BHIVA Pregnancy Guidelines: consultation comments

21 September 2012

Royal College of Obstetricians and Gynaecologists

Thank you for inviting the RCOG (Royal College of Obstetricians and Gynaecologists) to comment on this guideline. These comments are from the Guideline Committee at the RCOG, Chaired by Dr Philip Owen MRCOG.

This is a very comprehensive guideline. It is a little daunting to read given the plethora of initialisms and acronyms but suppose that is unavoidable. A separate glossary of terms that can be consulted whilst reading the text will improve its accessibility.

In terms of presentation some page breaks could be tidied up to avoid widows/orphans (for example at the foot of page 13).

There are a number of comments concerning additional maternal anti-retroviral therapy where there is a risk of preterm labour. My understanding is that this relates to problems of absorption. As it may happen that decisions around this issue may need to me made by obstetricians alone without ready access to advice from specialists in HIV, would it be sensible to indicate at what degree of prematurity such absorption problems are likely?

RB4F:

Do the authors really mean POCT? Units might be able to access laboratory-based rapid turnaround testing. There is considerable concern about POCT tests generally in delivery suites. Do the authors believe (especially in a low-risk population) that POCT is likely to be reliable?

In many units the numbers of women arriving totally unbooked (and therefore unscreened) will be very small. Is investment in POCT testing likely to be cost efficient? Will tests be reliable if done once in a “blue moon” by staff with questionable competence in conducting the POCT test? Any ideas on NNT?

If this is to be pursued could the authors make it clearer what intrapartum regime and mode of delivery should be followed in a woman who first has a “reactive” test on presentation in labour?

This section comes under the subheading 'Late presenting woman not on treatment' (ie already known to be HIV+) and the scope indicates that this guidance is aimed at women with a diagnosis of HIV. So, to whom does this recommendation apply within the context of this sub heading and scope? To my mind this relates to screening, so if the developers feel it belongs in this guideline at all then it belongs under the subheading dealing with screening. Some women will decline HIV screening (earlier in pregnancy) and I presume you are not recommending that they are approached to undergo POCT?

Section C:

Maternity units have KPIs around screening and management of Hep B in pregnancy. These include prompt referral to a Hepatologist. Are the authors suggesting that GU Physicians will also be responsible for Hep B care or do they accept the role of a Hepatologist? I would hope the latter and would ask that referral to a Hepatologist be included.

RC1r:

I'm not clear whether you are recommending HBVIg as well as vaccine to all babies born to HIV/HBV co-infected mothers. Is there a more elegant expression than "co-administrating vaccination"?

Hepatitis C virus (HCV):

Again what's the role for a Hepatologist?

RC2f:

Would it not be correct to say that such women are eligible for vaginal delivery as are HIV+ women not co-infected with HCV? Or is it really more complicated than that?

Section D: Obstetric Issues/Summary of Recommendations/1. Ante-natal Care

Please change "as per national guidelines " to "according to national guidelines".

RD1A & B:

These recommendations are not particular to HIV+ women, should they be included at all (if you think they are justified you ought to tell us about all the other elements of antenatal care (screening for Rubella, etc).

If you feel it necessary to include them then you should reference them to NSC!

RD1B Recommendation refers to the integrated test whereas the text refers to the combined test. Which do you mean please? (My understanding of the integrated test is NT, first and second trim biochem, whereas combined test is NT plus first trim biochem only)

RD2B:

Does that include the use of fetal scalp electrodes, particularly the very invasive ones needed for STAN CTG? Would fetal blood sampling be OK? Any issues with Amnihooks? Subsequent text implies 'yes' but can you make this more explicit in the initial recommendation please?

RD3A:

If you are aiming for as short a SROM to delivery interval, you might like to recommend we use Syntocinon form the outset and not use Prostaglandins.

D1. Antenatal Management:

I see you do refer to NSC here but why are you telling us obstetricians this bit when you (sensibly) don't aim to cover all other aspects of antenatal care?

RD2E RCOG GTG recommend steroids for women undergoing elective CS before 38+6 weeks so please ensure your guidance reflects this. Also, for women delivering vaginally between 24 and 34+6 weeks. Thank you.

RD3C 'Immediate caesarean section' means what timescale please. We have categories of urgency for CS, would be helpful to express the 'immediacy' in terms of this classification. thank you.

RD3D:

The authors should to be aware of contradictory advice on GBS prophylaxis in this context. Draft RCOG GTG and draft NICE guidelines are currently at odds on the matter of GBS prophylaxis where the indication is preterm labour. This is being addressed, but resolution may take a couple of months.

RF1 (page 76):

Does an MDT imply a joint clinic or communication between clinicians working in separate clinics and joint MDT meetings of staff from those two clinics? I currently work in a setting where the GUM team and the maternity care team see the patient separately, but they meet together for MDT meetings (and have joint educational meetings). Others work in setting of joint consultations. IS BHIVA making any recommendation over this?

Would you consider writing a patient information leaflet?

Boehringer Ingelheim

Boehringer Ingelheim welcomes the opportunity to comment on the draft Guidelines for the management of HIV infection in pregnant women 2012. We have restricted our comments to statements made about the molecule nevirapine and make no comment on terminology, reference sources or information presented for other antiretroviral therapy.

P14: statement about single dose nevirapine crossing the placenta

BI is unable to comment about the use of single dose nevirapine in these draft guidelines, as this lies outside the product's Market Authorisation. The company has source material available on this topic (e.g. case reports) unidentified from the reference list provided in the draft guidelines, in the event that the writing group would like additional information.

P23: reference to nevirapine XR

The draft guidelines refer to nevirapine XR. In the clinical trials for the modified release formulation of nevirapine, the formulation was referred to as NEVIRAPINE XR. The correct nomenclature as licensed in the UK in November 2011 is NEVIRAPINE PROLONGED RELEASE and we recommend that this terminology is used in the final guidelines. For further information, please refer to the product Summary of Characteristics (SPC), available at: http://www.medicines.org.uk/emc/default.aspx

In the event that the writing group has queries about the properties or use of nevirapine, or requires further information on management in pregnancy and the perinatal period with nevirapine, please do not hesitate to contact our medical information department: medinfo.bra@boehringer-ingelheim.com or phone 01344 742579.

Abbott

We have read your consultation draft of the Guidelines for the Management of HIV Infection in Pregnant Women 2012, with much interest.

We are grateful for the opportunity to provide feedback which we hope you will find constructive. Our feedback is aimed at maximising patient benefit, by aligning ARV selection to individualised patient need with concomitant protection against MTCT.

To facilitate your review of our feedback we have strived to be concise and to focus on key recommendations associated with our proprietary ARV, KaletraTM (lopinavir/ritonavir, LPV/r). These are listed below against the recommendations and associated text in the order they appear in the draft consultation guidelines document.

We welcome any opportunity to clarify our feedback, provide more extensive material on LPV/r, or to explain further by any means.

Feedback on Guidelines for the Management of HIV Infection in Pregnant Women 2012

1.

Page 18, Section B2: Naive to HAART – mother needs ART for herself

RB2c: In the absence of specific contraindications it is recommended that the 3rd agent in HAART should be nevirapine if the CD4 count is less than 250 cells/µl or efavirenz or a boosted PI. Grading: 1C

Page 26: Section B3: Naive to HAART – mother does not need HAART for herself

RB3b: In the absence of specific contraindications it is recommended that HAART should be boosted-PI-based. The combination of zidovudine, lamivudine and abacavir can be used if the baseline viral load is <100,000 HIV RNA copies/ml plasma. Grading: 1C

Specific populations who we feel LPV/r can provide optimal therapy are associated with specific sections such as patient monitoring. Maternal health and long term/difficult to monitor HAART driven effects such as fatty liver are described within the consultation Guidelines recommendations (see Page 13, Section A: RA2e). We feel that LPV/r merits recommendation in such cases with the aim of aligning ARV use with risk factor offset. Published data comparing stable patients switched from LPV/r to boosted atazanavir (ATV-RTV) vs. those remaining on LPV/r had statistically significantly greater visceral adipose tissue (VAT) levels (Ferrer et al 2010). As clinical studies have associated VAT pathogenesis and prognosis of fatty liver (and steatosis/fibrosis see Equchi et al 2011, van der Poorten et al 2008) we feel that LPV should be the preferred boosted PI in affected patients. This should also be considered in the event of gastro-oesophageal reflux symptoms which have been reported to occur in 30-50% of pregnancies, with the incidence approaching 80% in some populations (Majithia and Johnson, 2012). Treatment strategies for patients can include proton pump inhibitor (PPI) therapy if indicated by symptoms. LPV is not contraindicated with PPIs (no effect on ARV bioavailability). This is particularly relevant as HIV+ patient management of acid reflux treatment has been published to occur at high frequency using OTC medication without the knowledge of their HIV healthcare provider (Overton et al 2010).

2.

Page 28/29, Section B4: Late-presenting woman not on treatment

RB4a. A woman who presents after 28 weeks should commence HAART without delay. Grading: 1B

RB4b. If the viral load is unknown or >100K a 3 or 4 drug regimen that includes Raltegravir is suggested. Grading: 2D

The PROGRESS study highlighted robust and rapid viral decay for cohorts treated with raltegravir (RAL) and LPV/r, with long term (48w and 96w) suppression equivalent to LPV/r plus TruvadaTM (Soto Malave et al 2011, Reynes et al, 2011). The low level of virologic failure and resistance to RAL observed in this study has not been achieved by any other boosted PI in clinical studies. Indeed, rapid and high level virologic failure with RAL resistance was reported in the SPARTAN study which examined ATV plus RAL vs. ATV-RTV plus TruvadaTM (Kozal et al, 2010). A similar outcome was reported for Darunavir (DRV) plus RAL in ACTG 5262 (Taiwo et al, 2011). We feel inclusion of KaletraTM be particularly useful in an appropriate late presenting patient population where rapid RAL-driven viral decay is required, coupled with protection against RAL resistance.

3.

Page 37: Section C: HIV and hepatitis virus co-infections

LPV/r has been shown to have comparable activity in mono- and HCV or HBV-co-infected patients (Da Silva et al 2004), and is compatible with tenofovir-based regimes without TDM requirements for HBV co-infected patients. In light of this we feel LPV/r merits a specific recommendation for affected individuals.

4.

Page 68/69 Outlines choice of triple combination PEP in neonates. 'The panel therefore recommend that this PI [LPV] should be avoided in infant PEP, where possible, and should only be prescribed to preterm neonates in exceptional circumstances'

Neonates

The recent findings hypothesising on the cause of adrenal insufficiency described in the cited source reference (Simon et al 2011), suggest a class rather than a LPV/r specific effect (ritonavir-dependent cyp21 inhibition). Causality was not established as described in the publication. Whilst we agree with the overall recommendation, it would be more appropriate to cite 'boosted PIs' rather than 'this PI' in light of the proposed mechanistic cause of adrenal insufficiency by the cited study authors.

5.

Page 32. Stopping ART post partum RB6a. When stopping NNRTI-based HAART post-partum the NNRTI washout period should be covered by two weeks PI-based therapy. Grading: 1C

The STOP study (Taylor et al, 2011) highlighted LPV/r as a highly effective agent in enabling deliberate cessation of ARV therapy with concomitant avoidance of ARV resistance emergence. With

published evidence to support and the GRADE system being applied, we feel LPV/r should be the preferred PI for stopping ART post-partum, where desired.

References

Da Silva et al (2004). Lopinavir/ritonavir (LPV/r) safety, tolerability and efficacy & liver safety in Hep C and/or Hep B-infected patients: Review of kaletra trials
XV International AIDS Conference. Abstr. B3285
Eguchi et al (2011). The pathological role of visceral fat accumulation in steatosis, inflammation, and progression of nonalcoholic fatty liver disease J Gastroenterol. 46 Suppl 1:70-8
Ferrer et al (2010). Impact of switching from lopinavir/ritonavir to atazanavir/ritonavir on body fat redistribution in virologically suppressed HIV-infected adults. AIDS Research and Human Retroviruses. 27, 2-5
Kozal et al (2010). The SPARTAN study: a pilot study to assess the safety and efficacy of an investigational NRTI- and RTV-sparing regimen of atazanavir (ATV) experimental dose of 300mg BID plus raltegravir (RAL) 400mg BID (ATV+RAL) in treatment-naïve HIV-infected subjects. In Program and Abstracts: XVIII International AIDS Conference. Vienna, Austria. Abstract #THLBB204.
Majithia R and Johnson D (2012). Are proton pump inhibitors safe during pregnancy and lactation?: Evidence to Date Drugs. 2012 Jan 22;72(2):171-9
Overton et al (2010). The effect of acid reduction with a proton pump inhibitor on the pharmacokinetics of lopinavir or ritonavir in HIV-infected patients on lopinavir/ritonavir-based therapy. J. Clin. Phamamacol.; 50/9 (1050-1055)
Reynes et al (2011). Examination of noninferiority, safety, and tolerability of lopinavir/ritonavir and raltegravir compared with lopinavir/ritonavir and tenofovir/
emtricitabine in antiretroviral-naïve subjects: The PROGRESS Study, 48-Week Results. HIV Clin Trials 12(5):255–267
Soto-Malave et al (2011. Lopinavir/ritonavir (LPV/r) Combined with Raltegravir (RAL) or Tenofovir/Emtricitabine (TDF/FTC) in Antiretroviral-Naïve Subjects:
96-Week Efficacy and Safety Results of the PROGRESS StudyXV Congreso Panamericano De Infectología, Uruguay, 7-11 April 2011
Simon Aet al (2011). Association of prenatal and postnatal exposure to lopinavir-ritonavir and adrenal dysfunction among uninfected infants of HIV infected mothers. JAMA; 306(1):70-78
Taiwo et al (2011). Efficacy of a Nucleoside-sparing regimen of darunavir/ritonavir plus raltegravir in treatment-naıve HIV-1-infected patients (ACTG A5262). AIDS 2011, 25: (17):2113-22
Taylor et al (2011). Lopinavir/ritonavir single agent therapy as a universal combination antiretroviral therapy stopping strategy: results from the STOP 1 and STOP 2 studies. J Antimicrob Chemother. 2011 Dec 14
van der Poorten et al (2008). Visceral fat: a key mediator of steatohepatitis in metabolic liver disease. Hepatology. 48(2):449-57

Roche Products Limited

Roche Products Limited, the license holder of Viracept (nelfinavir mesilate) would like to make the following comments in relation to the ongoing revision of BHIVA's 'Pregnant Women Treatment Guideline 2012':

- Nelfinavir has been proven to be clinically inferior to newer anti-viral treatments;
- Nelfinavir is no longer recommended in virtually any treatment guideline including WHO and PENTA – this includes all pregnant women / mother-to-child transmission treatment guidelines;
- Compared to other compounds in this class, several tablets of nelfinavir have to be administered several times a day and always with food;
- Current usage of nelfinavir in the UK is extremely low (from sales figures it is estimated that approximately 10 patients were treated last year in the UK);
- CHIVA has mentioned that according to their knowledge no neonates (or other children) are being treated in the UK;
- Roche is considering not renewing the product license for nelfinavir in which case it will not be available after it's 5-year 'birthday' in January 2013;
- In order to ensure that the new 'Pregnant Women Treatment Guideline 2012' is up to date when issued we recommend that any references to nelfinavir should be removed from the guideline as the product is unlikely to be available in future.

Roche will happily assist with additional information as and when necessary.

Neal Marshall

NB Separate document from Neal Marshall is at the end of this document

Attached is my feedback on the BHIVA pregnancy guidelines. I think there are a lot of interesting and good decisions made in this document, and the authors should be congratulated on that.

My main concern however are the sheer volume of recommendations, one or two of which overlap and appear to have different grade appraisals despite saying similar things. Some recommendations don't appear to recommend a particular strategy (despite being strong recommendations) and give the reader an option (e.g. HBIG for neonatal HBV prophylaxis)

I think its much more difficult to read compared to previous incarnations (although appreciate the new style is dictated by GRADE and NICE). Have the clinical scenarios been taken out for a reason, or will they be available in another form?

There is a distinct difference in how recommendations are presented in these guidelines compared to in the BHIVA treatment guidelines 2012. In these pregnancy guidelines we have not used 'we recommend' or 'we suggest' for grade 1 and 2 recommendations respectively (in appendix 1 we state A strong recommendation usually starts with the standard wording 'we recommend' but this is very rarely done. I think this document suffers for that as it is at times difficult to interpret strength of recommendation based on the wording (although it obviously states 1 or 2 after).

Dr Alastair McKelvey

Hi. I'm a Maternal/Fetal Medicine consultant. I'm emailing to clarify about screening for Down syndrome. Page 48-50. The national recommendation is for the combined test. Not the integrated test, which was a different 2-stage screening test. The description in the text is of the combined test and so does not need changed. Women who 'miss' the window for the combined test are offered the quadruple test.

Syeda Sabina Absar

I am a Bangladeshi by birth. I have worked in the HIV programs of CARE and SMC (Social Marketing Company). I think there is very less discussion of these issues in our country but there are patients suffering from HIV,TB and Malaria and other STIs. Organisations working in these sectors should disseminate these informations elaborately. Otherwise the outcome will not reach cent percent.

Nathan Ford

Congratulations on an excellent set of guidelines. Very good to see a strong decision being taken on efavirenz use in pregnancy. One quick comment: the 2010 review has been subsequently updated, and it may be worth referring to that data as well to indicate that there as been no change in the overall estimates for congenital abnormalities in general and NTDs in particular: Ford, Mofenson, Calmy; AIDS 2011 Nov 28;25(18):2301-4.

Good also that you noted the duplication of reporting of congenital abnormalities (p17). Of particular concern is the duplicate reporting of the single NTD event, which has now been reported 3 times (Brogly et al, Knapp et al, APR) and also included in the meta-analysis. Congratulations again and good luck finalizing.

Dr Racheal Ayanga

1.I am from a resource-limited setting, in Uganda (East Africa). The 2010 WHO guidelines, in which an HIV positive mother can breastfeed upto one year have markely led to reduction in malnutrition rates for the HIV exposed infants. I am concerned that these new UK guidelines, in which a mother must stop breastfeeding at 6months will increase malnutrition rates. What is your comment?

2.if HAART (especially EFV-based) regimen is discontinued for women with CD4+ above 500, won't this increase the risk of mutations hence resistance? I am of the view that HAART should be continued for life

3. The fertility rate in my country is v.high at 6.4. If a woman on an EFV-based regimen with CD4+ >500 is discontinued on HAART, what will happen when she conceives again?

Anonymous

Thank you for a very good guideline. I only have two comments as follows:

Section B recommendations RB2b and RB3a. The wording of these recommendations sounds more like a statement than a recommendation. If using TDF +FTC or ABC/3TC are "suitable alternatives" does that mean that AZT/3TC is preferred? The statement that there is more evidence and experience with AZT/3TC falls a little short of clarity on whether this should be preferred in the absence of specific contra-indications.

Secondly Section E2. I would like to see stronger support from BHIVA for NHS trusts and health boards to fully fund all HIV prevention interventions which include not only the provision of free infant formula milk to HIV-positive mothers but also bottles and sterilisers. I think that for equality this should be provided free to all HIV positive mothers regardless of their recourse to public funds status. Where this is a medical intervention for HIV prevention, rather than patient choice, then the costs should be accounted for within HIV prevention budgets as condoms are. The costs would be minimal in relative terms compared with the costs of anti-retrovirals, intensive behaviour-modification interventions and pre-exposure prophylaxis.

Bristol-Myers Squibb

We thank you for the opportunity for Bristol-Myers Squibb Pharmaceuticals Limited, as the manufacturers of atazanavir, to provide feedback on the guidelines for the management of HV infection in pregnant women 2012, with relevance to this product.

In particular, we recognise that the recommendation RB2d - "No routine dose alterations are recommended for ARVs during pregnancy if used at adult licensed doses. Grading: 1C Consider 3rd trimester TDM particularly if combining TDF and Atazanavir. Grading: 1C" - is consistent with the current Summary of Product Characteristics (SmPC) for atazanavir (1) . The SmPC was updated in November 2011, following consideration of evidence from study AI424182 - a phase I study of safety and exposure of once daily ritonavir-boosted atazanavir in HIV –infected pregnant women (2). The study results have provided additional safety information and a greater understanding of the pharmacokinetics of atazanavir in pregnancy, which is captured in the SmPC.

Given that the data from this study is in the public domain, following presentation at the 1st International Workshop on HIV and Women in January 2011(3) and subsequent publication in October 2011 (2), we would like to seek clarification as to the reasons for not considering this data in the guidelines. We would respectfully suggest that this evidence be incorporated into the discussion on safety, dosing recommendations and pharmacokinetics of atazanavir in the final version of the guidelines.

References

1. Reyataz (atazanavir) SmPC November 2011
2. Conradie et al. HIV Med 2011;12:570–9
3. Hardy H et al. 1st International Workshop on HIV and Women 2011. Washington DC. Poster 018

Dr Indrajith Karunaratne

A summary of "What is new from the previous guidelines" would be very useful. The table of content is much more user friendly than previous guideline and I am very grateful for that.

Dr Sophie Forsyth

Really pleased to see advice on normal delivery and instrumental delivery etc and viral load. This is a very wordy document and would be great to be able to jump to sections from the index (like BASHH guidelines) and have more summary tables e.g. these tests need to be done at booking. these at 20/40, these at 36/40 etc.

Dr Liat Sarner

Really clear guidelines making great strides forward to normalise pregnancy management in women with HIV

HAART in pregnancy

These guidelines state there is insufficient evidence to recommend avoidance of efavirenz in the 1st trimester of pregnancy. Could the committee consider specifically recommending the continued use of efavirenz in women actively trying to conceive & further recommend that switching to an alternative is not necessary based on available evidence

Late Presentation

p 30, Section RB4E refers back to RA4b this should say RB4a

Section D4 p 62, makes reference to RC2D with regard to the use of IV ZDV in women on ZDV monotherapy-this should refer to RD2D

RD2D contradicts information given in elite controllers section which states that women on ZDV mono therapy should have PLCS irrespective of pVL, whereas in elite controller states that woman with pVL <50 can have NVD as long as taking antiretroviral therapy

IV ZDV in elite controllers (VL <50) taking ZDV monotherapy and having PLCS or vaginal delivery is not necessary-not clear from the text

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Dr Justin Daniels

re immunisation - I work in an area of high TB prevalence (Haringey and Enfield) so all babies apart from those born to HIV positive mothers receive BCG prior to discharhge from labour ward. Babies born to mothers with HIV have a higher risk of TB and we struggle to ensure 100% BCG vaccination because of the delay.

Our last 400 consecutive babies born to mothers with HIV have all been HIV negative and I would argue that the risk of TB in these children is now higher than the risk of HIV. I would therefore like you to consider changing the recommendation on p71 to say that BCG should be given as normal where the practice is universal vaccination unless the mother had a VL>50 or there were other significant risk factors. I realise that there is little evidence to support my stance but I feel this is a more pragmatic response than the one in the guideline.

My one other comment is that diagnosis in pregnancy is often shocking for a mother and that we are of course concentrating on the protection of the unborn child, but it is also very important to screen other older children following a diagnosis and this should not be delayed unduly - I did not see this mentioned in the guidance and I think it probably should be.

Ian Peate

Please can you confirm on page five of the document if “baseline CD4 count of more than 350 cells/µL” is the correct unit measure to be used?

Miss Emily Hamblin

I coordinate the Children and Young People HIV Network. My interest in relation to this document is in psychosocial issues and I just have one comment on the guidance on eligibility for free NHS healthcare, which is that I wondered if it might be relevant to mention recent changes. Since 1 November 2011, if a person has an unpaid NHS debt exceeding £1,000 which has not been written off and is not being repaid to a ‘reasonable schedule’, they will generally have future applications to enter or stay in the UK refused. I'm unsure if this is likely to affect many pregnant women in practice, but it may be important in helping healthcare professionals understand the issue of eligibility for free NHS care and anxieties around this, as well as to give clear information to patients.

You may be aware of the National AIDS Trust's overview for people living with HIV, updated in January 2012. If not, it could be of interest: http://www.nat.org.uk/media/Files/Policy/2012/Jan-2012-Will-I-have-to-pay.pdf

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Dr Paul McIntyre

My comments relate to section E3.

1. The use of a maternal sample to detect primer mis-match: the gudance should indicate that this is only relevant to the use of the DNA test, assuming that is the intention.

2. Infant testing is variously referred to as “infant HIV diagnostic testing” and “HIV molecular tests” and “HIV test”and “HIV viral diagnostic tests” and “HIV viral genome diagnostic tests” and “infant HIV tests”. Can we standardise the nomenclature please. For the sake of clarity I suggest that all these phrases are replaced with “HIV DNA or RNA tests” .

3. “For infants breast feeding from mothers on HAART (see above), HIV viral diagnostic tests should be undertaken at least monthly on mother and infant, and twice on the infant, ideally between 2-8 weeks after weaning.” I don’t know what is intended here. Minimum testing needs to be unambiguously stated.

4. “If all tests are negative and the baby is not being/has not been breastfed, then parents can be informed that the child is not HIV infected.” This statement sets up tension with the following statements “Loss of maternal HIV antibodies should be confirmed at 18 -24 months of age. Ideally an HIV antibody test should be used to confirm loss of maternal antibodies rather than a combined HIV antibody-antigen test. The newer combined tests are highly sensitive and may give a positive HIV result until up to 2 years of age310. Testing for loss of maternal HIV antibody remains important as rarely, late postnatal infection may occur, even when all early HIV viral genome diagnostic tests were negative (French Perinatal cohort 5 / 4539 cases)311 This may be due to covert breast feeding, premastication of infant food or unknown intra-familial exposure.”

If infection can (rarely) be due to covert breastfeeding AND we suggest doing antibody tests at 18-24 months, then there is a tension with being so categoric with the reassurance that HIV DNA or RNA test results that are negative 3 times exclude infection. It may be reasonable to be so categoric despite this tension, but I think the tension needs to be explicitly addressed in the guidance.

Philip Steer

There is a general consensus, supported by the latest Cochrane analysis, that treating women with asymptomatic bacterial vaginosis has not been shown to be effective in reducing the rate of preterm birth. The draft guidelines say that because rates of preterm birth may be increased in mothers treated with highly active retroviral therapy "it seems reasonable to also screen for and treat bacterial vaginosis in this high risk group". It is not clear to me on what basis is thought to be reasonable, given that to date there is no convincing evidence that such treatment is effective at any stage of pregnancy. Moreover, the Oracle II study has shown that use of antibiotics "just in case" can have serious long-term harmful effects, including increases in the rate of cerebral palsy{1;2}. Indeed, some studies suggest that treatment of bacterial vaginosis may even increase the preterm birth rate{3}. It seems to me that the use of antibiotics in pregnancy requires positive evidence of benefit and should never be used "just in case".

RD2A Vaginal delivery is recommended for women on HAART with an HIV viral load <50 HIV RNA copies/ml plasma at gestational week 36. Grading: 1C

In this recommendation, I would be interested to know why vaginal delivery is ‘recommended’, rather than the more neutral statement of "not contraindicated" or ‘offered’ (as in relation to VBAC). This implies that there is a particular reason why vaginal delivery is likely to be more beneficial than elective Caesarean section in HIV positive women. While this may be true if women are planning to have three or more children, the latest UK guidelines on Caesarean section (http://guidance.nice.org.uk/cg132) highlight the fact that there is no convincing evidence that for the first birth vaginal delivery is safer for the mother than Caesarean section, and that a mother

requesting Caesarean section should have their wishes respected. The majority of obstetricians in the United Kingdom consider that women should be able to exercise choice in this regard{4}. If the term "recommended" is to be used, then I think evidence should be given as to why vaginal birth is to be preferred over Caesarean section. There is some evidence that Caesarean section carries increased risks for the long-term health of the baby in relation to immune function{5}, which may relate to babies not acquiring the appropriate maternal bowel flora which is more likely at vaginal birth. On the other hand, the risk of birth asphyxia and traumatic damage is largely avoided by Caesarean section. Such complications may be of particular importance if the mother is HIV-positive. Moreover I note that on page 55, there is a statement that there are "conflicting data regarding the effect of mode of delivery on MTCT in women with a viral load of <400". Given this uncertainty, it might be wise to explain the situation to women and allow them to make the final decision.

On page 57, it is acknowledged that in relation to the use of fetal scalp electrode and fetal bloodsampling, "it is unlikely that the use of fetal scalp electrode or fetal blood sampling confers an increased risk of transmission in a woman with an undetectable viral load although this cannot be proven from the current evidence". Apart from the philosophical point that proving complete safety is always likely to be impossible, given that the use of external ultrasound fetal heart rate monitoring is generally satisfactory, and that fetal blood sampling is uncommonly undertaken in modern clinical practice (and almost never in some countries such as the USA) it seems perhaps premature at the current time to support their use. Unlike for example forceps delivery, both fetal scalp electrodes and fetal blood sampling required deliberate piercing of the fetal skin, which may be considered somewhat undesirable if the mother is HIV-positive.

Similarly, the statement that "if the woman has no other risk factors she can be managed by midwife either in the midwifery led unit or at home" is contentious particularly in relation to home birth. For example, the latest UK birthplace study{6} has reported that perinatal mortality and intrapartum related neonatal morbidities (stillbirth after start of care in labour, early neonatal death, neonatal encephalopathy, meconium aspiration syndrome, brachial plexus injury, fractured humerus, or fractured clavicle) are 75% more likely if in nulliparous woman gives birth at home than if she gives birth in a maternity unit. It might be wise to be a bit more explicit about what is meant by "no other risk factors".

Reference List

(1) Russell AR, Steer PJ. Antibiotics in preterm labour--the ORACLE speaks. Lancet 2008; 372(9646):1276-1278.

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(3) Shennan A, Crawshaw S, Briley A, Hawken J, Seed P, Jones G et al. A randomised controlled trial of metronidazole for the prevention of preterm birth in women positive for cervicovaginal fetal fibronectin: the PREMET Study. BJOG 2006; 113(1):65-74.

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Dr Liz Anderson

I think this is a magnificent document - thank you! Having just taken the Dip HIV I feel that sometimes the message of BHIVA guidelines can get lost in the detail. A snappy bullet-pointed quick-reference summary of the main points at the beginning or end would be much appreciated (like EACS and RCOG guidelines). This may already have been planned.

There is a small typo in Section B3 where RB3a and RB3b are repeated twice.

Mrs Marti van der Linde

As premastication of food has been cited as a source of late postnatal infection & was wondering why wet nursing has not been mentioned – wet nursing increases risk of HIV infection among babies BMJ 2005; 330 doi: 10.1136/bmj.330.7496.862-b (Published 14 April 2005).

Cite this as: BMJ 2005;330:862.3

Dr Bill Spice

While this is undoubtedly a scholarly work,it is too long and unwieldly and is not "user-friendly". Is it possible to produce an abridged version for ready reference?

Dr Susan Liebeschuetz

The recommendation about avoiding BCG until 2 negative tests remains. Was the need for this reviewed by the committee? Delaying BCG will reduce the uptake of the vaccine. With low rates of HIV transmission, I am concerned that the risk of the baby misssing out on BCG outweighs the theoretical risk of the vaccine in an infected child. Particularly in high TB prevalence areas.

Dr Hassan Gaili

The title is slightly misleading. Can we say "Guidelines for active prevention of vertical HIV"

Dr Andrew Riordan

Excellent document - I liked the "scenarios" in the previous version.

A few minor queries;

1. RE1a: Zidovudine monotherapy is recommended....irrespective of

the mother's viral resistance pattern or drug history.

This will require more reassurance that it's safe.

Data from the era when only maternal ZDV monotherapy was

available indicate preferential transmission of wild-type over ZDV-resistant virus.

It would be useful to give references to this data. Is this data relevant to women with AZT resistant virus who are on HAART not including AZT??

2. RE1c: Where vaginal delivery is planned and maternal viral load at 36 weeks gestation/delivery is

not <50 HIV RNA copies/ml three drug infant therapy.

Delivery with a maternal viral load >50 copies is not uncommon - what added benifit is there in giving all these infants 3 drugs?

The reason 3 drug therapy has increased in the UK is that the last BHIVA guidelines suggested it - it's not a good argument for encouraging more use.

Is this a place for "CONSIDER 3 drugs" based on viral loads, where resistance

is suspected or confirmed or where viral load is increasing despite treatment.

3. Immunisation

Is there an argument for all infants born to HIV infected women being given BCG (when safe to do so)? Most get it because the family comes from a High risk country, but given the high risk of TB in HIV infected adults shouldn't all of their children get BCG???

Prof Lorraine Sherr

I have read through these guidelines which are truly excellent, thorough and cover the issues comprehensively and in an up to date way. I have been involved in 4 court cases and this document would certainly have helped enormously and will possibly help obviate future cases, which was really good to see.

I was pleased to see the Psychological aspects covered - including adherence and disclosure, as well as post partum depression. A small expansion on these issues may be useful. For example recent systematic reviews show mental health problems associated with HIV generally and include depression (most common), anxiety, suicidal behaviours and post traumatic stress disorder/growth. It would be good if these ideas were simply mentioned in the psychological section. There are no mentions of anxiety in the whole document.

Disclosure of HIV status to the child is important (but perhaps beyond the scope of this document). However WHO guidelines have just come out (2012) and could be briefly introduced.

The issue of cognitive implications of HIV, and how these may be relevant in pregnancy as well as issues for the child could also be briefly mentioned. There is no mention of cognitive development or delay in the document.

Internationally there is a strong movement to include fathers in the management of pregnancy. Obviously this document is specifically geared to pregnant women, but again, it would be good if a brief mention of fathers, their role, their importance and consideration of inclusion strategies from conception to support and management were included. There were no mentions of the word father or paternal in the document, and this could be easily remedied. There is good evidence that paternal involvement enhances support, also that concerns about negative paternal reaction in themselves affect behaviour.

Some mention of pregnancy intention (both among women and men) would be relevant and there have been recent good systematic reviews that the readers could be referred to.

Finally under the psychological component there is discussion of negative psychological problems, perhaps a brief comment on positive psychological issues could be helpful (coping, adjustment, adaptation).

An excellent paper has just come out (French et al) on subsequent pregnancies and this may be important to mention. Also there is information about effects from exposure to HIV (or medication or ill parent) on exposed but uninfected children that should perhaps be mentioned (see Filtau et al).

Overall the authors should be congratulated on an exemplary document.