British HIV Association
BHIVA

BASHH

11 June 2015

Meindert Boysen
Programme Director, Centre for Health Technology Evaluation
National Institute for Health and Care Excellence
Level 1A, City Tower
Piccadilly Plaza
Manchester M1 4BT

Dear Mr Boysen

Joint response to NICE from the British HIV Association (BHIVA) & the British Association of Sexual Health & HIV (BASHH): 'NHS England Submission to Questions Raised by NICE Following Consultation Responses to Hepatitis C Drug Appraisals'

We are grateful to the NICE Appraisal Committee for allowing us to respond to comments received from NHS England with regards to the following treatments for hepatitis C (HCV):

- sofosbuvir/ledipasvir
- daclatasvir
- parateprevir/r, ombitasvir and dasabuvir

Although we appreciate the financial constraints facing NHS England, we are not in agreement with their comments with regards to the publication (and implementation, thereafter) of NICE technology assessments for the listed drugs.

Whilst the Viral Hepatitis group of the Infectious Diseases/Hepatobiliary CRGs were consulted on NHS England's response there clearly was not agreement from all CRG members in support of it (apparent in the covering e-mail.) As representatives of associations representing both patients and healthcare professionals caring for people with HCV and HIV/HCV co-infection, we too disagree with many of NHS England's assertions.

We have also sought views and input on this document form commentators within BVHG/BASL who will be commenting separately on this consultation.

There are a number of specific issues to which we would like to draw the NICE committee's attention:

1) **EFFICACY:** we need to question NHS England's assertion that there are uncertainties regarding treatment effects and comparative effectiveness:
   a) They state *'the evidence base is small particularly in more severe patients (i.e. patients with cirrhosis)'* – as the Committee are doubtless aware, a number of real-life cohorts [1] and phase 3 trials [2] have presented or published data on the effectiveness of IFN-free DAA regimens in cirrhotics, including de-compensated disease. Further data will not change this
   b) NHS England also states that *'there is lack of evidence in harder to reach populations (e.g. co-infection with HIV)'*. We strongly refute this; there are now data from trials and cohort studies that put beyond any reasonable doubt that DAA-based therapies perform just as well in co-infected patients [3-5]. Furthermore as NHS England are well aware, more than 80% of patients with HIV-infection in the UK are already in care, the vast majority with HCV are diagnosed (due to regular viral hepatitis screening) and most are linked into care for their viral hepatitis [6].

2) **COST-EFFECTIVENESS:**
    a. NICE employs clear criteria for determining cost-effectiveness, as such, although we appreciate the financial constraints facing NHS England, repeating cost-effectiveness analyses would surely draw the same conclusions, regardless of current financial constraints?
    b. NHS England question the static nature of the cost-effectiveness models stating re-infection and onwards transmission as sources of uncertainty. A number of modelling studies, including work from the UK [7] have taken into account the impact of re-infections on the effectiveness of testing and treatment; NHSE have not acknowledged the potentially significant benefits of 'treatment as prevention' nor that treatment will not only reduce the incidence of new infections but the prevalence of HCV. To reduce the burden of disease and new HCV infections amongst HIV+ MSM will require treatment with DAA-based therapy for >80% of those with acute HCV and within a year of diagnosis and 20% of those with chronic HCV, per annum [7]. We are not convinced that further data will change these assertions and now is the time to reduce the burden of HCV-related disease in these vulnerable, high-risk populations.
    c. We are concerned that basing cost analyses on list prices of new drugs over-estimates potential costs; NHS England would usually negotiate significantly lower prices

3) **WATCHFUL WAITING & SEQUENCING:**
    a. We must highlight that *'watchful waiting and monitoring for disease progression'* has associated costs; whilst this may be possible for patients currently in care, it will have significant resource-use implications for the future. Furthermore, such a strategy may be detrimental in the case of rapid progression in some groups (e.g. sub-groups of HIV co-infected patients). We also emphasise that HCV-infection is a chronic inflammatory condition with deleterious effects beyond the liver (renal disease, bone disease, cardiovascular disease, poor psychological health, fatigue); this may be particularly more pronounced in co-infected patients [8-10].
    b. We are also disturbed that given therapies with significantly fewer side-effects, and better SVR rates, NHS England would even consider sequencing therapies, with 'less expensive' PegIFN and ribavirin (+/- first generation PIs): these regimens are associated with unacceptably high rates of treatment-limiting toxicities and the strategy is clearly counter-intuitive in terms of patient (and clinician) acceptability. To accurately ascertain the impact of watchful waiting or drug sequencing require trials designed to investigate these questions; this is not what NHS England are suggesting and their proposed strategy does not address this.

4) **OPPORTUNITY COSTS OF HIGH-COST MEDICATIONS:** whilst there is a large population with HCV infection in England, the **vast majority** remain undiagnosed (28,500 diagnosed of an estimated 160,000 infected), and of those diagnosed not all are under regular follow-up and 'in care'. It is therefore highly unlikely that uptake of treatment according to NICE guidance will have anywhere near the suggested impact on NHS England's budget in a single year. Even if treatment is taken up by all HCV patients in care this would take place over a period of many years.

5) **CAPACITY CONSTRAINTS**:

a. We, and others, have highlighted already that the infrastructure delivery of DAA-based therapy was established by NHS England for the delivery of the EAP for decompensated cirrhotics. An expansion of the number of networks delivering DAA-based care is already underway and care networks for co-infected patients have been established. Further refinement of delivery can happen in parallel to establishing therapy; any further delay will not be helpful.
b. NHS England acknowledges that treating up to 7,000 individuals per annum would be manageable within current clinical services. It was as a result of NHS England's concerns that services would be unable to meet a similar capacity demand that the implementation time for Sofosbuvir/Ribavirin +/- Interferon was extended. The fact that NHS services are now deemed capable of treating this number of patients is reassuring and, as per point 4, treating 7,000 individuals a year would still enable us to treat all diagnosed people within 5 years.
c. We firmly believe that appropriate, equitable and controlled implementation of NICE guidance can be achieved within existing and evolving services.

6) **MULTIPLE TECHNOLOGY APPRAISAL:** NHS England state that 'all stakeholders who have advised NHS England have indicated the importance of forming a multiple technology appraisal…' We were certainly not consulted in this regard and are interested to whom 'all stakeholders' refers. We believe that with the fast evolving therapeutic landscape of HCV therapy, with several potentially beneficial agents still in development, a meaningful MTA would not be possible for a few years to come and would take a further 1-2 years to complete. As NICE and NHS England are both well aware MTAs are not feasible for all therapy areas; NICE-accredited guidelines (as per those for HIV treatment, for example) may be more useful and responsive to this quickly changing disease area. An MTA would unnecessarily delay implementation of therapy for groups of patients that would not meet NHS England's 'priority' criteria.

7) **PRIORITISATION STRATEGIES:**

a. Although we applaud the NHS England DAA EAP for decompensated cirrhotics, we are concerned about the already significant delays in the DAA programme for compensated cirrhotics (initially promised in May 2015 and yet to be implemented). We reiterate that the strategy of 'watchful waiting' is also associated with a cost to the NHS and a burden on already full clinics. Further delay would be detrimental to the sub-group of patients with rapidly progressing liver disease (a significant sub-group of HIV/HCV co-infected patients, for example) and patients who default regular follow-up creating inequalities in healthcare delivery for certain sub-groups of society (homeless, migrant communities and PWIDs, for example).

b. We are also concerned that 'prioritisation' strategies will be liver disease-based (as already implied in the NHS England response) and will disadvantage certain populations with major HCV morbidities not necessarily associated with significant liver fibrosis. As already emphasised, successful HCV treatment improves extra-hepatic HCV-related morbidities; in HIV-infected patients, even those with milder fibrosis (<F2), successful HCV therapy is associated with significantly improved overall survival [11]. National/international guidelines [12,13] recognise this and recommend prioritising treatment for certain sub-groups without significant fibrosis.

8) **'RECOMMENDED WITH RESEARCH':**

a. We remain unconvinced that the 'recommended with research' position NHS England urges for those without cirrhosis will deliver therapy to those most in need of DAA-based therapy. NHS England provides no evidence to support this strategy, nor any suggestions for a programme that would provide answers to the questions they raise. We believe that 'further research' in this area is best delivered by robust data-collection, as therapy is rolled-out as per guidance. Contrary to NHS England's assertion that there is insufficient data to support the use of these new agents we would argue that the extensive phase 2 and 3 trials, deemed sufficient for approval by the FDA and the EMEA, combined with extensive phase 4 and 'real world' data provide ample evidence. Clarity from NHS England about what evidence is lacking would be insightful.
b. We read with interest a paper outlining the principles underlying a NICE decision to 'approve with research' [14] and, based on this, believe that HCV treatment does not fulfil those principles:
    i. The 'uncertainties' that NHS England cite are around cost-effectiveness based on re-infections (driving up cost) and onward transmission (driving down cost) and failure to explore a stepwise approach (this would be unacceptable ethically as has already been accepted by FDA/MHRA)
    ii. The issues of re-infection/onward transmission may well not be answered by further research - modelling data already addresses these
    iii. The relatively high opportunity costs currently (almost all down to drug price) will be reduced considerably over the coming years as competition increases
    iv. 'Research' of this nature is best carried out with wider implementation of therapy

9) **IMPACT ON OTHER SPECIALISED SERVICES:** NHS England makes reference to this issue and use it as justification for altering NICE processes. We would be interested to see the data on which this is based.

10) **NICE:** we strongly advocate that NICE's robust and validated processes remain independent both in terms of external influences on their decisions and that interventions are assessed on their own merits, not relative to the potential impact on other disease areas.

We would urge NICE to move forward with its recommendations and for NHS England to engage fully with all stakeholders (including national organisations, patient advocacy groups) so that DAA-based treatment can be delivered efficiently and equitably. We would also suggest use of evidence-based clinical guidelines to guide use of particular DAAs in sub-groups of patients.

Please contact the BHIVA Secretariat if you have any queries regarding these comments.

Yours sincerely

Dr Sanjay Bhagani
Chair, BHIVA Hepatitis Society Subcommittee

Dr Elizabeth Foley
BASHH General Secretary

REFERENCES

1) Foster G, et al.: Treatment of decompensated HCV cirrhosis in patients with diverse genotypes: 12 weeks of sofosbuvir and NS5A inhibitors with/without ribavirin is effective in HCV genotypes 1 and 3. 50th International Liver Congress (ILC), April 22-26, Vienna, Austria; abstract O002

2) Manns M, et al.: Ledipasvir/Sofosbuvir with ribavirin is safe and efficacious in decompensated and post liver transplantation patients with HCV infection: Preliminary results of the prospective SOLAR 2 trial. 50th International Liver Congress (ILC), April 22-26, Vienna, Austria; abstract G02
3) Cooper C, et al. A single tablet regimen of ledipasvir/sofosbuvir for 12 weeks in HCV genotype 1 or 4 infected patients with HIV-1 coinfection: The phase 3 ION-4 study. 50th International Liver Congress (ILC), April 22-26, Vienna, Austria; abstract P1353
4) Nelson DR et al. All-oral 12-week combination treatment with daclatasvir (DCV) and sofosbuvir (SOF) in patients infected with HCV genotype (GT) 3: ALLY-3 phase 3 study. American Association for the Study of Liver Diseases (AASLD) Liver Meeting, Boston, abstract LB-3, 2014.
5) Cotte L et al. Telaprevir for HIV/hepatitis C virus-coinfected patients failing treatment with pegylated interferon/ribavirin (ANRS HC26 TelapreVIH): an open-label, single-arm, phase 2 trial. Clin Infect Dis. 2014 Dec 15;59(12):1768-76.
6) British HIV Association, HIV and Hepatitis B/C Co-infection Audit 2010. Accessed at www.bhiva.org 8th June 2015
7) Martin NK et al. Is increased HCV case-finding combined with 8 or 12 week interferon-free direct-acting antiviral treatment cost-effective in UK prisons? A cost utility analysis including treatment as prevention benefits. 2015 International Liver Congress: 50th Annual Meeting of the European Association for the Study of the Liver (EASL). Vienna, April 22-26, 2015. Abstract O124.
8) Womack JA et al. HIV infection and cardiovascular disease in women. J Am Heart Assoc. 2014 Oct 16;3(5):e001035.
9) Mocroft A et al. Development and validation of a risk score for chronic kidney disease in HIV infection using prospective cohort data from the D:A:D study. PLoS Med. 2015 Mar 31;12(3):e1001809.
10) Giesbrecht CJ et al. Select neurocognitive impairment in HIV-infected women: associations with HIV viral load, hepatitis C virus, and depression, but not leukocyte telomere length. PLoS One. 2014 Mar 4;9(3):e89556.
11) Berenguer J et al. Effects of sustained viral response in patients with HIV and chronic hepatitis C and nonadvanced liver fibrosis. J Acquir Immune Defic Syndr. 2014 Jul 1;66(3):280-7.
12) AASLD/IDSA/IAS–USA. Recommendations for testing, managing, and treating hepatitis C. http://www.hcvguidelines.org. Accessed 8th June 2015.
13) EASL Recommendations on Treatment of Hepatitis C 2015. J Hepatol. 2015 Apr 21. pii: S0168-8278(15)00208-1.
14) Karl Claxton & Stephen Palmer & Louise Longworth & Laura Bojke & Susan Griffin & Claire McKenna & Marta Soares & Eldon Spackman & Jihee Youn, 2011. "Uncertainty, evidence and irrecoverable costs: Informing approval, pricing and research decisions for health technologies," Working Papers 069cherp, Centre for Health Economics, University of York.