would be an appropriate precursor to treatment for these young people. The biopsy recommendation has been modified to 'consider' rather than 'offer', and the role of biopsy to assess the need for treatment has been removed. The treatment recommendation thus covers more than one type of patient.
SH	Royal College of Paediatrics and Child Health	4	Full	5 (72)	52	The vast proportion of perinatally acquired HBV results in eAg positivity in childhood. These are immune tolerant, with a low short	Thank you for your comment, the recommendation has been amended to 24 weeks.

						term risk of progression of liver disease. It would be a major change in practice to start seeing these children every 3 months, when the majority need no intervention throughout childhood. We do not see any evidence-base presented as to why this might be necessary.	
SH	Royal College of Paediatrics and Child Health	5	Full	General	General	This guideline makes no recommendation at all on hepatitis B treatment in children co-infected with HIV. This no doubt this reflects the paucity of evidence, but it seems inappropriate to completely omit this group of patients.	Thank you for your comment. This area is outside the guideline scope.
SH	Royal College of Paediatrics and Child Health	6	Full	Recommendations	General	There are no specific comments within the recommendations with regard to children and young people. Most paediatric hepatologists would agree that in the absence of proven effective therapy, children should be treated with anti-viral therapy only in clinical trials, except for compassionate use.	Thank you for your comment. The GDG agree that in the absence of proven effective therapy, children and young people should ideally be treated with anti-viral therapy only in clinical trials, except for compassionate use or clinical need. Their recommendation for children is that antiviral drugs could be considered, but, in the footnote to the recommendation, they state that each of the antiviral drugs did not have UK marketing authorisation for use in children and that the prescriber should follow relevant professional guidance, taking full responsibility for the decision. The GDG felt that the professional guidance and good practice would ensure appropriate treatment of children.
SH	Royal College of Paediatrics and Child Health	7	Full	46	19	Include in baseline tests anti-HBc IgG as well as IgM	Thank you for your comment. This test is not relevant for people who are HBsAg positive.
SH	Royal College of	8	Full	46	26	Children with chronic HBV should be	Thank you for your comment. We have

	Paediatrics and Child Health				No. 11	managed by a paediatric hepatologist or a specialist with interest in hepatology in a specialist centre with the paediatric MDT trained to manage and support children with HBV and their families.	recommended that children are seen by paediatric specialists. There are very few centres currently available and therefore it would not be practical to make such a recommendation.
SH	Royal College of Paediatrics and Child Health	9	Full	46	28 No12	Consider adding: • The referring health professional should include the child's HBV vaccination schedule with dates when applicable. • Include information of parents and siblings to ascertain transmission route	Thank you for your comment. Whether infection of a new-born occurs as a result of no vaccination or inadequate vaccination has no significance in terms of further action as regard treatment of the infant.
SH	Royal College of Paediatrics and Child Health	10	Full	47	27 No 24	ALT levels, in paediatrics, are age and gender specific. The levels quoted may be within normal range. It may be better to state ALT above the normal level.	Thank you for your comment. The primary sources of data are thin and confounded by ethical constraints of taking blood samples from healthy children. Most children without liver disease run transaminases in single figures or low teens. This is a research priority, but it is valid to challenge current 'received wisdom' and in the absence of better data we should stand by the realignment of paediatric values in keeping with thresholds for young adults.
SH	Royal College of Paediatrics and Child Health	11	Full	48	10 No 29	Liver biopsy is not a requirement before initiating treatment. Treatment decisions in children are based on ALT levels and HBV DNA levels. No paediatric hepatologist would insist on demonstrating fibrosis before considering treatment. Selection of children with abnormal ALT has been accepted as an entry criteria for clinical trials because these children are more likely to respond.	Thank you for your comment. We accept that not every child/young person requires a biopsy prior to starting treatment. However in young people arriving for example as migrants from endemic regions with high viral loads and active transaminitis, it will be unclear how long they have been in an immune-reactive phase of infection and they may have advance fibrosis. Perhaps more

							importantly, the liver biopsy may reveal other pathologies and save the need for embarking on antiviral treatment. Recommendation 25 has been amended to read 'consider' rather than 'offer'.
SH	Royal College of Paediatrics and Child Health	12	Full	49	50	There is no evidence to base the recommendation that children should be treated with 48 weeks pegylated interferon, nor to start with an antiviral if no response to pegylated interferon. Clinical trials are now in progress to evaluate the efficacy of this treatment	Thank you for your comment. These recommendations were based on GDG consensus as noted in the linking evidence to recommendations section.
SH	Royal College of Paediatrics and Child Health	13	Full	46	7 No 8	Consider adding: Screen other children in the family	Thank you for your comment. The guideline cross refers to the NICE Public Health Guideline 43; Hepatitis B and C: ways to promote and offer testing to people at increased risk of infection. This clinical guideline should be used in conjunction with the public health guideline.
SH	Royal College of Paediatrics and Child Health	14	Full	52	16 No 72	There is no rationale for testing ALT in children every 12 weeks, especially those in the immune tolerant phase do not require 3 monthly follow up. We need to consider that these are well children and they are not keen to take time off school or provide explanation about non-attendance to their school teacher.	Thank you for your comment. We have amended recommendation 77 to read as follows: Monitor ALT levels every 24 weeks in children and young people with HBeAg positive disease who have normal ALT levels (less than 30 IU/ml for males and less than 19 IU/ml for females) and no evidence of significant fibrosis (METAVIR stage less than F2 or Ishak stage less than 3)..
SH	Royal College of Paediatrics and Child Health	15	Full	52	22 No	Children in the immune clearance phase should be reviewed every 12 weeks or more frequently to monitor their LFTs and	Thank you for your comment. We have amended Recommendations 77 and 79 to reflect this:

					74	disease progression.	77. Monitor ALT levels every 24 weeks in children and young people with HBeAg positive disease who have normal ALT levels (less than 30 IU/ml for males and less than 19 IU/ml for females) and no evidence of significant fibrosis (METAVIR stage less than F2 or Ishak stage less than 3) 79. Review every 12 weeks children and young people with HBeAg-negative disease who have abnormal ALT (greater than or equal to 30 IU/ml for males and greater than or equal to 19 IU/ml for females) and HBV DNA greater than 2000 IU/ml.
SH	Royal College of Paediatrics and Child Health	16	Full	52	26 No 75	Pegylated Interferon – monitoring schedule in children differs to that in adults. Children require close monitoring at 0, 2, 4 and every 4 weeks whilst on pegylated interferon.	Thank you for your comment. We have added in a recommendation (80) to address this that reads: Review injection technique and adverse effects weekly during the first month of treatment in people taking peginterferon alfa-2a.
SH	Royal College of Paediatrics and Child Health	17	Full	52		Monitoring of weight and height in children on PEG-IFN is essential and needs to be included, especially children during puberty. In general, interferon should be avoided during puberty because of the detrimental effect on growth and nutrition.	Thank you for your comment. We agree with your comment and have amended recommendation 81 to reflect this. Monitor full blood count, liver function (including bilirubin, albumin and ALT), renal function (including urea and electrolyte levels) and thyroid function (and in children, weight and height) before starting peginterferon alfa-2a and 2, 4, 12, 24, 36 and 48 weeks after

							starting treatment to detect adverse effects.
SH	Royal College of Paediatrics and Child Health	18	Full	52		Children who require PEG-IFN therapy should be appropriately addressed for the timing e.g. not during puberty, their year of important exams, carer's commitments. Consideration will need to be given to the need for proper preparation especially the need for play therapy due to anxiety, training preparation and psychological preparation in case of non- response to treatment. This also includes when and how to inform school when some parents do not want to disclose their child's diagnosis to the school.	Thank you for your comment. We agree that this consideration is important. This is standard paediatric practice and does not need to be included in the guideline.
SH	Royal College of Paediatrics and Child Health	19	Full	53	4 No 79& 80	It is very important that antiviral treatment is considered in treatment centres equipped with adequate resources to monitor clinical and psychosocial need of the child. These should include paediatric multi-disciplinary team and specialists (preferably paediatric Hepatologist) with viral hepatitis case load of at least 20 children per year. The team should be the main carers and share care with the local consultant or GP. The child should not be shunted from one centre to another.	Thank you for your comment. We have recommended that children are seen by paediatric specialists, and whilst the GDG agree continuity of care and adequate resources are essential, there are very few specialist paediatric centres currently available.
SH	Royal College of Paediatrics and Child Health	20	Full	53	4 No 79& 80	In paediatrics, children and particularly young children should be monitored every 3 months when on treatment for side effects and compliance.	Thank you for your comment. We have added in a recommendation (80) to address this that reads: Review injection technique and adverse effects weekly during the first month of treatment in people taking peginterferon

							alfa-2a.
SH	Royal College of Paediatrics and Child Health	21	Full	53	4 No 81	HBV DNA monitoring in children on lamivudine for more than 48 weeks should be considered to detect viral breakthrough due to resistance.	Thank you for your comment. This recommendation now states that HBV DNA should be monitored at 12, 24 and 48 weeks and then every 6 months for all people taking lamivudine.
SH	Royal College of Paediatrics and Child Health	22	Full	53	14 No 82-83	There should be a 3 monthly review for children on Tenovofir to monitor side effects. Children who developed a rash while on the treatment will need a review by a paediatric dermatologist and consider discontinuation of Tenovofir if the rash is moderate or severe.	Thank you for your comment. Rash is a very uncommon adverse event in children receiving tenofovir. Clinicians prescribing tenofovir should be familiar with managing adverse events. A paediatric dermatologist's opinion may be sought in unusual clinical presentations.
SH	Royal College of Physicians	1	Full	50	26	Recommendation is to stop tenofovir 4-12 weeks after delivery. Why not stop at delivery if mother doesn't require further treatment?	Thank you for your comment. The continuation of antivirals after delivery is related to post-partum flares in hepatitis B. The GDG considered a possible benefit in treating beyond 4 weeks to provide additional protection for the mother.
SH	Royal College of Physicians	2	Full	51	2	Clarification needed – if the mother is having treatment for herself treatment can be continued during breastfeeding. For mothers who were only having treatment in pregnancy to reduce neonatal transmission they do not require to continue therapy as there is no risk of transmission with breast feeding.	Thank you for your comment. The GDG considered that continuation of treatment while mothers are breast feeding is not about risk of transmission to the baby but is for protection of the mother to avoid the risk of 'post-partum' flares.
SH	Royal College of Physicians	3	Full	43	20	Should recommend testing for Hep A and possible vaccination	Thank you for your comment. Vaccination is outside the scope of the guideline. We agree that Hep A should be tested for and have added lgG antiHAV to the list of tests in recommendation 6.

SH	Sheffield Teaching Hospitals NHS Foundation Trust	1	Full	43	13	Hepatitis B screening Delta antibody is unlikely to be requested by primary care. In reality, GP physicians have difficulty requesting the correct laboratory tests for hepatits B screening without complicating the matter further. It is typically a specialist reference test. If guidelines are suggesting this should be done on all HBV positive patients this will drive the need to make the test available at all regional virology centres and there will be significant funding implications.	Thank you for your comment. A large proportion of HBV infections occurring in first generation migrants all over the country and delta infection is increasingly a problem. The GDG have provided a list of the serological tests that need to be done in recommendation 6 in the full guideline.
SH	Sheffield Teaching Hospitals NHS Foundation Trust	2	Full	43	23 ,34	PEG IFN as first line therapy for all An unusual choice given the poor tolerability and effect on quality of life. An expensive choice when additional demands for MDT support and specialist nursing time is considered. How robust is the mathematical modelling? Some data for the directly acting anti-virals suggest that sero-conversion rates over time might not be that much lower than with PEG IFN. No back to back comparison/RCT data available to our knowledge.	Thank you for your comment. Pegylated interferon alfa-2a is currently recommended for the initial treatment of adults with chronic hepatitis B based on the NICE Technology Appraisal 96. Our economic model shows that a strategy where this is the initial treatment is the most cost-effective among the strategies compared. The results of the sensitivity analyses conducted on the model and the limitations identified are reported in Appendix I (sections I.3 and I.4). We are not aware of any RCTs comparing directly optimal treatment with PEG IFN versus optimal antiviral treatment (e.g. PEG IFN given for 48 weeks followed by 24 weeks off-treatment versus Tenofovir for 48 or 72 weeks).
SH	Sheffield Teaching Hospitals NHS Foundation Trust	3	Full	43	27 -30	TDF second line ETC third line Aware of imminent changes to entecavir cost reduction at major centres, with plan to role out to DGHs if pilot results in increased use. Given the added costs of the renal	Thank you for your comment. We are aware that a change in the cost of drugs may change the outcome of our economic model. However, we have to make recommendations based on the costs applicable at the time of the guideline

						monitoring with TDF the group felt that the difference between them might not be great enough to limit the element of patient and physician choice between the two drugs.	publication. Any reduction in costs will be taken into account when the guideline is next updated. The cost of monitoring patients who receive TDF was already included in our model and therefore results are already reflective of this additional cost.
SH	Sheffield Teaching Hospitals NHS Foundation Trust	4	Full	44	5	TDF and breast feeding TDF used if third trimester if HBV viral load >log7 and continued for 4-12 weeks beyond birth. Breast feeding encouraged if baby vaccinated. Accepted as current practice. Emphasis on pre-treatment discussion to allow patient to accept treatment withdrawal if therapy was purely for prevention of MTCT.	Thank you for your comment, this has been noted.
SH	Sheffield Teaching Hospitals NHS Foundation Trust	5	Full	47	1 -23	Transient Elastography for every adult newly referred Access to a Fibroscan facility is likely to be limited in some centres. The Group appreciates this guidance would be a powerful tool to secure funding for those centres. This is a novel approach for much of the country outside London and will take time to implement given the financial and staffing implications. The guidelines suggest that fibroscanning is being used to 'rule in' cirrhosis in those with TE pressure scores over 10kPa, and to rule out cirrhosis in those with scores below 6, to guide the need for cirrhosis surveillance, with biopsy used to exclude significant fibrosis and the need for cirrhosis surveillance in the "indeterminate" 6-10kPa	Thank you for your comment. The GDG consider that this test is becoming more widely available, although some patients may be required to travel until the recommendations are fully implemented. The recommendations on when to offer treatment specify the HBV DNA and ALT levels that would trigger prescribing antiviral treatment. The sections on treatment and assessment of liver disease have been reviewed for clarity, and cross referral between the two sections has been made where appropriate.

						group. The decision as to whether treatment is indicated is, in many circumstances, independent of fibrosis assessment, however, e.g. based on age, HBV DNA and ALT alone. In this section of the guidance, the 'fibroscan arm' and the 'treatment arm' don't flow well together, resulting in a lack of clarity and some confusion about when to progress from fibroscan to biopsy and when to consider treatment. This particularly affects the group of patients with TE values between 6 and 10kPa with the potential need for biopsy. It seems as though the fibroscan guidelines and the treatment guidelines have been constructed by 2 separate teams with insufficient overlap. This makes the algorithms and text detached from each other.	
SH	Sheffield Teaching Hospitals NHS Foundation Trust	5	Full	47	1 -23	The guidelines do not refer to the use of liver biopsy to help identify alternative aetiologies for liver inflammation, e.g. steatohepatitis, e.g. in patients with abnormal ALT but low level HBV DNA, to see if HBV treatment would be of benefit or not.	Thank you for your comment. The GDG therefore decided to differentiate between an active CHB and an inactive CHB infection, in which the ALT elevation is due to some other chronic liver disease, by adding an HBV DNA requirement to the transient elastography recommendation for cirrhosis. They also recommended fairly frequent monitoring of these people with high TE levels, but low levels of viraemia, for example every 12-24 weeks, at the discretion of the clinician. If HBV DNA levels became detectable on any one occasion, the

							patient would be offered antiviral treatment. Therefore the monitoring recommendation 75 was also changed.
SH	Sheffield Teaching Hospitals NHS Foundation Trust	6	Full	52 -53	31 - 33,1 -2,8- 10,1 8-20	Surface antigen quantitation Suggestion is this should be used for monitoring. This is an expensive test not available at many centres. It should be reserved for use in very specific circumstances in which DNA quantitation is unreliable. This would include some patients on PEG IFN and those who are HBV/HDV co-infected on PEG IFN. An HBVDNA <2 log drop from baseline at 12 weeks of treatment is an acceptable stopping rule. HBV DNA testing is reliable, widely available and easy to interpret. No guidance has been provided on how to interpret the quantitative surface antigen results.	Thank you for your comment. We have revised the review on the use of HBsAg in stopping rules for people on peginterferon, and included three additional studies identified during consultation. The revised review is in chapter 12 of the full guideline. The GDG recognised that a first-line recommendation of peg interferon should be accompanied by accurate stopping rules appropriate to that therapy. This was particularly important in view of the known adverse events of peginterferon. On the other hand, the GDG wished to maximise the opportunity of achieving immune control and adopted fairly conservative stopping rules that include HBsAg and HBV DNA at 24 weeks. The GDG did not consider this to be an expensive test. Recommendations 83 and 84 have been modified accordingly.
SH	Sheffield Teaching Hospitals NHS Foundation Trust	7	Full	Gene ral	Gen eral	Audit No auditable outcomes have been suggested.	Thank you for your comment. These outcomes were based on what the GDG believed was clinically important. An audit tool will be produced to accompany the guideline.

These organisations were approached but did not respond

Abbott Diagnostics Division

Addaction

Aintree University Hospital NHS Foundation Trust
Alder Hey Children's NHS Foundation Trust
Allocate Software PLC
Assocation of NHS Occupational Physicians
Association of Anaesthetists of Great Britain and Ireland
Association of British Healthcare Industries
Association of British Insurers
Barchester Healthcare
Barnsley Hospital NHS Foundation Trust
Baxter Healthcare
Birmingham Children's Hospital NHS Foundation Trust
Bradford District Care Trust
British Dental Trade Association
British HIV Association
British Medical Journal
British National Formulary
British Nuclear Cardiology Society
British Paediatric Allergy, Immunology & Infection Group
British Psychological Society
British Renal Society
British Society for Antimicrobial Chemotherapy
British Society for Immunology
British Specialist Nutrition Association
British Transplantation Society
British Viral Hepatitis Group
Cambridge University Hospitals NHS Foundation Trust
Camden Link
Capsulation PPS

Capsulation PPS
Care Quality Commission (CQC)
Central & North West London NHS Foundation Trust
Central Lancashire Primary Care Trust
Central London Community Health Care NHS Trust
Cepheid Uk Ltd
Children's Liver Disease Foundation
Clarity Informatics Ltd
Croydon Health Services NHS Trust
Department for Communities and Local Government
Department for Education
Department of Health, Social Services and Public Safety - Northern Ireland
Dorset Primary Care Trust
Drinksense
East Cheshire NHS Trust
Equalities National Council
Expert Patients Programme CIC
Faculty of Occupational Medicine
Faculty of Sport and Exercise Medicine
Five Boroughs Partnership NHS Trust
Frimley Park NHS Foundation Trust
Frontier Therapeutics Limited
George Eliot Hospital NHS Trust
Gloucestershire Hospitals NHS Foundation Trust
Gloucestershire LINk
Great Western Hospitals NHS Foundation Trust
Greater Manchester Sexual Health Network
Greater Manchester West Mental Health NHS Foundation Trust

Haag-Streit UK
Hammersmith and Fulham Primary Care Trust
Havencare
Health Protection Agency
Health Quality Improvement Partnership
Healthcare Improvement Scotland
Healthcare Infection Society
Hepatitis B & C: Ways to promote and offer testing Programme Development Group
Hertfordshire Partnership NHS Trust
Hindu Council UK
Hockley Medical Practice
Humber NHS Foundation Trust
Independent Children's Homes Association
Independent Healthcare Advisory Services
Infection Control Nurses Association
Infection Prevention Society
Institute of Biomedical Science
Integrity Care Services Ltd.
iQudos

Lancashire Care NHS Foundation Trust
Leeds Community Healthcare NHS Trust
Letterkenny General Hospital
Liverpool Primary Care Trust
Luton and Dunstable Hospital NHS Trust
Medical Foundation for AIDS and Sexual Health
Medicines and Healthcare products Regulatory Agency
Milton Keynes Clinical Commissioning Group
Ministry of Defence

National AIDS trust
National Clinical Guideline Centre
National Collaborating Centre for Cancer
National Collaborating Centre for Mental Health
National Collaborating Centre for Women's and Children's Health
National Institute for Health Research Health Technology Assessment Programme
National Kidney Federation
National Patient Safety Agency
National Public Health Service for Wales
National Treatment Agency for Substance Misuse
National Users Network
NHS Clinical Knowledge Summaries
NHS Commissioning Board
NHS Connecting for Health
NHS County Durham and Darlington
NHS Direct
NHS Hertfordshire
NHS National Programmes
NHS Plus
NHS Sheffield
NHS South Birmingham
NHS Warwickshire Primary Care Trust
NICE technical lead
North and East London Commissioning Support Unit
North Tees and Hartlepool NHS Foundation Trust
North West London Perinatal Network
Northumberland, Tyne & Wear NHS Trust
Nottingham City Council

Nottingham City Hospital
Nottingham University Hospitals NHS Trust
Oxford Health NHS Foundation Trust
Parenteral and Enteral Nutrition Group
Pfizer
Positively UK
Primary Care Society for Gastroenterology
Primary Care Society for Gastroenterology
PROGRESS

Public Health Wales NHS Trust
RioMed Ltd.
Roche Diagnostics
Royal Berkshire NHS Foundation Trust
Royal College of General Practitioners
Royal College of General Practitioners in Wales
Royal College of Midwives

Royal College of Paediatrics and Child Health , Gastroenetrology, Hepatology and Nutrition
Royal College of Pathologists
Royal College of Psychiatrists
Royal College of Radiologists
Royal College of Surgeons of England
Royal Pharmaceutical Society
Royal Society of Medicine
Sanofi Pasteur MSD Ltd
Scottish Intercollegiate Guidelines Network

Sickle Cell Society

SIFA Fireside
Social Care Institute for Excellence
Society for General Microbiology
South Asian Health Foundation
South East Coast Ambulance Service
South London & Maudsley NHS Trust
South West Yorkshire Partnership NHS Foundation Trust
Southport and Ormskirk Hospital NHS Trust
St Andrews Healthcare
St John Ambulance
St Mary's Hospital
Sue Ryder
Teva UK
The Association for Clinical Biochemistry
The British In Vitro Diagnostics Association
The Chartered Institute of Environmental Health
The Haemophilia Society
The Hepatitis C Trust
The National LGB&T Partnership
The Rotherham NHS Foundation Trust
UK Clinical Pharmacy Association
UK Liver Alliance
UK National Screening Committee
UK Thalassaemia Society
Unison
United Kingdom National External Quality Assessment Service
University Hospital Birmingham NHS Foundation Trust
Wales Viral Hepatitis Management Group

Walsall Local Involvement Network
Welsh Government
Welsh Kidney Patients Association
Welsh Scientific Advisory Committee
West Midlands Ambulance Service NHS Trust
Western Cheshire Primary Care Trust
Western Sussex Hospitals NHS Trust
Westminster Local Involvement Network
Wirral University Teaching Hospital NHS Foundation Trust
Worcestershire Acute Hospitals Trust
York Hospitals NHS Foundation Trust