

# BHIVA Guidelines for the Treatment of HIV-1-positive Adults with Antiretroviral Treatment 2012

## Consultation Comments

This document contains the comments received by the BHIVA Secretariat during the web consultation process.

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## London Specialised Commissioning Group

Dear Jacqueline

Many thanks for the extension to comment on the draft BHIVA treatment guidelines. Please find attached.

Regards

Claire

Claire Foreman, Senior Commissioning Manager, London Specialised Commissioning Group, Portland House, Stag Place, London SW1E 5RS

Dear Prof Anderson

### **Commissioning Response to draft BHIVA Treatment Guidelines 2012 – London SCG and Commissioning Lead for HIV CRG**

Thank you for the opportunity to comment on the draft guidelines. We have 10 key points to raise. We'd like to receive feedback on these and to ask that you consider updating the final guidelines to address these issues.

#### **Evidence**

- 1) We have reviewed the application of the GRADE system and have some questions about this. In the grade tables shown in the appendices there seems to be a lack of consistency between the quality of the research and the importance of the findings. The results of some research studies were judged to be critical or very important in informing decisions, based on low quality evidence and even on the basis of good practice points. What was the rationale of the writing group in making such strong recommendations where this might not be supported by the strength of the evidence? We would also suggest that some improvements in presentation could be made so the reader can easily track each evidence source for the recommendations listed.
- 2) We also note that the writing group used a number of outcome measures to compare agents. This is a useful approach. Can you confirm how the writing panel prioritised these outcomes? We were surprised to see that avoidance of outcomes such as renal failure or cholesterol events were given a relatively low priority, in comparison to avoidance of outcomes such as diarrhoea. Further information on this would be welcome.
- 3) We note that the draft guidelines recommend that on the basis of low quality evidence and a good practice point, that treatment as prevention should be initiated should a patient ask for it. There was some discussion in the London Drugs & Treatment sub committee about whether the guidelines actually recommend initiation of treatment on this basis or not. Can this be made clearer in the final version?
- 4) We note that the writing panel has assigned a Grade 2 recommendation for the use of Kivexa® first line. The recommendation is based on the same evidence considered by the London HIV clinicians and the same scenarios for usage agreed in London. This was the subject of discussion at the London Drugs & Treatment sub group and the view was that based on the same evidence, the use of Kivexa® could be recommended in the scenarios outlined. Can you clarify why the draft guidelines can only suggest use of Kivexa® and not recommend it?

#### **Cost impact**

- 5) The draft guidelines refer to the importance of cost in making decisions about the appropriate use of agents and this is clearly important. However, given the financial constraints facing the NHS, it is disappointing that cost and benefit does not play a more prominent role. Whilst investing now may

reduce costs in future, reducing costs now also remains a key concern to ensure delivery of the QIPP agenda. A greater focus on cost and value considerations will help clinicians and commissioners to manage patient expectations in this context. This will be especially important when the availability of generic drugs in the next few years will provide a real opportunity to ensure continued access to ARVs within constrained budgets. There is already some evidence that patients have interpreted the draft guidelines to mean that whatever drug is requested will be received, irrespective of clinical need. It would be helpful for BHIVA to give further advice to clinicians, commissioners and patients on how cost consideration can be taken into account? Work undertaken in London reached consensus on the importance and legitimacy of clinicians taking account of cost in prescribing decisions with patients. Based on this collaborative experience we would suggest further consideration is given to the presentation of cost and value considerations in the guidelines. We would also like to suggest that cost effectiveness of prescribing might be an area of collaboration for commissioners and BHIVA to work on. We would welcome your views on the value of working together on this.

- 6) We note that as a consequence of some recommendations, a sequencing approach to use of drugs is much less clear. The recommendations for first line treatment include agents in all classes, including those that have been used and priced for very selective use. The basis of the recommendation is in terms of clinical effectiveness equivalence. Would BHIVA agree that if all agents are equivalent, and taking into account individual cases, that as an approach it is reasonable to use the least expensive regimen available? We would welcome a clearer view on this being included in the final draft
- 7) With respect to availability of generic drugs we also note that the guidelines recommend use of fixed dose combinations to increase compliance. Whilst there is good evidence for improved compliance when using a once daily dosing schedule (as opposed to twice/three times a day) as noted in the guidelines, we are not aware of any robust evidence regarding the number of tablets to be taken at any one time. Given that the emergence of generics is likely to require patients taking separate drug entities we would ask that less emphasis is placed on fixed dose combinations when the frequency of taking the drug is not affected.

#### **Implications, impact and status**

- 8) Does BHIVA intend to make any comment on an acceptable time frame in which implementation of guidelines might be achieved? Commissioning is currently in transition and the ability of commissioners to respond immediately to any final guidelines is likely to be limited, particularly where they represent a shift from current practice. Should HIV commissioning be undertaken by the NHS Commissioning Board, this should offer additional opportunities for a national commissioning response to the final guidelines over the next 2 years. What is the review date BHIVA has set for these guidelines?
- 9) Will the finalised guidelines include a list of the membership of the writing panel? We would be interested to know whether the membership included commissioners, public health or other speciality doctors such as GPs. Will the document also set out the conflict of interest policy used and the interests declared and registered by panel members?
- 10) We note that the draft guidelines have been produced in such a way to achieve NICE accreditation. For commissioners, ensuring guideline recommendations are supported by high quality evidence assessed against key outcome indicators is an important principle. We would value an update on whether the accreditation has been awarded by NICE and what accredited status will mean for such guidelines.

Yours sincerely,

Claire Foreman, Lead Commissioner for HIV, London Specialised Commissioning Group  
Malcolm Qualie, Commissioning Lead, HIV Clinical Reference Group

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**Department of Health**

Kay Orton, Lead, HIV and STIs Policy and Services

Jane

Thanks you for sharing the latest draft of the BHIVA treatment guidelines with us we do appreciate it.

We have no specific comments on the detailed recommendations. However, since the draft was circulated as you know we have agreed to remove HIV from the provisions of the NHS Charging Regs, with effect from October 2012. This will mean that HIV treatment will be treated the same as other STIs and infectious diseases for which there is no charge. This change is intended to promote and encourage the offer and acceptance of earlier HIV testing for people already present in the UK.

However, given the open-access nature of HIV services compared to some other countries, as you know we will be issuing guidance to support implementation of the change in a fair and consistent manner. In connection with this and the fact that front-line clinicians will be on the receiving end of potential HIV health tourists (i.e. with no other apparent reason to be present in the UK), it would be helpful if the DH guidance was consistent with the BHIVA Treatment Guidelines and the Guidelines acknowledged the issues raised by the policy change in some way.

For example, perhaps adding overseas visitors to the section at the end on "Routine monitoring recommended for specific patient groups" and providing some wording along the lines of increasing the number of monitoring and follow-up visits or frequency of prescriptions, if a clinician has concerns that a patient has no valid reason for being present in the UK other than for free HIV treatment. I'm sure there is a better form of wording which we would welcome working with you to agree. From the meeting you attended and the follow-up meeting there were anecdotal reports of inappropriate use from HIV patients who would probably pay for treatment in the home country but chose to make periodic visits to the UK to collect ARVs and undergo monitoring etc.

Our concern is not so much around newly diagnosed patients who would be required to attend several visits in the first year following diagnosis, but rather for example, a stable patient from overseas with no reason to be present in the UK other than free NHS treatment which they can access by visiting the UK up to 4 times a year - or even twice a year if reduced frequency of monitoring is adopted.

We're happy to meet with you and or the Guidelines committee to discuss if that would help.

Best wishes  
Kay

Kay Orton  
Lead, HIV and STIs Policy and Services, Sexual Health Team, Department of Health, Room 621 Wellington House  
133-155 Waterloo Road, London SE1 8UG

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**Dr Clifford Bryn Jones**

Dear Sir,

I would like to ask whether reference could be made to CD4% count in the guideline? I note that this is included in the prophylaxis section of the recent opportunistic infection guidelines and feel that it should be included for consistency (even if to say that there is no evidence).

Kind regards  
Bryn Jones

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## Academic Directorate of Communicable Diseases, Sheffield Teaching Hospitals

Dear Jacqueline,

Please find attached the response from the Academic Directorate of Communicable Diseases, Sheffield Teaching Hospitals, to the draft HIV-1 Treatment Guidelines.

We thank you again for the extended consultation period you have allowed us.

With best wishes,

Ben Stone

Response to draft BHIVA guidelines for the treatment of HIV-1 infected adults with antiretroviral therapy 2012 on behalf of the Academic Directorate of Communicable Diseases, Sheffield Teaching Hospitals NHS Foundation Trust

### General comments

We welcome these new treatment guidelines and overall, we welcome the shift towards starting treatment earlier. There is still, however, a significant knowledge gap that needs to be addressed in clinical trials. Some of the recommendations in the guidelines may affect our ability to collect that data, e.g. our ability to recruit patients to the START trial.

There is some inconsistency from section to section, with most sections offering graded evidence recommendations or suggestions, but some, e.g. Section 4.2.2.4 offering conclusions. The structure should be uniform for all sections.

### Section 2.1 When to start?

**“The absolute risk of disease progression is significantly higher for a given CD4 count in older people (see Table 2.1), so consideration should be given to starting at higher CD4 counts in older persons.”**

Greater clarification as to what is defined as “older” would be helpful. We can extrapolate a potential age cut-off above which to start HAART earlier from the CASCADE data presented in Table 2.1, e.g. at age more than 55 years, start HAART at CD4 cell count >500 cells/ul, although it would be clearer if the authors could generate their own conclusion and a recommendation from this data instead of leaving readers to interpret the table themselves.

### Section 2.3 Treatment of primary infection

**“We suggest patients presenting with primary HIV infection and meeting any one of the following criteria start ART:**

**Short test interval (eg ≤12 weeks from a negative HIV Ab test) or laboratory evidence of ‘acute infection’ including negative Ab test with either positive proviral DNA or p24 Ag. (2C)”**

Although immunologically this is a good suggestion, there is no evidence that starting treatment within 12 weeks of seroconversion is of clinical benefit, balanced with the cost to the patient of longer duration of therapy and its financial cost.

By starting treatment early without time for adjustment to diagnosis, long term adherence may be less good downstream. Drug fatigue could also become an issue.

### Section 2.4 Treatment to reduce transmission

**“We recommend following discussion, if a patient with a CD4 count above 350 cell/μL wishes to start ART to reduce the risk of transmission to partners, this decision is respected and ART is started. (GPP)”**

Although we welcome a more patient-centred approach to starting treatment, we have some concerns with this recommendation.

This recommendation has major implications for the delivery of HIV care in the UK. There is obviously a balance to be struck between the potential public health benefit from reduced transmission of HIV vs. significantly increased costs, not just financially but to the patient, committing them to life long treatment at an earlier stage of infection.

The wording of this statement suggests that any patient, regardless of other indications, can ask to start antiretroviral therapy and that we as physicians are duty bound to provide it. The use of “recommendation” for what is stated as “good practice” over “suggest” or “suggest in specific circumstances” seems overly strong.

We are concerned that the more informed and vocal patients may, using this recommendation, have better access to treatment than patients who are less informed and/or who defer more decisions to their physicians. This seems unjust.

There are less expensive alternatives to reducing transmission. We have significant concern that starting HAART solely to reduce transmission could reward high risk behaviours and could lead to increased transmission of other STIs.

Such a recommendation also has other ethical implications: it could impact on prosecution for reckless transmission and this needs to be explored further.

The potential detrimental impact of this recommendation on current and future clinical trials is also of concern, e.g. the START trial.

### Section 3.3 Which NRTI backbone?

**“We recommend therapy naïve patients start combination ART containing tenofovir and emtricitabine as the NRTI backbone. (1A)**

**We suggest abacavir and lamivudine is an acceptable alternative NRTI backbone in therapy naïve patients who prior to starting ART have baseline viral load of  $\leq 100,000$  copies/ml. (2B)**

**Abacavir must be avoided in patients who are HLAB\*5701 positive.”**

We felt that this section underestimates the potential long term problems of tenofovir, focussing on the short term detrimental effects of abacavir. Whilst we agree that abacavir should be avoided in certain patient groups, we felt that kivexa should be recommended equally alongside truvada as first line therapy, with the caveat that kivexa is not used in patients with high viral loads, who are HLA-B\*5701 positive or who have a significant cardiovascular risk.

### Section 3.4 Which third agent?

We generally support the recommendations and suggestions in this section, which fits our current local practice, putting aside cost and a lack of long term data for raltegravir.

### Section 4.1 Patient involvement with decision making

**“A patient’s decision not to disclose their status to their GP should, however, always be respected.”**

We feel that the statement has the wrong emphasis and gives undue support to patients who are reluctant to disclose to their GPs. We should be strongly encouraging patients to disclose their HIV status to their GP, especially regarding non-antiretroviral drug prescribing and potential drug interactions. We feel that not disclosing a patient’s status to their GP without that patient’s prior consent is already implicit, that GMC “Confidentiality” guidelines offer clear enough instruction on this already and that this sentence should be removed from these treatment guidelines.

**“Communication with GPs and other medical specialties involved in the patient care is fundamental in minimizing the risk of adverse drug–drug interactions. All clinic letters should carry as a standard header or footer advice to check for interactions, and links to resources such as [www.hiv-druginteractions.org](http://www.hiv-druginteractions.org)) to address the potential for drug interactions.”**

We support this recommendation, although would advocate that, if there is any doubt, other healthcare professionals communicate with HIV physicians directly when starting new drugs with potential for interactions.

#### Section 4.3.3 Stopping therapy: pharmacological considerations

**“We recommend patients stopping ART containing a NNRTI in combination with tenofovir and emtricitabine, stop all drugs simultaneously. (1C)”**

The evidence to support this recommendation is not cited. We assume that this is relation to data published on the intracellular half-life of tenofovir/emtricitabine. This should be clarified.

#### Section 4.3.4 Switching therapy: pharmacological considerations

We notice that this section is structured differently to other sections, with conclusions as opposed to initial recommendations followed by rationale (please refer to ‘General Comments’).

#### Section 5.3 Patients with no or limited drug resistance

**“We recommend patients experiencing virological failure on first-line ART with WT virus at baseline and without emerging resistance mutations at failure, switch to a PI/r-based combination ART regime. (1C)”**

In our experience, poor compliance is the most common reason for failure to respond to 1<sup>st</sup> line ART. In the absence of documented resistance we do not see that all non-PI based regimes should be excluded as an option.

#### Section 6.1 HIV with tuberculosis co-infection

**“CD4 <100: Start HAART as soon as practical within two weeks after starting TB therapy. (1B)  
CD4 100-350: Start HAART as soon as practical, but can wait until after completing two months TB treatment, especially when there are difficulties with drug interactions, adherence and toxicities. (1B)”**

In published studies from resource-poor settings, TB co-infected patients with CD4 counts <50 cells/μl had unequivocally worse outcomes when HAART was delayed for more than 2 weeks after initiation of TB treatment. We feel that this should be stated explicitly in the guidance. Conclusions were less clear in patients with CD4 counts between 50 and 200 cells/μl, in part due to the difficulties in managing IRIS in resource poor settings.

As we are able to monitor for and manage IRIS more safely in the UK, however, we should feel more comfortable starting HAART earlier in this patient group. We should therefore aim to start HAART within two weeks in patients with CD4 counts < 200 cell/μl.

For these reasons, we think the CD4 groupings in this recommendation should be changed. We would advocate starting HAART as soon as practical within two weeks after starting TB therapy in patients with CD4 counts <200 cells/μl. We would advocate starting HAART as soon as practical, but being able to wait until after completing two months of TB treatment, in patients with CD4 counts of 200 to 350 cells/μl.

##### Section 6.1.2.1

**“We recommend efavirenz in combination with tenofovir and emtricitabine as first-line antiretroviral therapy in TB/HIV co-infection. (1B)”**

Our opinion is that this should give the option for abacavir-lamivudine as an alternative to tenofovir-emtricitabine, taking into account the caveats outlined in section 3.3.

Section 6.2 HIV and viral hepatitis co-infection

For patients with hepatitis B co-infection and CD4 counts > 500 cell/ $\mu$ l, an option should be given for pegylated interferon-based treatment in specific circumstances, i.e. low HBV DNA and raised ALT as per chronic hepatitis B management guidelines (see EASL Management of Chronic Hepatitis B Guidelines 2009). This may mean that patients could completely clear the hepatitis B virus, becoming surface antibody positive, which would allow greater choice of ART regimen at a later stage.

Dr B Stone  
Dr A Tunbridge

March 2012

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**Royal College of Physicians**

Dear Ms English

Re: HIV Association guidelines for the treatment of HIV-1 infected adults with antiretroviral therapy 2012

The Royal College of Physicians (RCP) plays a leading role in the delivery of high quality patient care by setting standards of medical practice and promoting clinical excellence. We provide physicians in the United Kingdom and overseas with education, training and support throughout their careers. As an independent body representing over 25,000 Fellows and Members worldwide, we advise and work with government, the public, patients and other professions to improve health and healthcare.

The RCP is grateful for the opportunity to respond to the above consultation. Overall, we wish to convey our support for the guidelines. However we would like to make the following comments:

Our experts believe that it is appropriate that the guidelines group has recommended that the starting CD4 count for antiretroviral medication (ARVs) should remain at 350. This is a sensible assessment of the evidence (or rather lack of evidence) for starting any earlier.

We have some concern about the decision to downgrade abacavir/lamivudine (Kivexa) from its 'preferred' status to 'alternative'. It is the view of some that the more recent publications would support retaining Kivexa as a preferred option and it therefore seems unsound to change its status now.

Yours sincerely

Dr Patrick Cadigan  
Registrar

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**MRC**

**BHIVA draft guidelines Feb 2012 – comments**

Name: Kholoud Porter, Fiona Ewings, Abdel Babiker; MRC Clinical Trials Unit

**Comments:**

Our comments relate to section 2.3 "Treatment of primary HIV infection".

a. Data from CASCADE being presented at CROI 2012 indicate that severe clinical symptoms, including but not limited to neurological involvement, is associated with more rapid HIV disease progression. Presence of an illness with neurological involvement in itself was not predictive of HIV disease progression. Furthermore, a single CD4 measurement <500 cells/mm<sup>3</sup> (not just a confirmed CD4 <350 cells/mm<sup>3</sup>) was also predictive of HIV disease progression (Lodi et al., poster 550).



b. The HR and p-value quoted from the post-hoc analysis in SPARTAC were from a preliminary analysis restricted only to patients with short duration of infection at randomisation. The appropriate p-value to provide is from the test of interaction between duration of infection and treatment (p=0.09). Given this result, we would strongly recommend that the sentence is re-worded to replace “significant benefit” with “trend”. In addition, the primary endpoint was, in fact, time to CD4 <350 cells/mm<sup>3</sup> \*or initiation of lifelong treatment\*.

c. The correct references for the statement “This randomised study supported cohort studies in which a more rapid rate of CD4+ cell loss was seen in individuals presenting within 12 weeks of a negative HIV antibody test” are The CASCADE Collaboration (2001) and Tyrer et al. (2003), not the one given by Lodi et al.

d. It is important to note that in the SPARTAC trial we found no evidence of an increase in the rate of adverse events in the short-course treatment arms (12 or 48 weeks) compared to the no-therapy arm.

The CASCADE Collaboration, 2001. The relationships between the HIV test interval, demographic factors and HIV disease progression. *Epidemiology and Infection*, 127, pp.91–100.

Tyrer, F. et al., 2003. The relationship between HIV seroconversion illness, HIV test interval and time to AIDS in a seroconverter cohort. *Epidemiology and Infection*, 131(3), pp.1117–1123.

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## THT

Dear Jacqueline,

Here is Terrence Higgins Trust's response to the consultation on the new BHIVA HIV treatment guidelines. I believe Lisa Power has let you know that I was experiencing some IT problems which delayed my reply so thanks for taking our submission direct.

Best regards, Blake.

**Blake Smith**  
**Information Officer**  
**Policy and Information**

### **THT consultation response to BHIVA treatment guidelines update 2012**

Terrence Higgins Trust (THT) is the UK's largest HIV and sexual health charity, with 30 service centres across England, Scotland and Wales. THT is a membership and campaigning organisation which works with and advocates on behalf of people living with or affected by HIV including the provision of services. A proportion of our work involves providing information, advice and support to people living with HIV about their care and treatment options. We discuss treatment issues with service users through the THT Direct helpline, our health support trainers, in group-work settings and also by providing information in our publications and on our websites. These comments have been collated in consultation with THT staff, volunteers and service users across the country who shared with us their views and, where applicable, those of their clients. We consulted service users and other people living with HIV by informing staff and volunteers regarding the guidelines, by posting on our social media presence and by creating a community forum topic thread on THT's 'myHIV' website which received a number of responses.

Terrence Higgins Trust broadly welcomes these new guidelines and in particular their expansion to include sections on supporting patients on therapy, including adherence, and starting therapy early in circumstances such as acute or primary HIV infection and where treatment to prevent onward transmission is requested by a patient. As well as welcoming these changes we also have a number of comments on some aspects of the guidelines which are detailed below.

### **Process**

THT welcomes the involvement of the two patient representatives on the writing committee and the openness of the patient and public consultation exercise including a preliminary community consultation meeting with

UKCAB HIV treatment advocates and a subsequent broader consultation meeting involving patient representatives and HIV sector organisations including THT.

We also support the emphasis on an evidenced based approach and in particular the process of evidence sifting based on GRADE (The Grading of Recommendations Assessment, Development and Evaluation Working Group) for sections where evidence from trials and studies was available (section 1.2.3).

## **Introduction**

### **Section 1.4 Resource use:**

THT strongly supports the evidence based nature of the treatment guidelines – individualised treatment decisions should primarily be made in relation to efficacy, drug resistance and drug associated toxicity including adverse side-effects and not on the comparative price of individual drugs. That the cost of drugs is likely to affect future commissioning decisions is recognised within the guidelines; however, the recommendations should mean that cost decisions are made within the recommended drugs and will not lead to less effective or less well tolerated drugs being prescribed to save on costs.

THT has reservations about the projected figure for costs in 2013 given as £721 million. The Mandalia study referenced (14) uses figures based on 2006 costs and although figures are adjusted, there has been continued improvement in late diagnoses in recent years which we believe is not reflected in the Mandalia projection. The study assumes a very high rate of symptomatic non-AIDS and AIDS patients, 28% and 22% respectively, in contrast HPA SOPHID data shows 70% of patients accessing HIV care having CD4 counts over 350 and so unlikely to have symptoms either non-AIDS or AIDS related. It is also based on treatment costs from the highest-performing UK clinics rather than an average for all clinics. There is also no consideration of cheaper generic drugs becoming available and these combined factors mean therefore that the cost projection is likely to be an over-estimate. This is apparent in the Mandalia report estimating a far higher lifetime treatment cost for an individual patient (£485K) than Department of Health figures (£280K-£320K).

## **When to start**

### **Section 2.3 Treatment of Primary HIV infection**

THT supports the suggestion that patients with an indication of ‘acute infection’ (i.e. within 12 weeks of infection) are considered for treatment. However, we think it is also important to consider the psychological state of the person coming to terms with a new diagnosis and how starting treatment might impact further psychologically. This should be fully discussed with the patient (and psychological support made available if necessary) before any final decision is made. This is particularly important as the recommendation is that treatment would continue indefinitely. The guidelines state that no study has examined this issue of continued treatment but we would note that treatment was discontinued after the trial period in the SPARTAC trial if the patient’s CD4 count was within the correct parameters. We recommend further discussion on whether continuous treatment is really necessary. The guidelines also state that there is no clear evidence of long term clinical benefit. If this is the case and there is no delay after initial treatment to going on continuous treatment, it would be helpful to have some clarification on the benefit to the patient.

We support the expansion of treatment to those whose viral load  $\leq 500$  with associated AIDS related conditions and other specified co-infections and co-morbidities as well as to older people as there is evidence of some health benefits to starting treatment early in these cases. However, with treatment for people with acute infection, THT does not believe the case has been clearly made and we would recommend that these patients are advised of the modest benefits of early treatment and also that early treatment would usually mean an additional number of years on medication.

## **2.4 Treatment to reduce transmission**

THT welcomes the decision to include people with CD4 counts above 350 who want to reduce the risk of transmission to their partners as candidates for treatment, in particular because of the benefits to patients’ peace of mind in this regard and also in terms of the implications for the wider public health in reducing onward transmission and the potential impact on the rates of new diagnoses.

### **2.4.1**

Discussion with patients should include all the relevant cautions and any factors that may mean a viral load above undetectable levels:

- the viral load should have been suppressed ( $< 40$  copies/ml) for at least six months (UNAIDS statement)

- the presence of another sexually transmitted infection/s
- virological failure

The psychological state and subsequent impact of starting treatment early and potential side-effect should also be considered and discussed. This is covered in the 'Supporting patients' section but it would be helpful to highlight this again in this section.

People who are living with HIV may want to conceive without the complications and expense of sperm-washing and/or IVF treatment and it may be useful to mention this along with the other discussion points.

#### **Treatment to reduce transmission and anal sex:**

As stated in the guidelines, evidence for treatment as prevention mostly relates to vaginal sex and so we would recommend that some indication of risk should be given in relation to anal sex. There is a study which examines viral load and transmission in gay men which is not referenced in the guidelines but has useful information (the following extract is from NAM/Aidsmap):

"Attia and colleagues did not include in their meta-analysis a prospective study examining the effect of antiretroviral treatment on HIV transmission in gay men first presented in February 2009 to the Sixteenth Conference on Retroviruses and Opportunistic Infections in Montreal,<sup>1</sup> with further information presented in April 2009 to the Fifteenth Annual British HIV Association Conference in Liverpool.<sup>2</sup> This study, involving 1144 gay men attending an HIV treatment centre in Brighton between 2000 and 2006, is the first to examine the risk of transmission in a cohort of gay men, and other men who have sex with men (MSM).

The investigators used clinical and epidemiological information to identify the factors involved in new HIV infections in gay men and, by performing phylogenetic analysis on the HIV from 859 individuals, 41 'likely transmitters' were identified, 29 (70%) of whom had never taken HIV treatment and nine of whom had interrupted their treatment at the time of transmission. As expected, the study found an association between a higher viral load and a greater risk of HIV transmission, with each log<sub>10</sub> increment in viral load increasing the risk of HIV transmission by 68%.

Taking HIV treatment was associated with a 96% reduction in the risk of HIV transmission; of the three transmissions on treatment seen during 3556 person-years of follow-up, one is thought to have originated in an individual with an undetectable viral load. No further details are available.

This is not the first recorded case of HIV transmission during sex between men where the infected partner has an undetectable viral load, however. In a case report from Germany, published in August 2008, and confirmed by phylogenetic analysis, a gay man who had maintained an undetectable viral load on treatment since 2000 apparently infected his partner between 2002 and 2004 after reporting unprotected anal intercourse on a number of occasions. Neither partner reported a sexually transmitted infection and both reported that their relationship was monogamous.<sup>3</sup>

#### **References**

1. Fisher M et al. *HIV transmission amongst men who have sex with men: association with antiretroviral therapy, infection stage, viraemia and STDs in a longitudinal phylogenetic study*. Sixteenth Conference on Retroviruses and Opportunistic Infections, Montreal, 2009
2. Fisher M et al. *HIV transmission amongst men who have sex with men: association with infection stage, viraemia and STIs in a longitudinal phylogenetic study*. HIV Medicine 10 (Supp 1), 018, 2009"

THT recommends that patients who have anal sex should be advised of the 96% reduction figure specified in this study and that while this is a much lower risk than for those not receiving ARV medication it does not mean that there is no risk. This would also reinforce the message that condoms in combination with other risk reduction strategies should be considered in addition to treatment.

#### **What to start with**

##### **3.1 Summary recommendations of preferred and alternative drug combinations**

THT welcomes the significant expansion in first line preferred treatment options in these new guidelines since the 2008 BHIVA guidelines. It is encouraging to see a wider range of choice and the inclusion of some of the newer drugs. We look forward to HIV commissioners using these new guidelines as a basis for bulk purchase and price negotiations with the pharmaceutical companies when contracts are renewed

### 3.4 Which third agent?

Efavirenz is still recommended as a third agent with only minor reference given to the often severe side effects experienced by a significant proportion of patients (14 to 50% according to the studies referenced below). Studies consistently show the other suggested third agents as having significantly reduced adverse side-effects compared to Efavirenz. For THT, it is the one of the most common presenting issues in regards to treatment and side-effects on our online community forum, with our health trainers and from callers to THT Direct and so we would recommend that further detail is given about the side-effects including psychoactive effects, vivid dreaming and sleep disturbance. Some feedback within THT suggests that certain population groups, such as HIV positive black Africans, are less likely to complain about side-effects and other issues with treatment and less likely to question a doctors decision for cultural reasons. A footnote in the main table (3.1) as is already included for other alternative agents would seem advisable.

### References

1. Gallego L et al. *Analyzing sleep abnormalities in HIV-infected patients treated with efavirenz*. Clin Infect Dis 38: 430-432, 2004
2. Boly L et al. *Depressive symptoms predict increased incidence of neuropsychiatric side-effects in patients treated with efavirenz*. J Acquir Immune Defic Syndr 42: 514-516, 2006
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### 4. Supporting Patients on Therapy

THT is very supportive of the inclusion of this new section on supporting patients including patient involvement in decision making. THT also welcomes the patient assessment criteria listed as beneficial in discussing treatment choices with patients, to both clinicians and patients. The many issues that may affect adherence or a patient's readiness to start medication are well covered and in particular we strongly support the inclusion of discussions on adverse effects of medication; social and economic factors; psychological problems, such as depression and anxiety, or neurocognitive issues as well as alcohol and/or recreational drug misuses issues. It may be helpful to tie in the psychological elements of this support section to the "Standards for psychological support for adults living with HIV" recommendation published by BHIVA, the British Psychological Society and MedFASH in November 2011.

THT believes that this section of the guidelines is vital to best practice in HIV clinical settings and the development of improved relationships between doctors and patients. We would also suggest that the section be given more prominence, perhaps by being placed immediately after the introduction as the issues considered are so important in making the decisions about when and what to start in terms of ARV medication. Alternatively, prominence could be increased by specific reference to this section in the other relevant sections such as 'When to start' and 'What to start'.

#### 4.1.1 Recommendations

“We recommend patients are given the opportunity to be involved in making decisions about their treatment...Provision of treatment support resources should include in-house, independent and community information providers and peer support resources.”

This is the only specific reference in the guidelines to independent and community information providers and peer support resources. HIV organisations, such as THT, NAM, George House Trust and AHPN are not directly mentioned and it may be useful to clinicians and patients to expand this section to give more details on what independent information, advice and support services are available.

### **Women**

During the consultation meeting on 28<sup>th</sup> February, it was mentioned that care and treatment guidelines specific to women would be published at a later date and THT welcomes this as an important addition to existing resources and recognition of the significant differences in clinical needs and outcomes for women.

### **GPs and HIV care**

There is only one specific reference to GPs being involved in the care of people living with HIV:

#### **4.3.1 Drug interactions - 4.3.1.2 Rationale**

“Communication with GPs and other medical specialties involved in the patient care is fundamental in minimizing the risk of adverse drug–drug interactions”

It would be helpful to have more clarification and detail on the role of GPs in HIV care beyond drug-interactions including monitoring of the cardio-vascular system, blood lipid levels, kidney and liver function etc. If there is no room in this guidance for the detail required to cover this subject then an alternative would be to reference other reports, guidelines or resources that do.

### **Audience**

The guidelines are written with an audience of clinicians and other HIV and health specialists in mind and this is entirely appropriate. However, in terms of patient engagement with, access to and understanding of the information in the guidelines, it may be useful to have a summarised version available for patients that is easily understandable to people without a medical or scientific background and cuts down on references to research but makes clear the recommendations and suggestions.

### **HIV Organisations, the charity and voluntary sector**

HIV organisations, such as THT, provide people living with HIV with valuable information and advice on care and treatment and on prevention, including treatment as prevention. We are also involved in providing care services to people living with HIV and are included in some care pathways. THT and other HIV organisations have networks of people working with, living with and otherwise affected by HIV and the guidelines need to be communicated to these people effectively. It would be useful to have more recognition of the role played by HIV community organisations in general within the guidelines, in communicating the guidelines to patients and some detail on how such organisations fit into treatment and care pathways.

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## **African Health Policy Network (AHPN)**

AHPN welcomes these guidelines, and recognises that given their clinical nature there is limited scope for detailed feedback from community organisations. However, there are specific gaps within the guidelines which we would like to highlight.

### **Consultation**

Section 1.2.2 on patient involvement refers to the process by which community perspectives were added to the drafting process. We are concerned that the two appointed patient representatives are: recruited through only one agency; not identified in respect of their representative role. The community of people living with HIV in the UK is diverse, and as such true ‘patient representation’ ought to reflect this diversity. Given the specific and diverse impact and experience of HIV across different populations, including distinct side effects, beliefs and

contexts around treatment, it is vital that a broad cross-section of the community of people living with HIV in the UK are engaged in processes to develop guidelines which will impact on them. This includes African men, African women, migrants, as well as MSM, drug users and other population groups (defined by transmission route). This section would benefit from more clear explanation of how the representatives were selected, and which part of the population they were chosen to represent, as well as what specific representative functions they were required to fulfil. In addition, an understanding of how UKCAB was selected as the agency to recruit patient representatives would benefit transparency. Further, more detail on the meetings referred to, including the demographics of attendees, where and when they took place, and so on, would aid our ability as a representative body to determine whether the voices of African communities were fairly heard and appropriately engaged in this process. The Ffena network of African people living with and affected by HIV in the UK, is increasingly concerned that their input is not sought in these processes, given the unique representative function the network fulfils.

### Socioeconomic Factors

Section 4.1 on patient involvement in decision making, in its reference to socioeconomic factors likely to impact on adherence, would benefit from a more detailed perspective on those factors affecting adherence, clinic attendance and so on for specific communities. For the African community, factors including shared housing, immigration detention, benefits payment through voucher systems (restricting access to cash for travel) and having no recourse to public funds, should all be taken into consideration. 'Immigration status' as a broad umbrella lacks the specificity necessary to ensure that the actual needs and circumstances of individual patients are recognised.

### Accessibility

Section 4.1.2 refers to the need to make information accessible and understandable, and gives examples such as using pictures and different languages. This does not go far enough in making clear that the linguistic and cultural competency of patient information is not only essential in delivering high quality care, but is also a right of the patient. A recommendation to seek support from and joint working with relevant community or faith based organisations locally would be a step towards ensuring this is given due weight.

### Non-adherence and religious belief

Section 4.2.1.2 refers to intentional non-adherence being informed by beliefs. It is increasingly clear that there is a specific correlation between the teachings in some churches regarding 'healing through prayer' and intentional non-adherence to HIV treatment. The majority of those cases documented relate to African diaspora churches and individuals. In individual instances, clinicians are likely to struggle to find means of addressing this issue, and so would greatly benefit from specific guidance from BHIVA as to how to approach faith-based treatment rejection. The current wording here lacks specificity and clarity, and so could be improved.

### Stability

In determining the right combination of treatment for an African person living with HIV, it is essential that the clinician includes the immigration status of that individual in their decision-making process. For many of the African people living with HIV in the UK, a return to their country of origin, either on a short to medium term basis, or permanently following an unsuccessful immigration claim, may be a real possibility. In such circumstances, it is vital that their treatment is not interrupted. We would therefore recommend that the guidelines additionally include a recommendation to clinicians to be aware of the impact of a potential temporary or permanent return to country of origin, discuss this with their patient, and consider both: the availability and accessibility of different combinations in the potential country of origin; and how they may contribute to facilitating continuity of treatment through a migration.

## Women

The majority of women living with HIV in the UK are African and of reproductive age. Given the differing side effects of different treatments on women who are pregnant or may become so, the guidelines should include a recommendation to take this into account when determining which treatment regimen is most suitable for a women in this age category.

## Disclosure

The possibility of unintentional disclosure should also be included in the guidelines, with respect to both: physical side effects of different treatments (such as lipoatrophy) and consequent non-adherence; and to the impact of repeated clinic visits, private post and so on, given the perception this may generate within people whose status is not disclosed to those around them.

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## Abbott

Dear BHIVA Secretariat and Adult Guidelines Subcommittee Members,  
We, at Abbott Laboratories, have read your consultation draft of the BHIVA Guidelines for the Treatment of HIV-1 Infected Adults with Antiretroviral Therapy 2012 with much interest. Abbott Laboratories acknowledge the rigour applied in the writing of these guidelines and are in agreement with the much of the content. We also applaud the inclusion of bold progressive new guidance sections (e.g. Primary HIV Infection, treatment to prevent transmission).

We appreciate the opportunity to provide feedback which we hope you find constructive and indeed supportive for accreditation, especially as this will enable the Guidelines to include breaking data more frequently for continuous therapeutic improvements in specific patient groups. Naturally, we have focused on key feedback points associated with our proprietary ARV Kaletra™ (lopinavir/ritonavir, LPV/r). These are listed below in order as they appear in your consultation draft recommendations or associated body text, together with the aligned evidence based information. Our feedback is aimed at providing evidence to maximise patient benefit, by aligning ARV selection to their needs. We feel this is important in light of the diversity of populations within the HIV+ community, and the complexities in treatment needs both within and between such groups.

Our predominant concern with the draft BHIVA Adult Treatment Guidelines is the tabulated recommendations in Section 3 where LPV/r is listed as 'alternative'. We feel that this will restrict appropriate selection of LPV/r for specific patient groups, especially HIV+ women. The citation and acknowledgement of women as a specific patient group within the draft Guidelines, but the absence of details or aligned treatment options is a specific concern. With the draft BHIVA Pregnancy Guidelines generally referring to the Adult Guidelines, yet recommending against the use of darunavir (DRV) due to insufficient evidence against birth defect risk from the Antiretroviral Pregnancy Registry (APR), we feel it is inappropriate to cite DRV as preferred to LPV in such a significant proportion of HIV+ adults. This, coupled with various data highlighting LPV/r long term safety and particular strengths in treating women, substantiates our belief that LPV/r should be a tabulated 'preferred' ARV for women (Section 3), or at least be tabulated as such in a specific population grouping for women (Section 6). We feel this would be constructive, provide clarity and is prudent in light of the majority of HIV+ women in the UK being of child-bearing potential. We have detailed this case below.

We also appreciate that the global HIV community looks to the BHIVA guidelines as a reference when preparing local guidelines. The listing of LPV/r, which is widely available throughout the developing and developed world, and recommended in international guidelines (<http://www.europeanaidscinicalsociety.org>), as an alternative 3rd agent may affect the confidence when making choices in geographies with already limited choices of ARVs.

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

With regards,

Jon Ryland  
Medical Director: Abbott UK

BHIVA Guidelines for the Treatment of HIV-1 Infected Adults with Antiretroviral Therapy 2012:

Feedback to Recommendations

1. Page 16, Section 2.3: Treatment of Primary HIV-1 Infection

Primary HIV 1 Infection (PHI) is associated with high viral load, a period of high patient distress and confusion with respect to therapy if diagnosed with a recommendation for treatment. Many PHI patients present with severe illness and inflammation. Rash is also relatively common (Chu and Selwyn, 2010). The Draft Guidelines recommend initiation of a PI-based regimen. We feel that LPV/r should be the cited 'preferred' or the specifically recommended/exemplified PI in light of its relative lack of skin effects such as rash and jaundice within its class (see CASTLE and ARTEMIS and TITAN trial results; Molina et al 2008 & 2010, and Mills et al 2009, Madruga et al 2007). With respect to the Draft Guidelines using the GRADE criteria, LPV/r as the 'third agent' has by far the most evidence for efficacy and tolerability (viral load reduction and CD4 recovery), amongst other positive outcomes in PHI treatment as shown by the SPARTAC study (Fidler et al 2011). With test and treat being widely advocated and the observation that very early ARV intervention yielding sustained advantages for patients in the SPARTAC study, treatment as proven by regimes underpinned by LPV/r could benefit a particularly vulnerable group of patients.

2. Page 22, Section 3: What to Start, and Page 26, section 3.4: Which third agent

We disagree with the 'alternative' categorisation of LPV/r in the table of summary recommendations for ARV selection in naïve patients (Section 3.1, page 22). For the boosted PIs, we fully acknowledge the qualities of ATV and DRV and their positioning as 'preferred', but believe strongly LPV/r also belongs in this category. LPV/r complements DRV and ATV with respect to many patient groups. Indeed, LPV/r has distinct advantages relative to the listed 'preferred' ARVs in significant numbers of specific patient groups, especially women who constitute over 30% of the UK HIV+ population. We feel the 'reach through' of a single table generalising HIV+ patients to certain specific populations, particularly women, is a significant risk to achieving optimal ARV selection and downstream clinical outcome, particularly in pregnancy. Greater alignment of clinical outcome parameters and their associated health benefits and risks to each patient group would also help with accreditation (notably the AGREE II quality domains on, Rigour of Development: The health benefits, side effects, and risks have been considered in formulating the recommendations - Domain 3, item 11).

Stratifying tabulated treatment recommendations across the specific populations within the guidelines would enable treatment to be aligned to patient need. In light of this we feel that additional tabulated recommendations for women in particular would be constructive as this is a growing population that currently constitutes over 30% of the UK HIV+ community and have specific needs, particularly for MTCT prevention (see [www.hpa.org.uk](http://www.hpa.org.uk), [www.nat.org.uk](http://www.nat.org.uk), and [www.unaids.org](http://www.unaids.org)). We feel this would have most impact for women if tabulated preferably in Section 3 or as a specific population group in Section 6. This is extremely important, as the draft Adult Guidelines highlight DRV as preferred to LPV/r in adults, which inherently includes HIV+ women, the vast majority of which are of child bearing potential. The draft BHIVA Pregnancy Guidelines specifically recommend against using DRV in pregnancy due to a lack of statistical evidence to conclude a less than 2-fold birth defect risk. LPV/r is recommended in these Guidelines as it meets this criterion. Indeed, LPV/r has the largest and tightest APR dataset of its class, demonstrating no greater risk than evident in non-HIV-associated pregnancy (Antiretroviral Pregnancy Registry International Interim Report for 1 January 1989 – 31 July 2011). The draft Pregnancy Guidelines also refer to the draft Adult Guidelines for treatment, so risk exists for inappropriate ARV selection for women due to the current tabulated recommendations in section 3 as they stand. It is therefore illogical and inappropriate to list LPV as 'alternative' to DRV in adult groups such as women of child bearing potential. In large meta-analyses, LPV/r has proven to have equal efficacy and effectiveness in men and women (Hermes et al 2011). ATV showed equal virologic efficacy vs. EFV in ACTG 5202 and thus been cited in the guidelines for 'preferred' status alongside EFV. However, this was true for men only. Relative virologic inferiority was apparent in women (Smith et al 2011, Squires et al 2011).



The strength of recommendation for Section 3 tabulated recommendations and third agents are cited as 1A, yet acknowledgement of cross trial comparisons and use of consensus opinion is described. For the studies cited, legacy LPV/r formulations (i.e. soft gel capsule formulations rather than tablet), and selective classifications of virologic superiority were used.

Cross-trial and even within-trial analyses are highly complex. The clinical significance of observed efficacy differences (e.g. by virologic response) is particularly difficult to discern between PIs in the studies cited. Side/adverse effects can vary as can their impact of effects on different patients. Comparative conclusions for DRV vs. LPV/r studies are very much analysis-dependent. For example, ARTEMIS was designed to test for non-inferiority at weeks 48(primary endpoint), 96, and 192, and test for superiority in the event of non-inferiority. At 48 weeks, DRV demonstrated non-inferiority, and not superiority, to LPV/r. At 192 weeks, virologic failure was similar between both PIs (TTLVOR) however, the snapshot method demonstrated superiority of DRV+RTV at 192 weeks. These results need to be interpreted with caution as an assessment of superiority at multiple time points is only valid within the context of a pre-specified analysis plan that takes into account multiple testing in order to prevent inflation of a type I error rate and require the primary endpoint to be statistically significant for non-inferiority and superiority. As a result, there is no meaningful interpretation of the “superiority” results at 192 weeks since only non-inferiority, and not superiority, was met at the 48 week primary endpoint. Moreover, there was no pre-specified multiple testing plan that could have limited inflation of a type 1 error. Therefore, any claims of superiority at any visit in the ARTEMIS study should be viewed with caution. ARTEMIS was open label and as such was also prone to information bias (see Schultz et al 2002). The extensive use of the legacy formulation of LPV/r over the preferred tablet formulation (especially for GI side effects; Schrader et al 2008, Ofotokun et al Yeh et al 2010), has also not been taken into account in the comparisons (as also apparent for the studies comparing ATV and LPV/r such as the CASTLE study). To this end, the small numerical values to describe differences between cohorts cited in the associated publications raise doubts over claims of virologic superiority. Stratification by region in ARTEMIS has highlighted variation in response to DRV and LPV/r. In Europe, albeit in relatively small patient numbers, there was a lower virologic response in the DRV group compared with the LPV/r group (difference in proportions achieving HIV RNA <50 copies/mL: 4.3; 95% CI: -15.5 to 6.92, which is outside of the definition of noninferiority – see EMEA Assessment Report for Prezista 2008: EMEA/CHMP/637631/2008).

Clinical evidence from ACTG 5142 is cited for underpinning recommendations in Section 3. This study also used a legacy SGC formulation of LPV/r that has significant disadvantages to the tablet formulation currently used in clinical practice. The clinical endpoints for the trials highlighted in the draft Guidelines in Section 3 are varied, as are the benefits/risks they bestow on a given patient population, which remains a subject of controversy in selecting ARVs to this day (Mani et al 2012). Highly adherent patients who tolerate EFV well and do not experience CNS effects would indeed benefit from this drug as part of triple therapy. A conclusion ACTG 5142 states is that ‘if 1000 people were treated with EFV rather than LPV/r, there would be 130 fewer with virological failure, 28 fewer with grade 3 or 4 diarrhoea and 39 fewer with grade 3 or 4 triglyceride events’ (see page 191 of Appendices to draft Adult Guidelines). However, the clinical endpoints from this study would also conclude that CD4 elevation (as with all LPV/r comparative trials) was higher with LPV and 25 more people would fail with drug resistance, 32 more would have with Grade 3/4 clinical side effect at week 48, 16 more with rash, 20 more with lipodystrophy (which is often cited as the most distressing and stigmatising of effects, particularly in women (Huang et al, 2003, Rankin et al 2005). Failure with drug resistance has been reported to correlate with at least a 3-fold increase in mortality as shown in a UK CHIC study (Grover et al 2008). The adverse events cited for LPV/r also score lower than those for EFV from ACTG 5142 according to the GRADE table (Appendices to the draft Guidelines, pg 14). As the Guidelines emphasise, it is extremely difficult to predict future adherence to ART in naïve subjects and at detecting non-adherence during ART (Section 4.2.2. pg 38). LPV/r has clear advantages in both late stage presentation and poorly adherent patients due to its high genetic barrier to resistance and unique ability to raise CD4 counts as highlighted in ACTG 5142. Indeed, in the clinical studies cited where LPV/r is used as the comparator arm vs. EFV, DRV and ATV, CD4 elevation had always been highest in the LPV/r arm without exception. As CD4 recovery is particularly important in these special populations, we feel the inclusion of LPV/r as a ‘preferred’ option is merited.

3. Page 30, Section 3.5: Novel ART strategies

The recommendations associated in this section cover PI-based monotherapy (section 3.5.1, page 30) and PI-based dual therapy (section 3.5.4, page 31) in ARV-naïve subjects. We agree that these approaches are emerging and as yet should not supplant traditional triple therapy as the starting regime in treatment-naïve patients. We eagerly await data from PIVOT (<http://www.clinicaltrials.gov>) for monotherapy use in pre-suppressed patients, as a potential sea-change in regime practice to reduce comorbidities, costs, and extend treatment options. However, we feel detailed discussion of monotherapy and dual therapy is merited in the sections associated with ARV-experienced patients (ARV switching, resistance, and specific populations – see Section 5 below).

4. Page 51 4.4 Switching ART in virological suppression and  
Page 59. 5.2 Blips, low level viraemia and virological failure

The statement that ‘switching boosted PIs or NNRTIs in virologically suppressed patients has in a small number of studies has not been associated with loss of virological efficacy’ (page 52 section 4.4.2.2) is merited as a means to provide options to reduce side-effects, or comorbidities. However, some studies have highlighted resistance-associated risks. In the SLOAT study (Soriano et al, 2008), failure in patients switched to ATV were associated with higher PI mutation levels, whereas resistance mutation was absent in the LPV/r control arm (pre-switch). Published studies on switching to ATV (van Vonderen et al, 2009) showed that patients switching to ATV had virologic failure more often (17/224 [7.8%]) than those continuing on their original regime (73/3100 [2.4%],  $P < 0.0001$ ). Naturally a switch to improve ARV tolerability is merited where virological failure and resistance mutation risk can be managed. To this end we feel that mono and dual therapy options require more detailed inclusion and description in sections for ARV-experienced patients.

The draft guidelines acknowledge that boosted PI monotherapy, in particular with DRV-RTV and LPV/r, has met with very encouraging results in pre-suppressed patients in particular. The PIVOT study will analyse boosted PI monotherapy effectiveness further, in particular with respect to ‘blips’ and resistance frequencies (<http://www.clinicaltrials.gov>). The availability of evidence from various LPV/r-containing dual therapy studies highlight new regimes that provide significant evidence of overcoming concerns with boosted-PI based monotherapy, whilst addressing issues with NRTI tolerance, long term effects and resistance. Many LPV/r based dual therapy studies were either excluded or only briefly mentioned in the draft Guidelines. These studies were pilot in nature, but they offer significant evidence to support improvements in clinical management and cost reduction for HIV treatment. The Kalead study (Pinola et al 2011) 48-week results demonstrated comparable virologic efficacy and tolerability when a dual regimen of LPV/r + TDF was compared to LPV/r + 2 NRTIs in ARV-naïve patients. CD4 increase was higher in the dual therapy arm. A trend for lower incidence of lipid elevations was observed in the dual arm. Favourable outcomes were observed in the Loreda study (Andrade et al 2011) where a combination of LPV/r plus 3TC proved efficacious with a good safety profile in ARV-naïve subjects over a 48 week study. LPV/r plus raltegravir (RAL) dual studies in pre-suppressed ARV-experienced patients have highlighted impressive efficacy, tolerability and robustness, equivalent to that of standard of care HAART in a pilot study (Ofotokun et al 2011). This NRTI-sparing regime is associated with comorbidity reduction as demonstrated by the PROGRESS study (LPV/r plus RAL vs. LPV/r plus Truvada™; Qaqish et al 2011, Reynes et al 2011, Soto-Malave et al 2011, van Wyk et al, 2011) also showed virologic efficacy, tolerability and robustness equivalent (non-inferior) to triple therapy standard of care over 48 and 96 weeks. Resistance to RAL was infrequent and slow to emerge (relative to other RAL plus boosted PI dual studies), and measured comorbidity profiles such as bone mineral density were significantly better in the dual therapy arm (Qaqish et al 2011). These results highlighted LPV/r plus RAL as a potentially useful option for specific patient groups (for example ageing populations with reduced bone mineral density) where switch due to NRTI intolerance/resistance may be appropriate.

The VEMAN study (LPV/r plus once-daily maraviroc (MVC) vs. LPV/r plus Truvada™ in HIV naives; Nozza et al 2011) also showed the same overall effect of dual therapy achieving at least non-inferiority (efficacy, robustness and tolerability) to triple therapy. Indeed 100% of patients achieved total suppression on the dual arm (observed data). This further highlights potential cost saving aspects of dual therapy. To date, LPV/r alone is the only boosted PI that has demonstrated combination with RAL and MVC to achieve virologic outcomes at least as good as triple therapy, with advantages in terms of comorbidities (e.g. bone mineral density preservation with RAL (Qaqish et al 2011), and triglyceride reduction with MVC (Nozza et al 2011)). Whilst we appreciate the underpinning studies are pilot in nature, have been run mainly in treatment naïve populations, we feel the flexibility within GRADE merits GPP use in specific sections where such regimes could offer clinical advantages to certain patient groups (e.g. those facing specific comorbidities such as osteoporosis, liver fibrosis (in combination

with MVC – see Nasta et al, 2011), lipid elevations, low CD4 recovery, NRTI - intolerance/failures etc). We feel that LPV/r merits specific recommendation or mention in light of the relative depth and strength of evidence amongst the boosted PI class of ARVs when used in combination with RAL and MVC. For example, the recommendations in this section, notably those in Section 5.2 box 2 (page 61: Best practice for the management of patients with three class virological failure) cites using PI/r plus novel ARVs such as CCR5 antagonist or integrase inhibitors. We feel that LPV/r merits specific exemplification as a dual option according to GRADE, as the data published to date is more extensive and encouraging with respect to achieving similar virologic and resistance outcomes as seen with triple therapy SOC, with concomitant reduction in comorbidities. LPV/r data in combination with RAL extends to 96w with low virological failure and resistance (magnitude and rate), yet dual studies for DRV-RTV plus RAL (Taiwo et al 2011) and ATV plus RAL (Kozal et al, 2010) reported higher virological failure and a relatively rapid emergence of resistance. Similarly, evidence to date from pilot studies highlight LPV/r plus MVC as the boosted PI combination of this type with the most favourable evidence to merit exemplification within the guidelines, based upon the VEMAN study (virologic response and CD4 elevation). We acknowledge (as do the draft Guidelines in section 3) the caveats associated with cross-trial comparisons, but flexibility exists within GRADE to align recommendation weightings, evidence grade and GPP clauses to enable expert opinion.

#### 5. Page 74. Section 6 : ART in Specific Populations

As discussed above, the citation of women but lack of discussion of specific issues facing women, the inherent link to the draft Pregnancy Guidelines, and the associated recommendations highlights a gap. Inclusion of a section dedicated to women is merited either in section 3 or in this section. This is also supported by our data from PROGRESS highlighting the advantages of dual LPV/r plus RAL therapy having a favourable bone mineral density profile at both 48 and 96w (Qaqish et al 2011), and a large meta-analysis highlighting no difference efficacy and effectiveness for LPV/r in men and women (Hermes et al 2011).

Other groups for which LPV/r may provide unique advantages include Black Africans. LPV/r is the most widely available and accessible boosted PI in Africa. UK-based Africans, especially those on short term visas, or those returning to homelands for extended periods may benefit from LPV/r, (assuming it matches standard of care ARV choice within the UK). As an option this may provide benefit by avoiding the need to switch therapy when stable.

We would like to highlight the importance of the BHIVA Adult Treatment guidelines as an influencer of treatment trends for the global HIV community. The importance of these guidelines to national guideline committees throughout the developing and developed world cannot be underestimated. This is particularly so in the developing nations where the HIV disease burden is highest. LPV/r remains the widest used PI in the developing world through its availability as Aluvia™ in these countries. As a result we believe that the recommendation of LPV/r as an alternative third line agent and the subsequent interpretation of this in other geographies will restrict the choices of ARVs in areas with already limited choices.

#### 6. Page 79. Section 6.2: HIV and Viral Hepatitis co-infection

LPV/r has been shown to have comparable activity in mono- and HCV or HBV-co-infected patients (Da Silva et al 2004). In patients presenting with fatty liver/steatosis, the relative low propensity of LPV/r to induce visceral adipose tissue (VAT) (Ferrer, 2010) to reduce risk of VAT-associated liver effects (Eguchi et al 2011, van der Poorten et al 2008) suggests clinical advantages as a boosted PI. Emerging evidence of MVC-dependent reversal of liver stiffness (postulated to be a consequence of CCR5-signalling blockade in fibrogenic stellate cells) highlights potential utility of this ARV in liver disease, potentially with boosted PIs (MVC is boosted by ritonavir) in dual therapy. There is a complex relationship between lipid profiles and HCV infection (HCV-dependent lipid reduction, and lipid transporter-mediated HCV-cell entry etc). The triglyceride elevating profile of LPV/r may indeed be a positive factor in HCV clearance (Ryder et al 2007). Naturally, more research is required, but this coupled with LPV/r possessing comparable efficacy in co-infected patients suggests LPV/r is appropriate as a treatment option.

#### 7. Page 94. Section 6.4: HIV-associated neurocognitive impairment (NCI)

We acknowledge the concerns surrounding the use of the CPE score, and the lack of data enabling clear association of ARV therapy with NCI. However, progressive combinations targeted at ARV-dependent neuroinflammatory marker normalisation effects have been reported for MVC-containing regimes (Garvey et al 2011). Such studies do provide substrate for guidance for treating HIV-associated neurocognitive effects. A larger prospective multicentre study to evaluate relationships between HIV-associated neurocognitive disorder and metabolic variables in HIV+ participants has recently been published (McCutchan et al, 2012). This showed that central obesity, but not more generalised increases in bone mineral density, was associated with a higher prevalence of NCI in HIV+ individuals and suggested avoidance of antiretroviral drugs that induce central obesity might protect from or help to reverse neurocognitive impairment in HIV-infected persons. LPV/r has been demonstrated to combine effectively with MVC (Nozza et al, 2011), and have a lower propensity for trunk and visceral fat deposition in the boosted PI-class from switch studies (Ferrer et al, 2010).

Page 100. Section 6.5: Chronic Kidney Disease

The relative risk of major bPI ARV -associated CKD is described. Other associated renal events include ARV deposition in kidneys to form stones. LPV/r has been associated with the lowest rate of kidney stone formation in the major PI class (Rockwood et al, 2011), and as such might be an appropriate choice where boosted PI therapy is required for affected patients.

Page 104. Section 6.6: Cardiovascular disease:

Dyslipidemia is a generalised CVD marker (not an event) that is associated with LPV/r to a greater extent than DRV or ATV. Lipid and lipoprotein changes associated with LPV/r-containing regimes have been studied in patients participating in the Swiss HIV Cohort Study (Magenta et al 2011). This study reported an increase in the majority of measured lipids and lipoproteins particularly in the first year after initiation, but could not detect an obvious increase of cardiovascular risk resulting from the observed lipid changes. Other JBS2 cited CVD risk factors such as VAT, which is a recognised factor alongside soluble marker dyslipidemia in CVD risk in HIV positive men and women (Janiszewski et al 2012). Studies in suppressed stable patients highlight significantly reduced VAT in LPV/r-maintained subjects in its class (Ferrer et al 2010).

D:A:D has reported that various CVD-related variables have not been collected or that the accuracy of the collection of these CVD-related variables has changed over time (Sabin et al 2008). Changes implicated include reduced prevalence of smoking and an increase in the proportion of patients receiving lipid-lowering therapy and undergoing invasive cardiovascular procedures prior to an MI or stroke. D:A:D also did not include the use of lipid lowering drugs in the MI analysis, and statin use has been clearly associated with reduced mortality in HIV (Moore et al 2011). The risk of CV events and the use of PIs has been assessed by other cohorts including Boston Healthcare System database (Triant et al. 2010), HOPS (Lichtenstein et al 2010), and US Department of Veterans Affairs (Bozzette et al (2003). These studies did not find an association between the use of PI (including LPV/r) and CV events. In light of so many datasets and studies highlighting an absence of evidence for CVD risk, we strongly feel a recommendation against LPV/r is not warranted. The positive aspects of statins in HIV and in addressing low level inflammatory effects, coupled with the relative weight of effective clinical use of LPV/r in combination with statins, also raises questions as to the merits of such a recommendation.

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## SWAGNET

To Whom It May Concern:

Please find attached the South West London HIV & Sexual Health Clinical Services Network response to the DRAFT Guidelines for the treatment of HIV-1 infected adults with antiretroviral therapy 2012.

Unfortunately the online Consultation feedback would not accept my email address.

Please do not hesitate to contact us if you have any queries

BW

The SWAGNET Management Team

### SWL Response to the DRAFT BHIVA guidelines for the treatment of HIV-1 infected adults with antiretroviral therapy 2012

SWAGNET would agree that the guidelines are generally very sensible.

We would support:

- Allowing patients to start treatment with seroconversion
- Allowing patient to start treatment to prevent onwards transmission whatever the CD4 count

This would require commissioners being fully aware of the recommended guidance and supporting these changes.

### 3. What to Start

**We recommend therapy naïve patients start ART containing two NRTIs and either a ritonavir-boosted protease inhibitor, or a NNRTI or an integrase inhibitor (1A)**

Summary recommendations for choice of ART: PREFERRED		ALTERNATIVE
NRTI backbone	Tenofovir + emtricitabine	Abacavir1,3+ lamivudine (2)
Third Agent	Atazanavir/ritonavir Darunavir/ritonavir Efavirenz Raltegravir	Lopinavir/ritonavir3 Fosamprenavir/ritonavir3 Nevirapine4 Rilpivirine2

Broadly this is difficult to challenge. The Pan London HIV Consortium specifies Kivexa as first line provided that VL is < 100 K and HLAB5701 negative. Does this fit with the guideline as written?

This mentions no special considerations for women.

We would support this recommendation as featured on (p66): **We recommend the use of lamivudine or emtricitabine to maintain a mutation at codon position 184 of the reverse transcriptase gene (1B).**

#### 4.4.3. Protease inhibitor monotherapy

##### 4.4.3.1 Recommendation

**We recommend continuing standard combination ART as the maintenance strategy in virologically suppressed patients (1C)**

We fully support this recommendation.

### 5.3 Patients with no or limited drug resistance

**We recommend patients experiencing virological failure on first-line ART with WT virus at baseline and limited emergent resistance mutations (including two-class NRTI/NNRTI) at failure, switch to a new PI/r-based regimen with at least two additional fully active drugs (1C)**

How much evidence is there for this? In our experience patient do fine with truvada and boosted PI particularly if M184V is present.

Using two fully active drugs will lead to increased expense and more rapid loss of drug classes if this next regimen fails. Clearly an area where further trials are needed.

SWAGNET fully supports all recommendations regarding:

- Cancer
- HIV associated NC disorders

#### 6.6.4 What to start

##### 6.6.4.1 Recommendations

**We recommend against the use of abacavir (1C), fosamprenavir/ritonavir (1C) and lopinavir/ritonavir (1C) in patients with a high CVD risk, if acceptable alternative antiretroviral drugs are available.**

**We suggest maraviroc is not used in patients with high CVD risk, if alternative antiretroviral drugs are available (2C)**

We would argue the recommendation against the use, is too strong. Perhaps a 'caution' recommendation would be more appropriate especially given that this is based on one observational study. In the case of abacavir – the meta-analysis from RCTs showed no increased cardiovascular risk. Randomised data should generally trump observational.

The DHHS Guidelines recommends a 'caution' of abacavir with high risk of cardiovascular disease, which is more appropriate.

The risk benefit equation needs to be taken into consideration for each individual patient.

**SWAGNET would like to thank the following clinicians for their input:**

Dr Phillip Hay – Reader & Honorary Consultant, St George's Hospital

Derek Macallan – Professor of Infectious Diseases and Medicine, St George's Hospital

Dr Ian Cormack – SWAGNET Lead Clinician & HIV / GUM Consultant, Croydon University Hospital

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## National AIDS Trust

### BHIVA TREATMENT GUIDELINES

Submission from NAT (the National AIDS Trust)

#### Introduction

NAT is the UK's HIV policy organisation and leading charity dedicated to transforming society's response to HIV. We provide fresh thinking, expertise and practical resources. We champion the rights of people living with HIV and campaign for change.

As an HIV policy organisation, NAT does not have specialist expertise on different treatment options and their evidence base. We therefore restrict ourselves to commenting on a few issues which have wider policy implications.

We congratulate the writing panel for producing guidelines which are both so carefully based on evidence and so well-written. We are confident this will enhance further their value, authority and reach.

#### Resource use

This is an important and of course sensitive and inevitably controversial section, and we are sure much thought and negotiation have already gone in to the current form of words.

NAT agrees with the approach taken on costs. In particular we welcome the principle that decisions involving cost should not result in significantly poorer treatment outcomes since we believe this will risk harming adherence, virological suppression, mental health and public health (through the increased risk of transmission). The UK has some of the best treatment outcomes in the world and this has been through clinicians having the



freedom to prescribe on the basis of guidelines which relate to clinical need and treatment outcomes. NAT strongly believes this approach should be maintained, and is in the longer term the most cost effective approach.

A very specific point, however, is that we do have reservations on the Mandalia paper cited at endnote 14, where we believe annual projected costs are inflated due to over-estimate of the costs of those with an AIDS diagnosis.

The BHIVA writing panel acknowledges that the cost of drugs is an important issue in the choice of drug regimen and then says that 'Equally important are the efficacy, tolerability of, and ease of adherence of ART regimens in an individual'. 'Equally important' is an odd phrase and does not seem consistent with the final paragraph of this section where local drug costs are only relevant once equivalence or similarity is established in treatment outcomes. It might be simpler to omit this second sentence in the penultimate paragraph of this section.

The first sentence of the final paragraph of this section is ambiguous and should be clarified – are the differences in critical treatment outcomes what determine the choice of preferred as opposed to alternative treatment regimens? Or are they simply what determines the choice of preferred and alternative regimens as opposed to those which are neither? This will be very relevant to commissioning and prescribing decisions going forward, and clarification would be useful.

A further question is what is meant by 'equivalent or similar'? This could leave significant room for interpretation and possibly inequitable variation in ART access. We note that the text does not add the word 'critical' in relation to this range of equivalent/similar treatment outcomes, and we think this sensible given the need to take account holistically of the overall impact of a treatment regimen on a particular individual patient's health and well-being. We recommend not referring to 'similarity' of treatment outcomes in the final paragraph of this section but simply 'equivalence' - there is already room in this word for reasonable flexibility.

#### **When to start – Treatment of Primary HIV Infection**

NAT has taken an interest in primary HIV infection for some time, in particular as it is for many a brief symptomatic opportunity to diagnose HIV infection with benefits both for the individual (who is diagnosed and in care in good time) and for prevention. We are therefore very interested in the additional possible benefit cited in the draft Guidelines of early initiation of treatment to reduce morbidity and increase life expectancy. We note this recommendation is a 'suggestion' and based it appears only on observational studies from SPARTAC. We are not in a position to comment on whether this is sufficient evidence to justify the suggestion.

We are conscious, however, that should this suggestion remain in the final version of the Guidelines, people just diagnosed and quite possibly very ill with seroconversion symptoms will be being advised to begin ART almost immediately. It also appears that they will then be advised that ART should continue indefinitely – people who have started ART in the very early weeks after infection are not included amongst those who in exceptional circumstances could be advised to stop therapy, at section 4.5.2.

We do not want to over-dramatise treatment commencement and it could well be argued that we should do more as a sector to emphasise its value. Nevertheless the draft Guidelines do now envisage someone in these circumstances starting treatment quite probably a number of years sooner than would otherwise be the case, and at a point when they may well be in some shock and quite vulnerable. It would be good for the Guidelines to acknowledge this fact and propose some care and precaution when discussing the possibility of early commencement with the patient. We note starting during primary HIV infection is not mentioned as an example at the bottom of page 34 of when a patient has to start ART immediately.

#### **When to start – treatment to reduce transmission**

NAT strongly welcomes the section on treatment as prevention which we consider very forward-looking. We consider it ethically right and sensible to recommend this for MSM also, despite the absence of RCTs but simply on the basis of biological plausibility. We suggest, given this approach, that the penultimate bullet on the

evidence relating to vaginal but not anal sex, also state that there is biological plausibility for there also being an effect on transmission risks in anal sex.

There is no reference in the bullets to co-infection with an STI raising viral load of someone on ART to infectious levels, though it is mentioned in the rationale. Also mentioned in the rationale is the importance of waiting until the viral load is suppressed before relying on ART's preventive impact. Both these points should be added to the bullet points on what should be included in 'discussion' since some readers will refer to these bullet points and not to the rationale.

NAT welcomes the emphasis on the decision having to be a free one of the patient. At the first bullet point it might be worth adding 'clinical staff' to 'partners or others' in the reference to inappropriate pressure. Guidelines in other countries, perhaps influenced by legal considerations, have required any commencement of treatment as prevention to involve counselling also of a patient's monogamous partner – whilst we welcome the fact that the BHIVA Guidelines do not limit themselves in this way, it might be useful to remind clinicians of the good practice of offering such discussion with an HIV negative partner where appropriate.

At the community meeting to discuss the Guidelines concern was raised by one participant as to how this section relates to those heterosexual couples wishing to conceive naturally - in particular given that one of the bullets for discussion states that 'Condoms continue to be recommended as protection from other sexually transmitted infections (STIs) and also to lower further any residual risk of transmission'. The phrase 'residual risk of transmission' could well be misunderstood by many readers and does not address those who wish to rely on the preventive benefits of treatment as an alternative to condom use. For those who have an established undetectable viral load as a result of effective treatment, it is as, if not more, reasonable to rely on this for the purposes of prevention as it has been for all people with HIV to depend on condom use to prevent transmission.

It appears in the Recommendation section at 2.4.1 there has been an attempt to avoid comparison with condom use as a preventive strategy as well as any reference to undetectable viral load - instead the wider point is made that treatment lowers infectiousness with transmission risk minimised by 'high and consistent adherence to ART'. We understand the reasons for this approach. But it does result in difficulties such as those we cite above.

We recommend that the second bullet point state simply that 'Condoms continue to be recommended as protection from other sexually transmitted infections (STIs)'. There should then be additional points recommended for discussion, for example - 'In the absence of an undetectable viral load, condoms (and other preventive strategies) should be recommended to lower further residual risk of transmission'. And also 'Those with an undetectable viral load may still wish to use condoms if they have continuing concerns over the very low risk of transmission or the possibility of a change to their viral load'.

### **What to start**

NAT does not have specialism to comment on this section. We note and support the concerns expressed by a significant number of people at the community meeting about contraindications for efavirenz and the value of this being explicitly noted in the Guidelines in section 3.1.

### **Supporting patients in therapy**

We welcome the full section on supporting people on therapy (and note, given its importance, the suggestion at the London community meeting that it be placed earlier on in the Guidelines).

It may be implied but it is worth stating explicitly that the helpful bullet points on assessment in 4.1.2 apply not just to commencing treatment for treatment-naïve patients but to any switch or change in regimen.

If this approach is relevant not just to starting ART but to particular decisions on treatment regimen then the wording in the bullets needs to be amended – a patient may not have concerns about taking ART in general but may have concerns about a specific drug being proposed for their treatment. So for example at the third bullet point it is not just 'Concerns about taking ART .' that should be assessed but also concerns about taking any specific HIV drug.

Similarly, one issue to be assessed is “Their knowledge of its mode and efficacy, and perceptions of their personal need for ART’. Again there is a question of assessing the patient’s understanding both of the need for ART in general and the rationale for a specific combination. Of course this need not be very technical but reference to Guidelines, contraindications and other relevant considerations, as appropriate, are important. In particular we were concerned when the new London prescribing messages were initially disseminated there was no accompanying clarity on the importance of explaining to relevant patients the rationale for a switching recommendation based on cost.

There is a useful reference to the new national standards for psychological support for adults with HIV, in the context of signposting to psychological support options. But the standards also have important content on mental health screening. It would be useful to refer to the national standards for psychological support slightly earlier in the text and as relevant to all aspects of the interaction between adherence and mental health.

The draft Guidelines recommend regular review at agreed intervals of ‘patients’ knowledge, understanding and concerns about medicines and the benefits they perceive ..’. This is a welcome recommendation. It is not clear whether this review has to be undertaken by the clinician or can be done by a specialist nurse or health advisor. Presumably the ‘agreed intervals’ are agreed with the patient? It would however be useful to indicate patients whose circumstances suggest particular vigilance (for example those in challenging socio-economic circumstances, and thus possibly vulnerable to depression, or with beliefs which bear on taking of medicine).

#### **Managing virological failure**

There is no discussion in this section of the implications of virological failure for the patient relying on treatment as prevention as set out in the relevant earlier section of the Guidelines. There are presumably some implications for advice to patients (and possibly their partners) which should be considered (even if it is mainly one of reassurance) and even some relevance to how any virological failure should be addressed. NAT suggests that the writing group consider possible reference to TAP in this Chapter on virological failure.

NAT

March 2012

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#### **ViiV Healthcare**

Dear Dr Williams,

On behalf of ViiV Healthcare Ltd I would like to thank you for the opportunity to comment on the draft 2012 BHIVA treatment guidelines.

We recognise the complexities of assessing the available evidence and we fully support the new process and application of the GRADE system, with the aim of providing robust evidence based guidance on best clinical practice in the treatment and management of HIV-infected adults. With this in mind, we have some comments in relation to Section 3: What to Start and on some elements within section 6 ‘ART in specific populations’, specifically 6.5 and Appendix 3 GRADE tables (Chronic kidney disease and renal failure) and 3.3.2 and 6.6 (Cardiovascular disease).

In particular, we are concerned that the 2012 draft guidelines:

- Fail to recognise that the benefit risk assessment for ABC-3TC (Kivexa) is comparable to TDF-FTC (Truvada) as an efficacious and well-tolerated NRTI combination for initial treatment in patients with viral load <100,000 copies/ml.

- Contains reference to the ‘regulatory recommendation’ for abacavir (ABC) in MI risk that differs from the MHRA approved Summary of Product Characteristics (SPC).
- Do not put sufficient emphasis on the importance of renal disease as a significant and serious complication in patients with HIV infections.

### **Section 3: What to Start**

The draft guidelines include different levels of recommendation for ABC-3TC and TDF-FTC based on interpretation of the results from the three head to head trials of ABC-3TC and TDF-FTC (HEAT, ASSERT and ACTG5202 trials). This is not consistent with the common assertion that the benefit risk assessment for both treatments is comparable when considering efficacy, tolerability and other factors including renal and cardiac disease, co-morbidities and patient preference.

Of note, with respect to benefit (efficacy), the ACTG5202 results indicate that for patients with viral loads <100,000 copies/ml there were no significant differences in treatment effect between the ABC-3TC and TDF-FTC groups for virologic failure at 96 weeks follow-up, [88.3% and 90.3% respectively (difference 2%; 95% CI: -7.5, 3.4)].

In relation to risk, we acknowledge that in observational studies of treatment experienced patients, ABC use has been associated with increased risk of MI. However, the majority of recent randomised clinical trials (RCTs) data, cohort analyses that control for known risk factors, and mechanistic data have not supported this association and four well-designed meta-analyses of RCTs have consistently shown no increased MI/CV risk associated with ABC.

In contrast, while it is reassuring that ABC has not been associated with an increased risk of renal disease, there have been several published cohorts that clearly demonstrate renal impairment associated with other antiretrovirals, including TDF-FTC. Indeed, recently published data (5) suggests this may not be readily reversible in some patients.

Therefore, based on the body of evidence assessing the benefit and risk of both treatments, we suggest that ABC-3TC should be recommended alongside TDF-FTC as a first line NRTI backbone in patients with viral loads < 100,000 copies/ml who are HLA-B\*5701 negative. Further, we recommend that the choice of which agent to use in this large group of patients should be individualised by mitigating all risk factors including choice of therapy where appropriate.

### **Section 6.5 Chronic kidney disease and Appendix 3 Grade Tables**

It is our view that renal disease should be given more significance within the guideline considering the potential impact on affected patients, especially in light of an increasingly ageing HIV population. It is clear regular monitoring of renal function is extremely important for the care of HIV infected patients, particularly in light of the fact that patients now live decades with HIV Disease. The guidelines currently assess the importance grade of renal failure as ‘4’, Important, while Overall grade3/4 adverse events are rated as ‘7’, critical. We suggest consideration is given to elevating the renal failure grade to ‘critical’.

### **Section 6.6 Cardiovascular disease**

Section 3.3.2 of the draft guidelines state that “based on the balance of current evidence and current recommendation from the regulatory authorities, ABC should be avoided in individuals at high risk of cardiovascular disease”. This is not consistent with the current MHRA position, taken from the SPC, section 4.4, Special warnings and precautions, which states:

Myocardial infarction: Observational studies have shown an association between myocardial infarction and the use of abacavir. Those studied were mainly antiretroviral experienced patients. Data from clinical trials showed limited numbers of myocardial infarction and could not exclude a small increase in risk. Overall the available data from observational cohorts and from randomised trials show some inconsistency so can neither confirm nor refute a causal relationship between abacavir treatment and the risk of myocardial infarction. To date, there is no established biological mechanism to explain a potential increase in risk. When prescribing Kivexa, action should be taken to try to minimize all modifiable risk factors (e.g. smoking, hypertension, and hyperlipidaemia).

We regard patient safety as an utmost priority and believe the current SPC reflects the available body of evidence regarding appropriate use of ABC/ABC+3TC and MI risk. Therefore, we recommend a change to the draft guidelines that is consistent with both the current regulatory position for Kivexa and good medical practice in general, i.e. to take action to try to minimize all modifiable risk factors before prescribing Kivexa or any other antiretroviral therapy.

With regards to the statement concerning the use of maraviroc in patients with high cardiovascular disease risk (Section 6.6.4.1, What to Start, Recommendations), we feel that this could lead to the perception of maraviroc being contraindicated in this patient population, which is not the case. In section 4.4, Warnings and precautions of the Celsentri (maraviroc) SPC it states:

Cardiovascular safety: limited data exist with the use of CELSENTRI in patients with severe cardiovascular disease, therefore special caution should be exercised when treating these patients with CELSENTRI. In the pivotal studies of treatment-experienced patients (MOTIVATE) coronary heart disease events was more common in patients treated with CELSENTRI than with placebo (11 during 609 PY vs 0 during 111 PY of follow-up). In treatment-naïve patients (MERIT) such events occurred at a similarly low rate with CELSENTRI and control (efavirenz).

We suggest that the draft guidelines be altered to reflect the SPC statement which recommends that special caution should be exercised when treating severe cardiovascular disease patients with maraviroc.

We would like to thank you again for the opportunity to review and respond to the draft BHIVA guideline. If you would like further clarification of any of the above comments, please contact Dr Andrew Clark

Yours sincerely

Dr Andrew Clark Simon Mackinder

European Medical Director UK Country Manager

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**Prof Derek Macallan**

Re 6.1.2.1 Treatment of HIV-TB

We now have a substantive body of evidence that efavirenz levels on treatment are highly variable, that giving 600mg of efavirenz is adequate for most subjects to achieve levels in the therapeutic range, and that body weight is a very poor predictor of response. This data has been presented at the British Infection Society in abstract form and is submitted for publication in full format. We include it below to the writing panel in confidence. We found that:

Of 33 patients started on efavirenz at 600mg daily with rifampicin who had EFV levels taken (and repeat measurements in 13), there was very wide inter-individual range in levels, from 580 to 15,325ng/dL (recommended therapeutic range 1,000-4,000 ng/dL). Of 39 measurements in 28 patients receiving 600mg efavirenz, only 3 subjects (11%) were sub-therapeutic (an additional patient became therapeutic on repeat measurement); 19 patients (68%) had therapeutic levels and 6 (21%) had supra-therapeutic levels. In the 3 patients with sub-therapeutic levels, there was no evidence of virological failure or efavirenz resistance (although two were subsequently switched to 800mg). Of seven further patients started on efavirenz 800mg daily, four had high efavirenz levels (>4000 ng/ml). We also found no correlation between body weight and efavirenz levels ( $R=0.0046$  for weight versus trough EFV levels on 600mg daily).

Can I suggest an additional line:

Since efavirenz levels in patients receiving rifampicin may be highly variable, where drug monitoring is available, starting with 600mg of EFV daily and monitoring levels at 2 weeks is an acceptable alternative approach.

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**Robert Fieldhouse**

Editor, BASELINE Magazine:

The absence of a dedicated section for women is a greatly missed opportunity. There needs to be some discussion about women and the menopause and greater discussion about conception- including guidance for HIV negative women with HIV positive partners.

Please could you replace the term HIV infected with HIV positive throughout the guidelines?

Whilst I understand that the guidelines are about antiretroviral therapy, they will inevitably be used as a precedent for how hospitals will provide services. With this in mind I think it would have been useful to have included some recommendations about how adherence support should be provided within individual clinics.

For example, I believe patients benefit from time with a specialist nurse or pharmacist.

I understand that BHIVA will look at the primary care interface in the Standards document but I feel greater clarity is needed within the BHIVA guidelines concerning the role of GPs in the provision of care for people living with HIV.

I would like to see BHIVA produce a shorter, simpler to read version, which could be taken up by non-specialists, patients and community support workers. Perhaps NAM would be a good organisation to help with the draft?

I would like to see BHIVA put on a series of roadshows to raise awareness of the new guidelines among doctors, nurses, pharmacists, and community workers.

I welcome the section on Supporting people on therapy and the treatment as prevention section.

In treatment as prevention I think it would be useful to further reinforce the message about the length of time it may take someone to become undetectable following initiating treatment.

Specific sections

1.3 I think it would be good to include the Lewden data showing the impact of having a CD4 > 500 on mortality J Acquir Immune Defic Syndr. 2007 Sep 1;46(1):72-7.

This could help patients understand the importance of high levels of adherence and achieving a good CD4 count.

2.4.2 please include femidoms alongside condoms as a barrier contraception

3.1 Please could you further explain what preferred and alternative mean?

3.1 Please could you further discuss the possible short-term CNS effects of efavirenz, including sleeplessness and underline that patients can change to alternatives if they should wish.

3.4.2 I think the term significant mental health problems is misleading- perhaps any history of depression may be better.

3.5.1 Is it not worth underlining when the pivot trial is to present data so that junior doctors better understand this is a question that is currently under debate and that guidance may change as a result of these new data.

4.1 I think this section needs to consider how and who- for example this is a great opportunity to discuss the role of task shifting and the greater involvement of specialist nurses.

Patients are more or less willing and able to be engaged with their care depending on where they are in their HIV journey- this section should reflect that.

There is an opportunity here to discuss the role of voluntary sector treatment information providers as advocates.

It is also worth thinking about vulnerable populations and making specific recommendations for African patients.

4.2 Adherence support needs to be throughout someone's HIV treatment career – a roadmap here detailing a minimum standard of support from the clinic would be useful.

6.1 I think it would be useful to include a section about transition of 16 year olds into adult care; particularly as this group often requires specific adherence support if they develop treatment fatigue.

6.3.2 I think it would be useful to see some basis recommendations for cancer screening among people living with HIV.

6.4 Again I think it would be useful to provide some recommendations about minimum screening for ANI.

I am slightly concerned that the default answer by the writing committee to the small number of unexplored issues in these guidelines such as women or conception or adolescents will be “there are specific guidelines for...” The BHIVA treatment guidelines are the only ones to be NICE accredited so by referring to other guidelines for information about sub-populations women may not carry sufficient weight for the guidance to hold weight with commissioners.

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### Counterpoint HIV Policy Alliance

This response is from the Counterpoint HIV Policy alliance, a partnership between the NAZ Project, Positive East and Positively UK. Together we strive to increase the voice of people and communities affected by HIV in the public policy arena. We believe through collaboration, that we can best share our experience, knowledge and collective learning.

We would like to commend BHIVA on the draft guidelines. These are comprehensive and pioneering in acknowledging new and emerging issues such as treatment as prevention, and involvement of patients in decision making. We welcome the inclusion and emphasis placed on these issues in the guidelines. Areas we would seek review of are:

#### **2.4 Treatment to reduce transmission**

We agree with the recommendations stated on page 19; and would ask point two ‘Condoms continue to be recommended...’ be separated into two points. The first point should state that people still need to protect against other sexually transmitted infections and lower further any residual risk of transmission. The second point should emphasise the options to achieve this; this should not be limited to male condoms, but include and state the use of female condoms, non-penetrative sex and behavioural change.

##### **2.4.2 Rationale**

ART to prevent transmission around natural conception is mentioned at the bottom of page 20 with reference to the BHIVA pregnancy guidelines. Our concern is that this needs to be raised as an important factor for sero-discordant couples from the outset and included in the initial discussions. The issue of treatments and natural conception should be included as a separate item within the discussion points of section 2.4.1

#### **3.1 What to Start Summary recommendations**

Within these guidelines Efavirenz is stated as a preferred option as front line treatment (pg 22). There is evidence that patients’ experience neurological side effects as a result of this Efavirenz. Alongside this there is evidence that key groups such as women, gay men and BME communities, communities highly affected by HIV, are also at greater risk of experiencing mental health issues. Currently the guidelines recommend clinicians consult another set of BHIVA guidelines (routine investigation and monitoring of adult HIV-1 infected adults 2011) for guidance on assessment. We do not consider this sufficient. The need to assess the mental health of the patient prior to prescription of Efavirenz needs to be made explicit within the current treatment guidelines.

The summary recommendations also state the preferred NRTI Backbone as consisting of

Tenofovir and emtricitabine . This is in contrast to the guidelines issues by the Specialist Commissioning Group which recommend Abacavir and lamivudine. This issue needs to be clarified; and the preferred option chosen to optimise the health outcome of patients.



## **4. Supporting patients on therapy**

As community organisations we welcome the inclusion of this section of the guidelines, and the recommendation that ‘patients are given the opportunity to be involved in making decision about their treatment’. BHIVA have always been at the forefront of patient involvement and we would like to see this further emphasised by section 4 being moved to the beginning of the guidelines. This change would also signify that this involvement is a pre-requisite and strengthen the doctor – patient relationship. It also supports current healthcare initiatives such as self-management and patient involvement through the ‘no decision about me without me’ initiative.

### **4.1 Patient involvement in decision making**

We are aware there will be further guidelines on the standard of care which will encompass psychological support including peer support. Nevertheless the BHIVA Treatment Guidelines will be significant in influencing policy and decision makers, including commissioners of health and social care. Taken in that context the guidelines need to provide direction and processes for patient decision making, and critical factors for patients to make informed decisions. Currently the guidelines state ‘Clinicians should establish what level of involvement the patients would like and tailor their consultation style appropriately’ (pg33), and the guidelines recognise that issues such as socio-economic status have effect. However for many communities there will be low levels of involvement in their healthcare due to cultural norms and lack of effective and tailored information. The current guidelines do not address this nor do they signify a need to increase levels of involvement, how to increase patient involvement, nor who will be responsible for supporting this.

The guidelines need to recognise the need to increase levels of involvement; and whether this is the role of the clinician or should be the responsibility of other agents e.g. community groups.

The rationale in assessing patients rightly includes factors such as ‘patients readiness to take therapy’ and ‘confidence they will be able to adhere’. However what if assessment concludes a patient is not ‘ready’ or confident to take treatments, yet clinical evidence indicates that commencing treatments is essential to the patients’ health? Guidance needs to address this issue, otherwise there is higher risk of the patient failing to adhere.

The headlines on page 33 identify a range of options including independent information providers and peer support, but the specific role of these interventions is not elaborated within the subsequent rationale. Community and peer support can be instrumental in supporting patient’s understanding and confidence around treatments. Advocacy, with a community support worker in attendance during appointments, can be pivotal in developing the doctor-patient relationship. Under the grading system we understand the guidelines cannot ‘recommend’ the involvement of community resources and peer support in patient involvement; it could suggest these interventions as support options.

### **4.2 Adherence**

The points above in supporting patients on therapy need also to be applied to adherence.

#### **4.3.1 Drug interactions**

The guidelines currently state that drug interactions should be checked before administration; they recognise problems of inaccurate medication recording and prescribing between hospital and community health services. These are real issues that can detrimentally affect health outcomes of patients. However the guidelines state ‘communication between GPs and other medical specialities are fundamental’. It should be noted that while most people living with HIV will now be registered with a GP, there is a cohort who will not disclose their HIV

status to the GP practice. Even for patients who have disclosed to their GP, with greater emphasis on HIV as a long-term condition, the role of the GP in healthcare, alongside less frequent appointments with the HIV clinic; patients will be prescribed medications by their GPs without any consultation with an HIV clinician. The guidelines are not explicit, but imply GPs will check for interactions routinely – we have found this not always the case. This should be acknowledged.

This section of the guidelines also places all power into the hands of healthcare staff, but has no indication of the role of the patient in managing drug interactions. Patients need to understand their HIV medications and how they might interact; thus giving patients greater control over their own healthcare. Patients need to be able to seek advice if they are prescribed drugs by their GP or other centres e.g. A&E; and mitigate against interactions, should healthcare staff fail to undertake this. Support should be provided to patients to be proactive in questioning prescriptions to avoid interaction with HIV medications. The guidelines should consider how to best address this issue.

Contacts:

Allan Anderson, Chief Executive Positively UK

Mark Santos, Director Positive East

Wondwossen Eshetu, Head of Programmes NAZ Project

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### Boehringer Ingelheim

Boehringer Ingelheim Ltd (BIL) welcomes the opportunity to comment on the draft Guidelines for the treatment of HIV -1 infected adults with antiretroviral therapy 2012. We have restricted our comments to statements made about the molecule nevirapine and make no comment on terminology, or information presented for other antiretroviral therapy (ART).

P22: (section 3.1) Summary recommendations

BIL recognises that the positioning of nevirapine as an alternative third agent in therapy naïve patients is unchanged from the 2008 recommendations. However, we wish to draw the writing group's attention to a product development. Since the last guidelines were published by BHIVA in 2008, a new formulation of nevirapine, nevirapine prolonged release formulation (VIRAMUNE PROLONGED RELEASE TABLETS), has become available (launched 1 November 2011). The product's Summary of Product Characteristics is available at: <http://www.medicines.org.uk/emc/default.aspx>

P44: (section 4.3.1 drug interactions)

BIL reminds the BHIVA writing panel that information on drug-drug interactions is also available from the medical information departments of pharmaceutical companies, who may have access to more up to date information not yet published. Information on drug interactions relating to specific product formulations is available from the electronic medicines compendium at: <http://www.medicines.org.uk/emc/default.aspx>

P47-49, references p50: (section 4.3.4 switching therapy: pharmacological considerations; subsection 4.3.4.1 switch from efavirenz to nevirapine)

The impression created by the current wording of the draft guideline is that a switch to HAART regimens including nevirapine is complex. BIL suggests that the review of data regarding switching to nevirapine based HAART (nevirapine as a third agent) be presented on its own merit within the guidelines, as has been done for other 'third agents' in this section.

The BHIVA writing group have cited De Lazzari et al (2008) (Ref 19) as the data source for the statement about consideration of nadir CD4 counts, rather than prevailing CD4 counts in attempting to assess the risk of rash or hepatic events in virologically suppressed patients switched to nevirapine. The data that supports the statement about nadir CD4 counts is from the ATHENA study (Wit F et al Clin Infect Dis 2008;46:933-40), not De Lazzari et al. The De Lazzari meta analysis showed that baseline (nadir) CD4 count, gender, hepatitis C co-infection or age failed to show a statistically significant association with an increased risk of hepatotoxicity or death at 3 months, using a meta-regression model. However, this data should be interpreted with caution due to an over-representation of male gender in this meta-analysis.

BIL wishes to highlight that since the publication of the ATHENA study, more recent information has been published (Kesselring A et al, Risk factors for treatment-limiting toxicities in patients starting nevirapine-containing antiretroviral therapy. AIDS 2009, 23:1689–1699) demonstrating that ongoing viral replication is the strongest predictor of risk of hepatic and cutaneous adverse events when nevirapine is initiated in HAART experienced patients. These studies found that the risk of hypersensitivity and/or hepatotoxicity in patients with an UNDETECTABLE VIRAL LOAD switching to Viramune® (nevirapine) is not increased in patients with higher CD4 counts (i.e. above the gender specific CD4-thresholds: women more than 250 cells/mm<sup>3</sup>, men more than 400 cells/mm<sup>3</sup>). This formed the basis of the change in the Summary of Product Characteristics for Viramune in 2010. In treatment experienced patients, switching to Viramune should only ever be considered in patients with an undetectable viral load.

The BHIVA writing group make the comment, based on data from Laureillard et al (study in Cambodian patients, 2008, cited as reference 17), that omission of the 14 day lead in dose of nevirapine 200mg once daily and commencement of nevirapine treatment using the full dose of 200mg nevirapine twice daily has been shown to be 'safe'. This is not a statement that BIL can support, either in terms of factual accuracy or in accordance with Clause 7.9 of the ABPI Code of Practice for the Pharmaceutical Industry 2012. BIL draws your attention to data from a UK study (Taylor S et al; 16th Conference on Retroviruses and Opportunistic Infections. Montreal Abstract #N-132; Poster Board #694, 2009) which suggests that initiation of full dose nevirapine is not advisable. A full dose regimen for initiation does not lie within the Market Authorisation for Viramune.

BIL reiterates the recommendation: Treatment experienced patients with an undetectable viral load (below 50 copies/ml) can be switched to an ART regimen containing nevirapine with a two week lead in of 200mg daily, consistent with the Viramune Summary of Product Characteristics and the product's Marketing Authorisation.

When switching from efavirenz to nevirapine, Boehringer Ingelheim recommends that efavirenz should be stopped and patients should be initiated at nevirapine 200 mg once daily (OD) with dose escalation on day 15 to nevirapine IR 200mg twice daily (BD) or nevirapine 400mg prolonged release tablet OD. This lead-in period should be used because it has been found to lessen the frequency of rash [Viramune® Summary of Product Characteristics, available at <http://www.medicines.org.uk/emc/>. Viramune® prolonged release, Summary of Product Characteristics, available at <http://www.medicines.org.uk/emc/>].

Data from Winston et al (2004, cited as reference 16) demonstrated that patients who were switched to EFV with a 2 week lead in dosing (nevirapine 200mg OD) all had undetectable viral loads at 3 months (n = 6), as did the patients who had immediate dose escalation (nevirapine 400mg OD; n=6, Group 2). Individuals given higher-dose nevirapine may potentially be at a greater risk of hepatotoxicity. Although this was not demonstrated in this cohort, it is important to note that all subjects were male in this study.

Although this study noted that 4 of 6 patients in Group 1 had sub therapeutic nevirapine levels during the lead in period (Day 8- 3131ng/ml; 1298ng/ml; 2839ng/ml; 3205ng/ml; 2269ng/ml; 1348ng/ml), the study did not demonstrate any virological failure in the group given the lead in nevirapine dose for 2 weeks, over the time period studied, although the authors stated that there is a potential for virological failure and the associated risk of developing drug-resistant mutants.

BIL draws the writing group's attention to the recommendation that, FOR PATIENTS WHO ARE THERAPY EXPERIENCED AND HAVE DETECTABLE VIRAEMIA, A SWITCH TO NEVIRAPINE IS NOT RECOMMENDED. (Data sources: Viramune and Viramune prolonged release SPCs, available from: at <http://www.medicines.org.uk/emc/>, Kesselring A et al, Risk factors for treatment-limiting toxicities in patients starting nevirapine-containing antiretroviral therapy. AIDS 2009, 23:1689–1699)

P49: (section 4.3.4.7 conclusion)

The draft BHIVA guidelines make a statement that there are no virological studies to guide a choice of strategy. The small study from St Mary's Hospital [Winston A, Pozniak A, Smith N et al. Dose escalation or immediate full dose when switching from efavirenz to nevirapine based HAART. AIDS 2004;18:572-574, cited as reference 16] does show virological outcomes at 3 months.

P104-107 (section 6.6 cardiovascular disease)

This section discusses cardiovascular risk, including the contribution of lipid disorders. The BHIVA writing group describes dyslipidaemia as a surrogate marker for CVD. BIL considers that the writing group should consider making an observation of those ARV agents that affect lipid profile e.g. atazanavir, nevirapine.

In the event that the writing group has queries about the properties or use of nevirapine, or requires further information on management of adult HIV-1 patients with ART including nevirapine, please do not hesitate to contact our medical information department: [medinfo.bra@boehringer-ingenelheim.com](mailto:medinfo.bra@boehringer-ingenelheim.com) or phone 01344 742579.

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### Dr Dave Pao

Even though the data for treatment of AHI are limited, the inclusion of this option will probably have the added benefit of:

- 1) driving AHI awareness campaigns in for healthcare and patient groups;
  - 2) increasing the likelihood of presentation to healthcare in those at risk of (symptomatic and asymptomatic) AHI because of the potential for definite intervention.
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### Body and Soul Charity

#### Recommendation 2.4.1:

We strongly endorse the decision of BHIVA to support elective uptake of treatment for those persons with a CD4 above 350. We believe this respects the patients' autonomy, and encourages proactive health promotion behaviours. We also strongly support that this decision should be a patient's free choice and the patient must be free from coercion.

Given the individual differences in comprehension of HIV, treatment, and transmission, Body & Soul also recommends that the elective treatment for transmission reduction is accompanied by a knowledge assessment to ensure the patient has a clear understanding of the implications of starting medication as it relates to transmission. Otherwise stated, ensure that patients understand that it can lead to a reduction in transmission risk rather than an elimination of transmission risk.

Additionally, we recommend that a social assessment is conducted to determine whether it is realistic for that specific patient to achieve high and consistent adherence to ART, critical considering the impact of poor adherence on transmission risks and on resistance. Any needs impacting potential patient adherence should be addressed through prompt referral to appropriate support services.

We also suggest that early elective treatment is openly discussed with patients, so that they are aware that this is an option. This is especially relevant in vulnerable populations who may not have the same degree of confidence in managing or advocating for their own health, or may not be culturally accustomed to challenging medical advice.

#### Recommendation 4.1.1

Body & Soul strongly advocates that patients are given the opportunity to be involved in making decisions about their treatment. This is a fundamental human right and is ethically appropriate. We support the assertion that treatment support is provided by multiple sources.

We believe another factor, overlooked by this document, is the influence on life-course factors on medication adherence and medication suitability. Younger or older adults may have specific life-course factors that serve to barriers to medication adherence.

Given the trends towards poor adherence amongst young people, preference may need to be given to treatment regimes that are easier to take and fit better into a young person's lifestyle in order to encourage adherence.

Similarly, evidence shows that older adult populations living with HIV are less likely to report that they experience side effects, even though the side effects of treatment may be more pronounced in this population for multiple reasons (including compounding factors related to aging). Older adults should be given opportunity and encouragement to openly discuss their experiences with treatment, including potential physiological, psychological, or cognitive factors.

Gender-specific lifecourse factors should be discussed openly with the patient. Similarly, since the patient may not disclose HIV status or medication to GPs, sexual health needs such as hormonal or intrauterine contraception methods should be discussed by HIV clinicians alongside discussions of condom use.

Additional support should be provided to individuals struggling with medication adherence, and this support should come from a variety of sources and be multidisciplinary in nature. Voluntary services are critical in addressing a number of barriers to adherence (such as housing, immigration status, social support, knowledge, understanding, and beliefs around treatment), and should work collaboratively with clinicians as part of the multidisciplinary team.

We believe that, as health professionals, GPs and GP practices should have the knowledge, skills, and professionalism necessary to handle any health information that is relevant to a patient's care and clinical picture. We believe that HIV status is relevant to a patient's clinical picture. We recognize that sharing HIV status with GPs is not always the safe decision for patients. We believe GPs should be accountable for poor or stigmatizing care, and that GPs should be penalized for negligent care rather than punishing patients.

## MSD

MSD response to the draft BHIVA guidelines for the treatment of HIV-1 infected adults with antiretroviral therapy (ART) 2012.

MSD welcomes the opportunity to consult on the draft BHIVA guidelines for the treatment of HIV-1 infected adults with ART. Please see below for detailed comments by section:

### SECTION 1

#### 1.2.3 Grade

MSD believes the GRADE system to be methodologically robust and objective, and that this approach provides an informative and transparent summary for clinicians, patients and policy makers. We would kindly seek clarity on when this methodology is expected to gain NHS Evidence accreditation and if BHIVA will be seeking NICE accreditation.

#### 1.3 Treatment Aims

MSD agrees that the primary aim of ART is the prevention of the mortality and morbidity associated with chronic HIV infection at low cost of drug toxicity.

#### 1.4 Resource Use

MSD recognises that the cost of medicines and associated service costs is an important issue in the provision of ART for a population. MSD fully supports the BHIVA panel in taking a patient-centric approach throughout this updated guideline and putting an equal emphasis on efficacy, tolerability of, and ease of adherence of ART to that of cost.

MSD would kindly suggest that in order to make this guideline more meaningful to UK policy makers, payors and clinicians, the ICER quoted in this section should be taken from the referenced UK publications and given in UK pounds sterling rather than in US dollars.

### SECTION 2

#### 2.3.1 Recommendations and 2.4 Treatment to Reduce Transmission

MSD recognises that BHIVA has taken a global lead to recommend a patient choice for those who wish to start treatment to reduce the risk of transmission. We fully support this recommendation.

### SECTION 3

#### 3.1 Summary recommendations

MSD agrees that the table of summary recommendations for choice of ART reflects published data and an evidence based medicine approach. We believe that the recommendations reinforce the importance of the efficacy, tolerability, and ease of adherence of ART regimens in an individual.

#### 3.4.2 Rationale

This section states that "ATV/r (ritonavir-boosted atazanavir) and raltegravir (RAL) have been compared directly with EFV (efavirenz) in randomised control trials. For critical virological efficacy and safety outcomes, no differences were identified between EFV and either ATV/r, or RAL. For these outcomes the quality of evidence was rated as high or moderate."

Page 26 details the references used in this comparison. The two references which have virological efficacy as a primary outcome of the publication are [3] and [7]. Study [3] is derived from the ALTAIR study and study [7] is derived from ACTG A5202. In both studies, the comparison of EFV vs ATV/r was open label. These studies contrast with STARTMRK – a fully blinded randomised controlled study, with a study design which set out to minimise the bias that could be associated with open label studies.

To be consistent with the GRADE system utilised in these guidelines, MSD would request that the comparison of ATV/r and raltegravir to efavirenz, be separated out and the quality of evidence rating applied accordingly.

On page 27 the draft guideline states that: "There was a difference in the rate of drug resistance favouring ATV/r (RR 3.94, 95 % CI 2.37-6.56;  $P < 0.00001$ ) but the overall rate of emergent drug resistance was low for both treatments. This difference is a class effect and has previously been reported for other NNRTIs and PI/rs". As the rate of drug resistance is stated for ATV/r, it is also important to state that the rate of virological failure was comparable for RAL vs EFV in the STARTMRK study. At 192 weeks, 1.4% of the patients receiving raltegravir had developed proven integrase resistance vs 2.5% of those patients receiving efavirenz who had developed proven NNRTI resistance [A]. MSD recommends that this data should be included in this section of the guideline.

On page 27, there is a statement: "Differences were also identified in the rate of grade 3/4 CNS events favouring ATV/r and the rate of lipid abnormalities favouring both ATV/r and raltegravir". MSD would suggest that this sentence be revised to read: "Differences were also identified in the rate of grade 3/4 CNS events and the rate of lipid abnormalities favouring both ATV/r and raltegravir". The STARTMRK study demonstrated that the percentage of patients who had reported one or more CNS symptoms was significantly lower with raltegravir than efavirenz by week 8 (20.3% vs 52.1%) and by week 48 (26.0% vs 58.5%) ( $P < 0.001$ ) [reference 10, Lennox et al] and at week 96, raltegravir recipients experienced cumulatively fewer nervous system side effects compared with efavirenz recipients [29% vs 61%, (95% CI) = -32% (-39 to -24);  $P < 0.001$ ] [reference 11, Lennox et al].

On page 27 it is stated "Although there was some heterogeneity between these studies, this was felt not to be great enough to invalidate an indirect comparison between EFV and DRV/r". MSD would seek some evidence to support the statement that the heterogeneity was not great enough to invalidate such an indirect comparison. What statistical test was performed to measure heterogeneity and what was the outcome? Has heterogeneity been adjusted for? We believe that including this information would ensure transparency and maintain the robustness of the methodology used in the development of this guideline.

#### 3.4.4 References

MSD requests that the guideline should reference the five year data from the Phase II trial PN004, comparing RAL against EFV [E] which was available when the literature search was conducted for this guideline. In addition, MSD suggests that the guideline should reference the four year data from the STARTMRK trial which was presented at the EACS and IDSA conferences in October 2011 [A, D].

#### Additional References

[A] DeJesus E, Rockstroh J, Lennox J, Saag M, Lazzarin A, Wan H, Rodgers A, Strohmaier K, Nguyen B-Y, Leavitt R and Sklar P. Raltegravir (RAL) – based therapy demonstrates Superior Virological Suppression and Immunological Response Compared with Efavirenz (EFV) – based therapy, with a favorable metabolic profile, through 4 years in treatment-naïve patients: 192 week results from STARTMRK. IDSA 2011, Abstract 30623, Poster H.405

[B] Lennox JL, DeJesus E, Lazzarin A, Pollard RB, Madruga JVR, Berger DS, Zhao J, Xu X, Williams-Diaz A, Rodgers AJ, Barnard RJO, Miller MD, DiNubile MJ, Nguyen, B-Y, Leavitt R and Sklar P. (2009) Safety and efficacy of raltegravir-based versus efavirenz-based combination therapy in treatment-naïve patients with HIV-1 infection: a multicentre, double-blind randomised controlled trial. *Lancet*; 374: 796-806.

[C] Martinez E, Larrousse M, Llibre JM, Gutierrez F, Saumoy M, Antela A, Knobel H, Murillas J, Berenguer J, Pich J, Perez I and Gatell JM (2010). Substitution of raltegravir for ritonavir-boosted protease inhibitors in HIV-infected patients: the SPIRAL study. *AIDS*; 24: 1697-1707.

[D] Rockstroh JK, Lennox JL, DeJesus E, Saag MS, Lazzarin A, Wan H, Walker ML, Xu X, Zhao J, Tepler H, DiNubile MJ, Rodgers AJ, Nguyen B-Y, Leavitt R and Sklar P (2011). Long-term treatment with raltegravir or efavirenz combined with tenofovir/emtricitabine for treatment-naïve Human Immunodeficiency Virus-1 – infected patients: 156-week results from STARTMRK. *Clin Infectious Disease*; 53(8): 807-816.

[E] Gotuzzo E, Nguyen B-Y, Markowitz M, Mendo F, Ratanasuwan W, Lu C, Bhanja S and Tepler H (2011). Sustained efficacy and tolerability of Raltegravir after 240 weeks of combination ART in treatment-naïve HIV-1 infected patients: final analysis of Protocol 004. IAS 2011, Abstract # WEPDB0102.

## SECTION 4

### 4.1.1 and 4.2.1.1 Recommendations

MSD supports the recommendation that patients should be given the opportunity to be involved in making decisions about their treatment and that adherence, and potential barriers to it should be assessed and discussed with the patient whenever ART is prescribed or dispensed. We believe these recommendations further reinforce the patient-centric approach taken by BHIVA throughout this updated guidance.

### 4.2.3 Dosing frequency

This section states that: “Another review of adherence interventions found that reducing dosing to once daily had some effect on adherence but no effect on treatment outcome was observed [32], then goes on to say “For ART regimens, a meta-analysis of once versus twice daily ART regimens found that in the sub-group of treatment-naïve trials, once daily ART was associated with a significantly improved adherence and virological outcome [33]”. MSD would suggest that as these references show differences in the effect of once daily dosing on unintentional non-adherence to ART the subsequent sentence should be changed to:

“Therefore once daily dosing may be a reasonable intervention to reduce unintentional non-adherence to ART”.

### 4.3.1 Drug interactions

MSD strongly support the recommendation that potential adverse pharmacokinetic interactions between antiretroviral drugs and other concomitant medications are checked before administration (with tools such as [www.hiv-druginteractions.org](http://www.hiv-druginteractions.org)). We agree that the importance of considering the potential for drug interactions in patients receiving ART cannot be overemphasized. Furthermore, and in support of the recommendation on page 45, communication with other healthcare professionals (e.g. HIV Specialist Nurses, Primary Care Physicians etc.) is fundamental in minimising the risk of adverse drug-drug interactions as more HIV patients are receiving treatment in the primary care setting.

## SECTION 5

### 5.3.2.4 First line treatment failure with II-based resistance



MSD feels that it is important to point out that virological failure in the STARTMRK trial up to 192 weeks was very uncommon. No patient in the RAL group has failed with detectable resistance to RAL since week 96. Only 4/281 (1.4%) developed proven IN resistance by week 192. The majority of those patients with detectable resistance in the raltegravir arm were resistant to the NRTI/s only. The data cited refers to 48 week data, and does not reflect the most recent STARTMRK data available [A, D]. Some of the references used in this section also seem incorrect. Reference [37] has nothing to do with RAL.

## SECTION 6

### 6.2.3.1 What to Start (Hep C)

MSD believes that it is important to provide information on drug-drug interactions of boceprevir, an oral hepatitis C virus (HCV) NS3/4A protease inhibitor, and ritonavir-boosted HIV protease inhibitors that was recently communicated to healthcare professionals – see Appendix 1 at the end of this document.

MSD would like to point out that there is an issue with the referencing of DDIs in this section of the guideline. The references do not in fact refer to boceprevir. In addition, the interaction between telaprevir and DRV/r has not been mentioned.

The interaction between boceprevir and raltegravir has been studied – please see the following:

<http://clinicaltrials.gov/ct2/show/NCT01288417?term=boceprevir+raltegravir&rank=1>

#### Additional References

[F] <http://www.clinicaltrials.gov/>

[G] <http://www.medicines.org.uk/EMC/medicine/24768/SPC/Victrelis+200+mg+hard+capsules/>

APPENDIX 1: Dear HCP letter regarding the use of boceprevir with ATZ/r, DRV/r and LPV/r

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## UK-CAB

BHIVA Guidelines Consultation: Treatment of HIV-1 in Adults

### Comments from UK-CAB

UK-CAB recognises the great deal of thorough and informed work that has produced these guidelines, and we extend our congratulations to the Writing Group for their hard work.

Although these are clinical guidelines for which the term ‘HIV-infected’ would ordinarily be regarded as appropriate, there is strong preference among People With HIV (PWHIV) for the term HIV-positive; there is additional anecdotal evidence of the term ‘infected’ being a deterrent to PWHIV involvement in clinical studies and trials. UK-CAB therefore feels that the term HIV-positive is preferred, at least in the title and main headings.

Section 1.1 we should like to see a minor but significant addition to the penultimate sentence to read: The guidelines are aimed at clinical professionals directly involved with and responsible for the care of adults with HIV infection, and at advocates.

#### Section 2.4 Treatment to reduce transmission

We welcome this section, and the overall clarity with which it is discussed. However, we would prefer the reference to 'heterosexual couples' in 2.4.2 paragraph 2 to be replaced with 'vaginal intercourse'. This is important because the term 'heterosexual' is more Western-normative than we tend to suppose, and people engage in anal intercourse for a variety of reasons including contraception as well as pleasure. In addition comparable data for anal intercourse are very sparse. There may be some correlation between VL in rectal mucosa and undetectable VL in the blood, but still no scientifically rigorous research.

#### Section 3. What to Start.

We recommend stronger caution around Efavirenz. We recognise that it works very well for many people; however, for a significant minority (c. 20%) it works badly to very badly, necessitating switching to an alternative. We feel this can be avoided, or at least minimised, by recommending early in this section that the doctor-patient discussion (a) takes place meaningfully and (b) probes into the patient's psychiatric/psychological history. As advocates, we are aware of too many PWHIV who have suffered acute depressive episodes, including those with suicidal ideation and actual self-harm, as a result of being prescribed EFV without this discussion exploring these issues.

We are also concerned that Black African people achieve higher blood levels of EFV with a longer half-life. If this is therapeutically significant, we should like this to be clearly stated here; equally if there is evidence, including consistent anecdotal evidence, of any impact on Quality of Life compared to White European people.

We feel that references to cost should be made in terms of Quality of Life and long-term effectiveness, including the additional cost of switching, not just absolute cost. We know that several patents expire in the next two to three years, and this will have impact on what is prescribed. However, a sentence on the sustainability of well-chosen (between doctor and patient together) regimen avoiding extra cost of switching to a possibly more expensive second- or third-line regimen might be added.

Concern was expressed that less than optimal attention appears to be paid to TDF with regard to HIV-associated Nephropathy (HIVAN). As HIVAN affects African people and people of African descent almost exclusively, and as TDF is associated with renal complications, it was felt that the guidelines should be more explicitly encourage greater alertness to possible renal complications in this broad patient group.

#### The Consultation Meeting

Concerns were also expressed, outside the meeting itself and on considered reflection, that the integrity of the meeting as a 'community' event was seriously compromised by the presence and participation of representatives of pharmaceutical companies. It does not seem acceptable to CAB that companies that stand to profit in greater or in lesser degree from the content and application of these treatment guidelines should have any role or voice in determining the content of the guidelines, or to affect any nuance of any detail therein, or the overall direction of them. We therefore ask that any and all comments made by members of the companies present be struck from the record.

We cannot be absolutely certain that all discussion was entirely free of constraints, given the presence of the companies. We feel it perfectly possible under the circumstances that legitimate negative comments may not have been made by some people present because one or other of their significant present funders or potential future funders was in the room.

We therefore wish to remind all concerned that professional boundaries and protocols in this highly sensitive area require the maintenance of a professional distance from, while keeping good professional working

relationships with, each and every pharmaceutical company and this includes the composition of meetings aimed at Community. We recognise that the Consultation Meeting was, in itself, a very positive and constructive exercise. However, we wish to make it clear that future Community consultations, which we readily support and encourage, should either not be open to commercial providers of care, treatment and/or services or be explicitly advertised in advance as inclusive of them. Members of Community can then make a properly informed decision about whether or not to attend.

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### Prof Lorraine Sherr

Read through the guidelines and really pleased to see coverage of mental health, coverage of adherence issues, inclusion of psychosocial issues, and cross reference to the Psychological guidelines. Some cross referencing to pregnancy and the reproductive guidelines, especially when it comes to the use of Efavirenz may be a usual addition.

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### Gilead Sciences

Gilead Sciences would like to acknowledge the high standards of the proposed guidelines and its methodology and appreciates the opportunity to respond.

The use of Atripla- section 4.2.4

Atripla is a Single tablet regimen of efavirenz, emtricitabine and tenofovir disoproxil fumarate. It is indicated for the treatment of human immunodeficiency virus-1 (HIV-1) infection in adults aged 18 years and over with virologic suppression to HIV-1 RNA levels of < 50 copies/ml on their current combination antiretroviral therapy for more than three months<sup>1</sup>

This is based on Study AI2660732, which was a 48-week open-label randomised clinical study in HIV infected patients comparing the efficacy of Atripla to antiretroviral therapy consisting of at least two nucleoside or nucleotide reverse transcriptase inhibitors (NRTIs) with a protease inhibitor or non-nucleoside reverse transcriptase inhibitor; however not a regimen containing all Atripla components (efavirenz, emtricitabine and tenofovir disoproxil fumarate).. Patients had never experienced virological failure on a previous antiretroviral therapy, had no known HIV-1 mutations that confer resistance to any of the three components within Atripla, and had been virologically suppressed for at least three months at baseline. Patients either changed to Atripla (N=203) or continued on their original antiretroviral treatment regimen (N=97). Forty-eight week data showed that high levels of virologic suppression, comparable to the original treatment regimen, were maintained in patients who were randomised to change to Atripla.

Gilead would suggest that this registrational study be reviewed in section 4.2.4 and the Atripla be provided as a therapeutic option for patients virologically suppressed for 3 months on either a PI based regimen or the components of Atripla.

Clarification of restriction on lamivudine use-section 3.1

In the table of summary recommendations in section 3.1 (page 22) a subscript is made in reference Lamivudine being only suitable for patients with a viral load of 100 000 copies/ml or less. Clarification should be provided as to whether this is in reference to lamivudine or the FDC Kivexa

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#### Single Tablet Regimens-Section 4.2

The guidelines highlight the importance of adherence and the role of simplified treatment regimens. Reduced dosing complexity, especially between OD and BD is acknowledged, and discussion is provided on the role of FDC. Whilst no RCT data exists to demonstrate the benefits of single tablet regimens (STR) vs components, there is an increasing cohort evidence base suggesting the health outcome benefit and patient preference of this clinical approach and potential cost consequences.<sup>3,4,5</sup>

Cohen<sup>3</sup> demonstrated from a Medicaid database a higher rate of adherence, less hospitalisation and subsequent reduction in health care costs with STR vs non STR. Gilead notes the limitation of this USA cohort, but it does suggest benefits of an STR.

Airoldi et al<sup>5</sup> demonstrated in a multicentre prospective study an improvement of adherence and QOL on switch to Atripla from its components. Patient preference for an STR over its components was further supported by Cooper et al<sup>6</sup> in the ONCE open label prospective study. The authors concluded that patients maintained efficacy, with improved preference of regimen, less intrusiveness and improved perceived ease of use on switch from the components of Atripla to the STR.

The Spanish FDAC group provide an extensive review<sup>4</sup> of fixed dose antiretroviral combinations (FDAC) and conclude that “FDACs represent a significant advance in the simplification of antiretroviral therapy, facilitating adherence to complex and chronic treatments, and contributing to a quantifiable improvement in patient quality of life”.

Italian HIV guidelines acknowledge STR by stating “STR regimens have a more effective durability of viral suppression vs. more complex regimens and the use of STRs can be a key element contributing to a better quality of life and to a better adherence of patients.”<sup>7</sup>

Based on the above data sets, and the fact that a significant and growing proportion of treated patients in the UK are switched to an STR today, Gilead suggests STR as an adherence strategy is discussed.

#### HIV and viral co-infection- section 6.2

In section 6.2.2.2 reference is made to the efficacy of agents extending out to five years and is referenced to the EASL guidelines published in 2009. The suggested reference for the 5 year Tenofovir data is Marcellin P et al AASLD 2011, poster 1375

Yours sincerely

Dr Keith Aizen

Associated Director Medical Affairs

1. Atripla Summary of Product Characteristics

2. De Jesus E et al *Acquir Immune Defic Syndr*. 2009 Jun 1;51(2):163-74.

3. Cohen C, et al 51st ICAAC Chicago II; Sept 17-20 2011; abs H2-791

4. Libre JM et al *AIDS*. 2011 Sep 10;25(14):1683-90.

5. Airoldi et al *Patient preference and adherence* 2010 :4 115-125

6. Cooper V et al . 13th EACS oct 12-15,2011 poster PE7.5/6

7. [http://www.newmicrobiologica.org/PUB/allegati\\_pdf/2011/2/109.pdf](http://www.newmicrobiologica.org/PUB/allegati_pdf/2011/2/109.pdf) accessed 5th March 2012

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## BMS

Dear Guidelines Writing Group

We thank you for the opportunity for Bristol-Myers Squibb Pharmaceuticals Limited, as the manufacturers of atazanavir, to provide feedback on the BHIVA guidelines for the treatment of HIV-1 infected adults with antiretroviral therapy 2012.

We would like to comment on the rationale related to the first part of recommendation 6.5.2.1:

“We recommend against the use of antiretroviral drugs that are potentially nephrotoxic, in patients with stages 3–5 CKD if acceptable alternative antiretroviral agents are available. (GPP)”

We recognize the merits of the recommendation as a good practice point, however, by limiting the discussions in the rationale to the conclusions of the EUROSIDA cohort study we feel this does not provide a balanced view of the role of antiretrovirals and in particular atazanavir in the treatment of HIV-infected adults with chronic kidney disease.

We feel it would be important to highlight, in the rationale, the limitations of the EUROSIDA cohort study, some of which, may account for the conclusions presented for ATV. These include:

- The lack of randomization and the common practice of prescribing ATV in patients with high CVD risk, which may have accounted for the higher proportion of patients with hypertension, diabetes and any cardiovascular event that were seen in the ATV group, and hence an increased risk of renal decline in this group.
- The nature of cohort study populations makes it difficult to exclude the potential role of concomitant comorbidities or exposure to other potential nephrotoxic drugs. As such this study is unable to definitely demonstrate that the observed associations are causal; only randomized controlled trials will be able to do so.
- Following sensitivity analyses censoring for tenofovir exposure, the association between ATV and CKD was no longer statistically significant.

It is also important to note that at present there is not sufficient follow-up to adequately address the role of more recently introduced ARVs such as darunavir, raltegravir, etravirine and maraviroc. This limited information does not exclude a potential association that needs to be further explored.

Indeed a trend toward significance has also been observed for darunavir/r1 suggesting the existence of a potential class effect involving boosted PIs, probably mediated by potential interactions with tenofovir.

CKD has not been specifically explored in clinical trials with atazanavir. However, renal safety of atazanavir has been studied previously in randomized trials where limited renal events have been reported, even in those with longer follow-up.

- In the 045 study [ATV/r versus LPV/r in 243 treatment-experienced patients with TDF plus another NRTI] renal events were infrequent and occurred in five subjects, who were all treated with LPV/r in combination with TDF and ddI. The majority occurred after 1 year of dosing.
- In the CASTLE study [ATV/r versus LPV/r both with TDF/FTC in 883 treatment naïve patients through 96 weeks], renal profile was similar for ATV/r and LPV/r.

- In ACTG 5202 study [ATV/r versus EFV, both with TDF/FTC in 1885 treatment naïve patients], a modest decrease in median creatinine clearance is observed in patients with ATV/r regimens but only in the TDF/FTC arm, suggesting a role for TDF.

Ultimately we feel that more in depth discussion of the evidence will assist in the considerations of which antiretroviral to select for patients with CKD, and respectfully suggest that this be incorporated into the rationale. In addition would it be possible to add an addendum to our comment, to the effect that we would recommend that additional data from the DAD cohort on cerebrovascular / cardiovascular and renal risk factors presented at CROI 2012, be included in the considerations of the writing committee as they finalise the guidelines (This addition subsequently requested by BMS when agreeing to their comment being in the public domain).

Yours sincerely

Dr Nicholas Adomakoh (Disease Area Specialist, Virology. BMS)

Reference:

1. A comparative analysis of risk factors associated with efavirenz, atazanavir/r, darunavir/r, lopinavir/r and renal impairment [Rockwood, et al. IAS 2011. Poster TUPE250
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**Neal Marshall**

On page 11 of the draft the non-AIDS malignancy grade brackets are (1C) rather than [1C].

In the 'what to start' the '(2)' next to ABC/3TC is different to the others. I wasn't sure if it was meant to be like that, or simply a '2'. Not sure if the brackets indicate it refers to the combination, or it's just a continuity issue.

Thanks

Neal

In addition:

Didn't notice this before (and can't remember if there is a reason for it). In section 6.6 LPV/r, fAMP/r and ABC are all recommended to avoid in high CV risk, and equally graded (1C), however in the what to start with box in section 3.1 only ABC has this listed (point 3). Should it be listed for lopinavir and fosamprenavir as well.

Also in the table in section 2.1 for the CV risk terms we use cardiovascular risk, whereas in section 6.6 we refer to cardiovascular disease (CVD) risk. - should we be consistent

Thanks

Neal

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**Mitesh Desai**

Dear authors,

P12 last paragraph referring to cervical cytology suggests that pregnant women should have cervical screening. It may just be a syntax issue but just for clarity, it may be worth specifying that according to the May 2010 guidance for colposcopy in the National Screening Programme, routine cervical screening should be deferred until after the pregnancy; surveillance following a previous abnormality however, should continue even during pregnancy with appropriate colposcopic follow-up.

Guidelines: <http://www.cancerscreening.nhs.uk/cervical/publications/nhscsp20.pdf>

Best wishes,  
Mitesh Desai

Specialty Registrar GUM, Guy's & St Thomas' Hospitals NHS Foundation Trust

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## Roy Trevelion

To: Gus Cairns; Williams, Ian

Subject: Efavirenz and the BHIVA Guidelines 2012

Dear Gus and Ian,

I'm writing to you because I'm not sure of the procedure for new feedback from the 2nd patient rep!

As you know I think the guidelines are truly excellent, it's a fantastic job. So... here's just one subject that I'd like to comment on:

- \* Chapter 3 What to Start: 3.1.2 Which third agent?

In the last paragraph we say: 'EFV may not be the preferred option [. . .] for patients with a current or past history of significant mental health problems'.

I've found the Guardian article about the possibility that a revised US manual might widen mental illness diagnosis. The US manual, which may be adopted by the UK, is called DSM-5. (I'm sure that's what you called it in the meeting Gus.) Here is an extract from the article:

Professor Nick Craddock, consultant psychiatrist in Cardiff and director of Wales' National Centre for Mental Health<<http://www.guardian.co.uk/society/mental-health>>, said: "Somebody who is bereaved might need help and even counselling, but they did not need a label saying they had a mental illness. I believe that a large proportion of psychiatrists in the UK and Europe are sceptical about DSM-5."

<http://www.guardian.co.uk/society/2012/feb/09/us-mental-health-manual>

An aspect of the BHIVA guidelines is that recommendations are 'determined not only by the quality of evidence for defined outcomes but also the balance between desirable and undesirable effects of a treatment or intervention . . .'

My own experience of EFV is very good in terms of virological outcomes and also for management of adherence. But I didn't realise that personal pressures - which in my case involved negotiations over multiple redundancy at work, and difficulties helping an ageing parent with advanced vascular dementia, as well as the ordinary difficulties of life - could produce such debilitating nightmares, which eventually (in my case) occurred every night. I didn't tell my clinician because I thought that my personal problems were causing them.

Therefore I'd like to suggest that the EFV guidelines sentence is re-written so that any sign of mental health deterioration could be spotted early; perhaps a suggestion that the patients quality of life is discussed at the clinic over time, so that changes in quality of life, or sudden difficulties such as bereavement, are considered early in treatment and that serious psychotic episodes might be avoided?

I feel that the present sentence is too vague, and I'm not sure if there's sufficient evidence to help clarify it. But, about this aspect of EFV, Dr Williams has said that the only statistically significant evidence we have is for sleep deprivation. There is plenty of evidence to show that long-term sleep deprivation leads to all sorts of complications from depression to psychosis to multiple personality disorder <<http://www.medicalnewstoday.com/releases/241692.php>>...so if the cause was that EFV disrupts sleep and the result was slowly accumulating psychological problems in some people, then long-term monitoring might be recommended.

With very best wishes,  
Roy

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### Prof Sebastian Lucas

This represents a tremendous body of work, and I like the special diseases' management sections at the end.

But I have one gripe. This document is (appropriately) directed to those clinicians who are actively treating patients with cART.

It is not of much use to anyone who is a (non-HIV) medical professional who wants to know about current cART but does not prescribe.

For example, I need a generic reference for cART in my new chapter on HIV neuropathology: what are the current drugs, their classification, their toxicities, in succinct and relatively simple depictions. This is for my pathology colleagues who need to know a bit, but not in depth.

There is nothing on the BHIVA website, neither in Links or Publications, that directly takes an interested person to such a summary. If there is such a locus on the website, then I retract this (depending on how accessible it is).

So, for consideration, might it be worth inserting as an Appendix to this document a couple of pages that lay out the current drugs by:

- class of action
- name - generic
- major toxicities

Sebastian

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### Ade Apoola

Dear Authors,

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I note on page 27 of the guideline – dealing with ‘which third agent’ there is a discussion about heterogeneity between the studies comparing DRV versus LPV and LPV versus EFV as there is no direct study between DRV and EFV. I would suggest the statement should be more specific about the amount of heterogeneity and why it was felt not to be important enough to invalidate an indirect comparison. This would seem to me to be important as it’s the reason why DRV is elevated to preferred status and not other PI’s.

Regards  
Ade Apoola

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### **Annemiek de Ruiter**

Well done everyone. Great piece of work.

One comment/suggestion and 2 queries.

With regard to EFV in pregnancy/women, you rightly say that EFV can be used in pregnancy and refer them to the pregnancy guidelines for the discussion. There we say that it should be continued if women conceive on it, and can be initiated in pregnancy. You would imagine that people would infer from that that it is therefore also OK in women of childbearing potential but i think people need that spelt out and we had some comments about this. We have purposefully not referred to women of child bearing potentialas we felt it was best placed in your guidelines.We only talk about pregnant women. I think that the issue of EFV in women of child bearing potential, i.e. that it is ok, should be specifically stated in the adult treatment guidelines. It would be good if on the website, at the relevant point in your guidelines there was an electronic link to our section on EFV so people could look at the detail.

4.3.3.2 Stopping NNRTI containing regimens with TDF/FTC - it is ok to stop all at the same time. I would worry about this and it would be worth spelling out what evidence there is to support that recommendation.

With regard to switching from EFV to NVP - I am not clear at all what you are actually recommending.

Thanks  
Annemiek

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### **Protap Gupta**

Concise and clear! My sincere thanks to the committee for their hard work.

One request: Please insert live link to the reference/bibliography so that, the reader can access the referenced article quickly.

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### **Helen Colver**

The format of these guidelines (key points in bold, then rationale and references) is very user-friendly and far more accessible than previous versions, especially for trainees. Thank you!

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## Simon Collins

Comments to 2012 BHIVA guidelines (Simon Collins, HIV i-Base)

These guidelines are appreciated and the considerable work involved to comply with NICE guidance has generally resulted in a clear standard that will support patient care.

The following comments refer to both content and style in case proofing notes are also useful.

Proofing comments

1. URLs for all references would be very helpful, even just to PubMed.
2. Both US and UK spellings are used - optimize, randomize, minimize, programs, metabolized appear in some of the sections..
3. The style for e-based learning modules used mL, rather than ml, as the lower case 'l' can be read as a numeral "1". CD4 is using uL.
4. Spelling of HLA B\*5701 is not consistently used (see p22, 23, 24, 60 etc).
5. CD4 count terminology changes (sometimes CD4 count, sometimes CD4+ T lymphocyte count etc)
6. Several recommendations refer to "avoiding" things. It is more direct and clear to say what should not be done.
7. Some generic drug names are capitalised (only Brand names ie FDCs in these guidelines (Truvada, Kivexa, Combivir, Atripla, Eviplera, Kaletra, Trizivir) should be capitalised.

Comment through text

### 1. Title

There is a strong community preference for the use of 'HIV-1 positive' rather than 'infected'. It would be very progressive for UK guidelines to follow this. Both terms are widely used in both medical journals (NEJM, AIDS) at conferences and clinical practice, but one is considerably more inclusive. By definition, everyone referred to in these guidelines will have tested antibody positive.

Ref: HIV-positive vs HIV-infected: reducing barriers to clinical research through use of appropriate and accurate language. IAS conference, Vienna, 2010. Poster THPE0516.

<http://www.iasociety.org/Default.aspx?pagelD=11&abstractId=200737137>

### 2. Section 1

- Section 1.1 Scope and purpose: Given importance of community input the following groups should be included:

“The guidelines are also a guide for patients and advocates for the minimum standard of care for HIV positive people in the UK.”

- Section 1.3 para 3. line 1: Suggest wording change to “reduction in sexual transmission” rather than limiting to “vaginal and anal”.
- Section 1.4 Resource use: para 4, line 2. choice of word 'Equally'.

Efficacy, tolerability and ease of use are more important than cost, which is just one factor, however important.

- para 5, last sentence. Suggest that inclusion of word 'significantly' is unnecessary.

Reducing treatment costs should not be at the cost of any increased risk of poorer outcome and quality of care. The earlier narrative is based on similar or equal outcomes when cost becomes an issue.

### 3. Section 2 when to start

- Section 2.2.1 When to start: chronic infection: Para 3: Title of bullet list of other indications to start should specify 'at higher CD4 counts than 350' if this is the meaning.
- Why is prevention of transmission not included as an option for earlier treatment given the earlier reference to HPTN 052 in section 1?

### 4. Section 2.4.1 TasP

Great that this sections is included so clearly.

- bullet 1: suggest that the word 'free' is unnecessary and reads strangely, given the definition of 'choice'.
- bullet 2: suggest that residual risk of transmission should come before STIs (or pregnancy which is not included).
- bullet 4: this emphasis on making a lifelong irreversible decision is not helpful. It adds an additional barrier and is not really supported by data. While CD4-based used of treatment interruptions as a strategy for long-term management of treatment has been shown to have increased risks compared to continuous treatment in SMART the absolute risk from a single treatment break, in people with otherwise strong CD4 counts is very different. If someone decided to start treatment with the aim of reducing their infectiousness and found later that this wasn't working out (perhaps due to unresolved issues associated with their diagnosis) they should know that absolute risk from a treatment break are likely to be very low, especially if treatment is discontinued following the recently published STOP protocol (switch to boosted-PI for last 4 weeks). These guidelines should be similar to options for women with high CD4 counts using HAART during pregnancy who probably take a similar risk if they discontinue treatment after the baby is born.
- bullet 5: could benefit from slightly expanding this concern. It is important that the evidence for TasP is highlighted as specifically coming from studies of vaginal sex. The mechanism for reducing the risk of transmission is the same for all risks of transmission though (not even just sexual). The uncertainly over protection from anal and oral transmission is related to having no data of the residual risk. It might be good to say that while risk will be reduced for anal sex compared to someone not on treatment, the residual risk could

be higher than seen in studies from vaginal sex, but that there is no data to inform this. Perhaps mention currently recruiting Partner Study.

- bullet 6: perhaps add:

The impact of ART on transmission risk is dependent on achieving and maintaining an undetectable viral load. This requires a high level of adherence. Lower adherence will increase the risk of transmission and drug resistance.

#### 5. Section 2.4.2 Rational

- para 1 line 2: to avoid two "or not's", single partner relationships and use of 'discordant' suggest:

"The discussion should include the HIV status of their partner (s) and whether ART is indicated for their own health."

- para 2: the data was not based on heterosexual sex but specifically vaginal sex. Confusing sexuality with vaginal sex is not helpful given that heterosexual anal sex is not uncommon, but was not reported in either of these careful studies. The last sentence in this para should specify 'heterosexual vaginal transmission'. Without a discussion or references to different mechanism for transmission from anal sex, which has been consistently documented a being a higher risk than vaginal sex, it is not accurate for the guidelines to use the term 'similar effect'. It will be reduced but there is no data to compare, and many reasons to think the residual risk of transmission could be significantly higher.

- Is there a reason that there is no reference to viral load in anal mucosa in discussion of anal sex?

- para 6: "significant proportions may take 9 months or more": It would help to give a percentage, however rough for this statement. The reference is to a paper from 1997-2004 - at least 8 years ago. Is this study sufficiently important for this statement to be included? The importance of a specific - or more recent - figure is because the guidelines otherwise assume that reaching <50 by 6 months is expected. More recent studies suggest this is less of a problem. If the factors associated with longer time to suppression include baseline viral load this might be important to state.

#### 6. Section 3.1 What to start - summary

- It is unclear why notes are only included for cautions for the alternative and not the preferred choices.

This is important both for the cautions and to clarify an important aspects of the guidelines.

For example pre-existing renal or bone complications would be expected for tenofovir and a history of depression and/or psychological problems and shift work would be reasonable for efavirenz etc.

- It is not clear whether the panel place Kivexa an alternative because of the limitations in how it can be used or because per se it is less effective? Currently the guidelines do not read like this. They read that Truvada is better compared to Kivexa in all circumstances but that when Truvada can't be used, then Kivexa should be used within the above caution.

This is a key point that needs clarification, not least because of the implication for London patients.

For example, in someone with VL <100,000, who is B-5701 negative and not at high CVD risk, is Truvada considered a better option based on the clinical review of the evidence?

If Kivexa is only an alternative however because of the limitations for its indication, this should really be made clear.

- With reference to the point above, it is not clear whether if the difference between NRTI options is considered similar to the differences between the recommended and preferred options for the third component.

For example is tenofovir vs abacavir similar to efavirenz vs rilpivirine or atazanavir/r vs lopinavir/r.

#### 7. Section 3.3

- 3.3.1 which NRTI recommendations
- para 3: "Abacavir must not be used" would be clearer that "Abacavir must be avoided"
- 3.3.2 para 2 and 3 - ACTG 5202 should have a space before the number
- para 2 line: given that the differences were not statistically significant, and that heterogeneity was high it is confusing to refer to a trend in favour of TDF/FTC.
- para 5: sentence is not clear,
- para 6: please include a figure for BMD differences

#### 8. Section 3.4.2

- para 9: "...comparing DRV/r versus efavirenz directly". Word "directly" is not needed.
- para 12 and later: could the document use "drug" or "medicine" instead of "agent" throughout? this is unnecessary jargon. Direct words are much clearer.
- para 17: this brief reference to potential cautions with efavirenz is not sufficient to cover the well documented side effects and cautions. This issue is consistently raised in every edition of the BHIVA guidelines. Consensus amongst doctors is that perhaps 20% of people either do not tolerate efavirenz or are thought unsuitable to use it. What about shift workers? Or potential for higher drug levels and toxicities with G516T genotype and African patients? Several studies have reported this association but the clinical implications are often dismissed by showing no relationship to discontinuation, which may be an indirect marker for issues of healthcare access by different groups of patients rather than a direct marker for presence of side effects.

An indication of these concerns from a patient based on current standard of care in a double-blind randomised UK study reported 21% of people having "ongoing neuropsychiatric adverse events" at week 48 (vs was 6% for etravirine) (P=0.011).

Ref: Gazzard B. Phase 2 double-blind, randomized trial of etravirine versus efavirenz in treatment-naive patients: 48-week results. AIDS. 2011 Nov 28;25(18):2249-58.

<http://www.ncbi.nlm.nih.gov/pubmed/21881478>

- Section 3.5.5 - para 2: typo - "an NNRTI"
- Sections 3.5.6 References: Is reference 5 applicable as a reference that the guidelines panel find acceptable? There is no online PubMed record and the abstract is not in English? Was this translated for the writing

committee to review? If the study was important this should have been presented at an English meeting or peer reviewed journal since.

#### 9. Section 4.1.2 Supporting patients - rationale

- bullet 2: "their knowledge of the way treatment works..." is clearer than "... its mode of action..."
- para 4 line 1 "Current problematic...": should "low adherence" be "lower adherence"
- para 6 line 1: "...than clinicians realise"

This statement stands out as being only anecdote.

- para 7 line 3: consider "...other negative healthcare behaviours..." – ie insert the word "negative".

#### 10. 4.2.1.2 Adherence rationale

- para 1 line 1: Perhaps add "drug resistance" as a complication, before "progression to AIDS and death".

#### 11. Section 4.3

- 4.3.1.2 Pharmacology: rationale: para 1 last line: "administration is contraindicated" is more direct than "must be avoided"

• 4.3.2.1 Para 1: If examples are going to be given this early, then renal and hepatic impairment should be added to children and pregnant women in parentheses. The clinical importance of this is clear in 6.2.1 page 79.

- 4.3.2.2 para 1: optimizing, randomized; para 3: optimize

• 4.3.3.2 para 2 line 5: Insert "Therapeutic" to "(Therapeutic) plasma concentrations of EFV can be detected..." The EFV levels in African women in Steve Taylor's reports had therapeutic concentrations 3-4 weeks after stopping. These were not residual or trace levels as it might currently be interpreted.

- 4.3.4.2 para 2 line 1: could "low" be quantified as a percentage, based on the referenced article please?

• 4.3.4.7 para 2 line 2. could "low" at the end of the line for VF risk be quantified as a percentage, based on the referenced please.

• 4.4.2.2 para 3 line 1 and future refs: II as an abbreviation for integrase inhibitors is confusing, even when you work out what it means. Is there a reason why INI is not used as in other guidelines or failing that, spelling out integrase inhibitor.

- para 3 line 3: can "more" discontinuations be quantified please.

• last para on NNRTI switch - why is results from EFV to ETV not included?

#### 12. Section 4.4.3.2 PI monotherapy.

• para 1: are there reasons why ATZ/r monotherapy studies are not referenced? Although quality of the studies probably don't score higher the clinical cautions against trying this seems important for the guidelines to note.

Ref: Karlstrom O, Josephson F, Sonnerborg A. Early virologic rebound in a pilot trial of ritonavir-boosted atazanavir as maintenance monotherapy. *J Acquir Immune Defic Syndr.* 2007;44:417-422.

Ref: Vernazza P, Daneel S, Schiffer V et al. Risk of CNS-compartment failure on PI monotherapy (ATARITMO-study). Poster abstract WEPE0073.

### 13. Section 4.5.2 Stopping therapy - rational

- para 2 - bullet list.

Why is early initial treatment with CD4 >500 (for example to reduce infectiousness) different to the use of treatment during pregnancy. The concern for stopping treatment that was started in advance of current guidelines would have the same concerns from a burst in viraemia. Absolute risk from stopping treatment is very low and probably lower than risk of resistance or treatment failure from remaining on treatment.

### 14. Section 5

- 5.1 VF – introduction: para 3 line 1 - VF failure rate is quoted as 10% "now" based on a reference from 2008-9. It would be better to use the date.

- 5.2.2 Rationale: para 1 line 6 "The majority of patients..." May be better to use "many" if this is not quantified, as the reference 7 later in the para quotes 28.6% which is not a majority.

- para 2, last line: should "repeated blips" be defined in number/time.

- para 5 line 3: The reference to 18% failure in patients who suppress to <50 seems high especially when not quantified by a period in time. Is this annually, over 5 years, 20 years? It is in contrast to lower figures referenced earlier.

- para 5 lines 5-6: The prevalence of resistance should make the denominator clear - is this in people who fail treatment with viral rebound on regimens containing each of these drug classes?

- Box 3, bullet 4: Use of II rather than INI or integrase inhibitor

- 5.3.2.1: para 5 last line: unclear sentence: perhaps "...high genetic barrier of PI/r reduces the risk of low level resistance"

- 5.3.2.4: sub head - II reads like II

- 5.4.2 - triple resistance – rationale: para 3 line 7: "...of achieving virological suppression is less..." - suggest "significantly reduced" in place of "less"

- 5.5.1- Recommendations: Suggest a sixth recommendation for following pipeline research, expanded access and named patient programmes to compile combinations with >2 active drugs.

This is very clearly discussed in the following section and adding a good practice recommendation would be helpful.

### 15. Section 6: ART in specific populations

- first section in not numbered.

- Last line of first para: guidelines are "regularly" updated. Perhaps more accurate to say "periodically"
- 6.1.2.1 Recommendations (TB): bullet points 2: the FDA recently recommended 800 mg EFV based on weight band > 50kg (rather than 60 kg). Is this a different interpretation of the same data? Standardised recommendations in guidelines are more helpful.

<http://i-base.info/htb/16098>

- 6.1.2.2: para 2 line 3 - as above re reference to 50 vs 60 kg
- para 3 line 2 - as above
- 6.1.3 References: ref 3 - space between Adbool and Karim
- 6.2.4 References: Refs from 20 are incomplete and differently formatted.
- 6.3 Great to see use of "HIV positive" throughout this chapter. Hyphenation is probably not needed.
- 6.3.3: para 7 line 1: "We suggest avoiding..." clearer to say "Do not use..."
- 6.4.5 Reference style is not consistent with previous sections. The Journal AIDS is included as Aids etc.
- 6.5.2.1 CKD Recommendations: The second recommendations should perhaps refer to "patients with reduced renal function" rather than "renal failure".
- It would be easy (and useful) to list the ARVs requiring dose modification either in a footnote or table, referring to the SPCs for details: 3TC, FTC, ddI, AZT, TDF and MVC (depending on PI use). Some of these meds require dose adjustment with moderate kidney disease and long before kidney failure.
- 6.6.4.1 CVD what to start recommendations: Although the guidelines have removed saquinavir as a recommended option, there should perhaps be a note here that there have been recent warnings about its cardiovascular risk.
- 6.6.4.1 para 2: in the discussion of abacavir, the D:A:D association was with patients who had high underlying cardiovascular risk and the GSK trial analysis and D:A:D results are therefore similar. The discussion suggests they are contradictory when they are not. This is commonly misrepresented. The GSK studies only enrolled people with low CDV risk.

#### 16. Appendices: 2.1

- Using upper and lower case for conference titles would be helpful and the acronyms would then make sense if included in brackets after each full title. (ie CROI, ICAAC etc)
- The "European conference on clinical aspects and treatment of HIV infection" changed it's name to European AIDS Conference (EACS) at least 10 years ago.
- As BHIVA only publishes abstracts for the spring conference, perhaps clarify that the BHIVA search was for the annual Spring conferences (if this was the case).

A few questions on the data:



- Why was TC:HDL ratio was not included as an endpoint as between drug differences in individual lipids often don't translate to a change in this parameter which is usually seen as more clinically relevant when assessing CVD risk and used by the JBS2 CVD guidelines that BHIVA encourage referral to?
  - Given strong lipid benefits (and lower CNS events) for raltegravir compared to EFV (p. 142-144) together with the low percentage of patients who even with lipid lowering drugs who achieve target levels, this might suggest discussing this benefit of raltegravir in the main body of the guidelines.
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## Janssen

Dear BHIVA treatment guidelines writing group,

Thank you for the opportunity to comment on your 2012 draft BHIVA Treatment Guidelines. We appreciate this was a momentous task, given the new GRADE system, and commend you on such a thorough and clinically relevant review. This will no doubt go a long way to further improving HIV care in the UK.

Re section 5.4 'Patients with triple-class (NNRTI, NRTI, PI) virological failure with or without triple-class resistance', we have a small, but in our opinion, important comment.

We believe etravirine has comparable efficacy to raltegravir and maraviroc in this patient group and deserves to be mentioned in the main recommendations rather than just the rationale section.

Virological efficacy is similar

Although baseline characteristics and study design in the DUET, MOTIVATE and BENCHMRK studies differed somewhat, all patients had triple class failure and documented resistant mutations to PIs and NNRTIs. Indeed the BENCHMRK and DUET studies had a similar proportion of patients (<20%) with a phenotypic sensitivity score (PSS) equal to 0; PSS was  $\leq 2$  in 62%, 77% and ~82% of patients in the MOTIVATE, BENCHMRK and DUET studies respectively [1-3].

In the DUET studies, etravirine plus optimised background regimen (OBR)– which included darunavir – achieved a significantly higher proportion of patients with undetectable viral loads at Week 48 compared with OBR alone, 61% vs 40% respectively ( $p < 0.001$ ) [1].

Similarly, at Week 48 in BENCHMRK 1&2 where ~40% of patients included darunavir in the OBR, patients in the raltegravir vs OBR arms achieved undetectable viral loads in 62% vs 40% respectively ( $p < 0.001$ ) [2].

In MOTIVATE 1&2, where darunavir was not included in the OBR, 42-47% of patients in the OD and BID maraviroc arms achieved viral loads less than 50 copies/mL vs 16-18% in placebo [3].

Etravirine may provide 'full activity' in some patients

While etravirine may not have a 'novel mechanism of action' in this group, most individuals can maintain high or partial susceptibility to etravirine depending on their weighted genotypic score. In the DUET studies, 70% of patients had  $\leq 1$  etravirine RAM and correspondingly, 67% of patients had virus with a fold change  $< 3$  (deemed susceptible) [4].

We believe the addition of etravirine to the main recommendations section is justified and supported by robust evidence. Clinicians referring to the BHIVA guidelines for guidance may miss this in the rationale section and

overlook etravirine as a viable treatment option. A small change in the wording of the recommendation could reflect the evidence in a more 'fair and balanced' way, for instance, as below:

We recommend patients with triple class resistance switch to a new ART regimen containing at least 2 and preferably 3 fully active agents with at least one active PI/r (such as DRV/r or TPV/r) and where appropriate ETR, and/or one novel mechanism (CCR5 receptor antagonist or integrase/fusion inhibitor)

Thank you for your consideration.

Sincerely, Dr Michael Aboud, Medical Lead, Anti-infectives, Janssen UK

#### References

1. Katlama C. et al. AIDS 2009;23(17):2289-2300
  2. Steigbigel R.T. et al. N Engl J Med 2008;359:339-354
  3. Gulick R.M. et al. N Engl J Med 2008;359:1429-1441
  4. Vingerhoets J. et al. AIDS 2010;24(4):503-514
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#### Australasian Society HIV Medicine

Thank you for the opportunity to review and comment on the Guidelines. This comments relates specifically to you consideration of the issue of treatment in the context or reducing HIV transmission, section 2.4

These comments are made from the perspective of our policy committees working on HIV testing.

Given there is a lot of information and a number of studies coming to fruition on the test and treat issue. We feel that the recommendation should be a recommendation to have discussion with the patient based on the current (and emerging) literature rather than a good practice point. Presentation of the information and weighing up potential risks should be recommended in all cases. Notwithstanding that any decision to treat or not would be up to the patient.

Also we would suggest clarification as to the upper limit of treatment. If someone is relying on the guidelines then we think it should be clear if there is an upper limit of CD4 at which treatment would not be recommended by HBIVA.

We would also suggest that viral load is discussed at this point and that viral load is measured so as to reinforce issues surrounding the patients infectivity (and thus need to practice behaviour practice to reduce onward transmission).

We have recently released a new HIV Testing Policy. We are making resources available to support the policy and the workforce as it implements it. The new policy makes testing more available and supportive materials are being developed to increase health care workers and their patients to better understand issues of infectivity and transmission. You may want to look at the testing portal [www.hivtest.org.au](http://www.hivtest.org.au)

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#### anyiliang

The Guidelines is important for me Thank you very much

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## Lewis Haddow

On the terminology of HIV Associated Neurocognitive Disorders: Sections 2.1.1 and 6.4:

Where the term “HIV Associated Neurocognitive Disorders” is used, the abbreviation HAND should be introduced. This is probably the most widely-accepted nomenclature [Antinori A et al, Neurology 2007].

Other terms such as HIV-associated neurocognitive impairment (HNI) and neurocognitive impairment (NCI) usually refer to scoring below some threshold on a neuropsychological battery, without comprehensive assessment to exclude other causes and assess daily function. Using the term HAND, or its sub-categories of HIV-associated dementia (HAD), minor neurocognitive disorder (MND) or asymptomatic neurocognitive impairment (ANI) implies that comprehensive assessment has been completed, according to the recommendations of Antinori et al.

Clinical symptoms of HAND:

Section 6.4.1 refers to the character of HAND. It would be more thorough to mention some of the other “classic” symptoms of HAND, such as difficulties with attention and concentration, slowed thought and movement, psychotic and behavioural symptoms, apathy, and movement disorders.

Rate of improvement in neurocognitive function on ART:

Section 6.4.2 provides a rationale for starting ART in patients with MND or HAD. Might it be useful to provide a figure estimating the proportion of patients likely to improve on ART? Figures could be sought in a good review article, but single-study estimates include: 56% after 45 months on thymidine- and indinavir-based regimens [Tozzi V et al, JAIDS 2002]; 53% after 6 months [Robertson K et al, JAIDS 2004]; 47% after median 65 months, although many of these patients were on ART at baseline [Tozzi V et al, JAIDS 2007]; 33% after 48 weeks [Cysique et al, Neurology 2009]. All of these studies had fairly small sample sizes. There are studies in which some patients deteriorated in cognitive function while others improved, further complicating the picture (see for example McCutchan et al, AIDS 2007).

Rather than referring to citations 8, 9 and 10 (an incomplete list of relevant papers), it would be better to cite just the review paper by Al-Khindi et al and a recent similar review by J. Joska et al.

Importance of nadir CD4 count as a risk factor for HAND:

It is an over-statement to say that the association between nadir CD4+ count and HAND is “well described” (section 6.4.2). The authors appear to be claiming that a causal link has been established. The cited study by Ellis et al may be large, and there may be smaller studies with a similar finding (?), but this was a cross-sectional study, and confounding and reverse causality are alternative explanations.

Tailoring therapy and measuring CSF viral load in patients with HAND:

It is very reassuring that the authors are circumspect about the role of the CPE score.

The authors recommend CSF HIV genotyping as best practice in patients with HAD or MND despite ART (section 6.4.4). While this seems reasonable, why not also mention plasma and CSF tropism testing, given the suggested role for CCR5-tropic viruses in the pathogenesis of HAND (see studies by S. Spudich, G. Schnell, and others).

The importance of CSF viral load should not be over-stated. Section 6.4.4 states “data from cohorts of untreated HIV-infected subjects would suggest CSF HIV RNA to be greater in subjects with HIV-associated dementia and cognitive decline”, citing two studies from the 1980s. These early studies are of limited relevance to ART-treated

patients. The evidence that CSF viral load is predictive of HAND in treated patients is scant. Cases of “compartmentalized” HIV (detectable in the CSF, undetectable in the plasma) are described in case reports and case series only. Work by Spudich et al and Eden et al gives the prevalence of detectable CSF viral load in asymptomatic, treated patients as 8-10%.

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### Kevin Kelleher

FYI refer <http://www.jiasociety.org/content/14/1/6> ,  
<http://www.sigmaresearch.org.uk/go.php?reports/report2009e/> ,  
<http://www.nice.org.uk/Search.do?x=0&y=0&searchText=hiv&newsearch=true#/search/?reload> , <http://forum-link.net/board/viewforum.php?f=1> ,  
<http://www.londonscg.nhs.uk/>,  
<http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0015677> ,  
[http://www.unaids.org/en/media/unaids/contentassets/documents/document/2011/20110523\\_manual\\_costin\\_g\\_HIV\\_facilities\\_en.pdf](http://www.unaids.org/en/media/unaids/contentassets/documents/document/2011/20110523_manual_costin_g_HIV_facilities_en.pdf) ,

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### Jason Mao

It is nice to have the documents in practice due to great work of the Treatment Guidelines Writing Group.

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### Tristan Barber

Many thanks to the whole Writing Group for these excellent guidelines. Just two small comments.

First, on p8 I wonder if the estimate of those living with HIV (and the proportion undiagnosed) could be referenced?

Second, with what to start in treatment naive subjects (page 22) would it be worth highlighting which treatments are not recommended as once daily?

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