BHIVA guidelines for the treatment of HIV-1-infected adults with antiretroviral therapy 2015

Comments received during the public consultation (June–July 2015)

1.	Bridie Howe from Dept. GUM, City Hospitals, Sunderland	I would like to recommend a list of abbreviations, as though the first use of the abbreviation has usually been preceded by the full term, it would make it easier for people looking at small sections to find. In some cases there is no explanation of the abbreviation e.g. PHI, WT virus, antiviral drug abbreviations, esp the new ones such as DTG. While these may be obvious to people who have been in the field for a while, this document is used by and available to patients and practitioners new to the speciality, such as myself (ST4 in GUM). The following comments are mostly copy editing. I hope they are helpful. There is inconsistency of formatting of the references in different sections - both in the reference listings and also in the citations. e.g. section 4.2 references cited as [1] and listed as 1. Author, Reference but in section 4.3 they are cited as1 and listed as 1 Author, Reference . Why are bullet pointed comments in a smaller font, including the recommendations, which surely should be at least as prominent as the other text? Auditable measures: these subsections are sometimes given their own subsection number, sometimes not, sometimes in blue colour, sometimes black, sometimes bold sometimes italics - I would recommend standardizing Cover page - Authors: What does the "†" refer to in front of M Fisher? Clarified Table of Contents: Where is point 2.0 etc? - i.e. why isn't Involvement of PLWH in decision making point 2.0? Section 2 has now been added

		1.2.3 Grading: to keep it consistent "Grade D evidence…." should be in a new paragraph. This also makes it easier to find if scanning through. 1.2.5 should read "The following measures have or will be…" - or replacing / 4.1.3 References 1, 15 and 17 are incomplete: 1 and15 - which BHIVA 2013 and 2008 guidelines respectively?; 17 - when was this accessed etc? 4.4.3 Reference 15 - which NICE guidance? 5.3.1 - double bullet points accidental? 5.5.2 "where there is need to avoid abacavir or and tenofovir (2A)" - shouldn't this read "where there is a need to avoid abacavir and tenofovir (2A)". Also is this whole section supposed to be bold? 6.1.2.2 Box 6.1 - should this be in a box? 6.1.5 References 12 and 14-23 are out of line 6.3.2.2 The headings "Within Class", "Switching from PI" etc. in this section are not obviously headings and are not in keeping with the formatting elsewhere in the document. I would recommend justifying to left without indent. 6.3.3.2 Same applies as above for the heading "PI Monotherapy as second line…" 6.3.3.3 Reference 1 in different font to rest 6.4.1 - in different font 6.4.2 - in different font 6.4.3 - in different font and References in bold Presumably the highlighted text in sections 5.4.2 and 7.2.2.1 and 7.3.2.1, 7.4.2, 7.5.2 will be altered as required BOX 7.1, 7.2, 7.3 - Should these be in boxes? 7.6 References in different format and font 8.2.2.1 The Recommendations and Rationale in this section don't have their own subsection number as they do in the rest of the document. 8.2.2.2 As 8.2.2.1

		8.2.3.1 As 8.2.2.1 and also Rationale is in black instead of blue as elsewhere 8.3.1.1 Same as comment for section 6.3.2.2 8.6.5.2 I recommend adding RCT= randomised controlled trial, alongside Co = cohort study in the table 1 description. This section uses superscript to identify citations, which differs from the rest of the document which uses [1] style- is this intentional? 8.7.3.2 Similar to 6.3.2.2 comment, but here it is also in bold italics and different font 8.9 I'd suggest numbering the subsections to make it consistent with rest of document. The references after 23. are not numbered and are in a different font size 8.11 - font size is larger in this section. 8.11.2.1 and 8.11.3.1- the text in the paragraph should be in black not blue, for consistencies sake. Thank you for your thorough and helpful comments – these have all been addressed in the revision
2.	Gilbert Simwapenga from Mahatma Gandhi Memorial Clinic	Working an ART clinic starting anyone on ART immediately after one is found living with HIV or suffering from HIV reduces such a one from having other clinical conditions. Those thst started in twenty ten are showing no signs of other assassociated illnesses. Sincerely Yours, Gilbert social worker Thank you
3.	Andrew Hill from Liverpool University	1. Section on 3TC versus FTC does not include the results of two randomised trials directly comparing these two drugs (one is unpublished) which showed no difference in efficacy between them. This is much stronger evidence of equivalence than the Dutch cohort, which has many flaws. WHO recommends TDF+3TC based on this evidence. Happy to send more details if needed. Thank you – these have been reviewed and incorporated/considered by the section by the section authors. We have emphasised the potential issues with the Dutch analysis and changed the wording of the concluding sentence slightly. This issue will continue to be reviewed at each update.
4.	Andrew Hill from	Section on EFV does not include details of the ENCORE-1 trial, which showed equivalent efficacy for the 400mg dose with trends for lower adverse event rates. 96 week data just published in Lancet Infectious Diseases

	Liverpool University	We agreed at the start of this update to only consider licensed agents and doses – to be re-considered at next update
5.	Andrew Hill from Liverpool University	Section on PI/r + 1NRTI treatments - mentions that the Kalead study "failed to show non-inferiority" but it was very small anyway (152 patients total), and the response rates were very similar in the two arms: 51% and 53%. Also the results from the OLE and SALT studies of PI/r + 3TC versus triple drug control show slightly higher efficacy rates - overall there is non-inferiority of PI/r + 3TC versus triple combination treatment. As a switching strategy, this could avoid the adverse events of TDF or ABC Thank you and sorry for this oversight – we have clarified the Kalead results in the text and added a section on dual ART to the switch section
6.	Guy Baily from Barts Health	On time to start: I think the wording around offering treatment on the basis of the START findings is excellent, but I wonder if we need something between the very gentle 'when they are ready' of 4.1.1 and the 'must start within 2 weeks' for advanced pts in 4.2.1 Is there not still a point around 300 or 350 where pts should be strongly encouraged to start even if inclined to prevaricate? Thank you - we have discussed the subtleties of the wording extensively and have elected to not add back any CD4 thresholds, mainly based on the lack of relationship between CD4 and clinical events in START.
7.	Michael Harkin from THT Scotland	Looking at your proposed changes to HIV guidelines I am disappointed that your organisation has asked for comments by the 19th July. This date is before the guidelines will be presented at an HIV conference. Surely asking for public comments to be delivered to you for consideration / collation the day before such a conference does not give you as a public body time to understand the UK publics feelings and concerns. Looking at your proposed changes of tried, tested and trusted front line hiv medication to change to now promote newer medication that is not so well known by the public could cause anxiety and concern one those who are currently adhering to a drug regime which for them and their HIV practitioners is working will not be conducive to either patient or practitioner. Come on BHIVA, you are there for the UK public, you are there to accept our feedback and responses in plenty of time to show our representation and actually be consider as important. I write this personally as an individual living with HIV who also works in health promotion for a national HIV charity in the UK. I support people living with HIV, predominantly MSM but also the BME community as an advisor to a recently formed charity in Glasgow. I am a member of UK-CAB snd SHIVAG amongst other HIV organisations.

		I look forward to your response and consideration. Thank you– we addressed these important comments by email and at the community consultation
8.	Paul Rafferty from Belfast Trust	I would like to comment on the preferred and alternative treatment table. This should be more consistent. If efavirenz is an alternative due to side effects only then Atazanavir should be classed as alternative also. If abacavir/lamivudine is preferred in combination with Dolutegravir, should dolutegravir be an alternative treatment also. I think there is no longer a case for the preferred and alternative table since the contents of the alternative are singular and not straigtforward with the emergence of the kivexa/dolutegravir STR. There should be a list of recommended backbones (Truvada/kivexa) and recommended third agents (including EFV) leaving the choice up to the clinician depending on the individual presenting patient. Apart from this the guideline is an excellent learning tool and the attachments for swallowing/renal/food are an excellent resource Thank you – we have clarified some elements of the table. The Writing Group did not rate jaundice to be a critical outcome which is why atazanavir remains preferred based on our GRADE analysis. We accept that we have downplayed the potential impact of jaundice on PLWH and have added a statement about the potential distress and stigma of this side effect. We do not say that Kivexa is preferred with DTG, simply that when Kivexa (which remains alternative for more than one reason as outlined in the text) is used with DTG t can be used at any VL. The point regarding agents vs regimens is important and will consider regimen-based recommendations for the next update. We disagree that we do not need preferred/alternative – the meanings of these are clearly defined and remain relevant.
9.	Alan Smith from Gilead Sciences Ltd	Many congratulations on the latest update currently out to consultation. The document will be an excellent resource to clinicians. Thank you This represents the last major guidelines update before Tenofovir alafenamide (TAF) is expected to become available. We therefore suggest that some minor changes to terminology to clearly distinguish where TDF may be different from TAF. In this context the document already generally uses "tenofovir" and "TDF" appropriately. However, as clinical trial data have shown safety differences between TDF and TAF we suggest minor wording changes to avoid potential confusion. These will not change the current interpretation but will mean the advice remains clear and accurate when TAF is available (or added to the guidelines). The suggested changes are found in the following sections. 8.5.2.1

		Changing tenofovir to TDF (single mention) 8.5.2.2 Changing tenofovir to TDF (both of 2 mentions) 8.5.3.1 Changing tenofovir to TDF (both of 2 mentions) 8.5.3.2 Changing tenofovir to TDF (all of 6 mentions) 8.11.3.2 ii Changing tenofovir to TDF (single mention) Best wishes Alan Thank you for highlighting this – we have made the recommended changes to the revision
10.	George Andrew Rodgers from H.A.D. (HIV And Diabetes Support)	Still no guidelines around AVR's/diabetes. I don't know which PDF file to attach to this. Thank you – at the community consultation we discussed that some work on this topic is underway and we will review the need to include diabetes in the next update. The issue has been reviewed before but in the absence of a clear relationship between modern ART and diabetes developments it was not included this time.
11.	Melinda Tenant-Flowers from King's College Hospital NHS Foundation Trust	Looking good! Thank you Section 5.4.2 small typo ref 19 should be EFV vs DTG not DTC Switching ART, still confusion among colleagues in several centres as to whether if V/L >100,000 pre ART, and patient well controlled but requires a switch for clinical reason e.g renal impairment, EFV side effects Is it safe to switch to ABC or RILP. I think this requires spelling out v clearly. Thank you – the table and the switch section have been amended to emphasise the issue regardless baseline VL and the typo has been corrected.
12.	Anna Goodman from Guys and St Thomas Trust	This section on 5.0 could read clearer: Use recommended only if baseline VL is <100 000 copies/mL: RPV as a third agent; ABC and 3TC as the NRTI backbone;

		ABC and 3TC can be used at any baseline viral load when initiated in combination with DTG (with the exception that in HBV-coinfected individuals ABC/3TC should not be used without TDF or entecavir also) I think a separate symbol for each of rilpivirine and kivexa would make the text clearer. Thank you – this has been clarified accordingly
13.	Dr Sadat Quoraishi from AbbVie Ltd	Thank you for the opportunity to comment on the draft 2015 BHIVA guidelines for the treatment of HIV-1 positive adults with antiretroviral therapy. We note that lopinavir/ritonavir (LPV/r) has been removed from the list of alternative 3rd agents. Section 5.4.3.8 (Previous alternative 3rd agents) states that "LPV/r may be an important option for some individuals such as those with PI resistance mutations and contra-indication to DRV/r." We believe that having this statement far removed from the main third agent recommendations may lead to clinicians not being aware of the alternatives to DRV/r in this patient group. We therefore suggest the statement is placed underneath section 5.4.2 (Rationale) as a footnote. We also believe the statement should be placed as a footnote to the table in Section 5.1 (Summary recommendations). Thank you for your comment – we reviewed this issue at the post-consultation writing committee meeting and we stick to preferring DRV/r in this context – these guidelines do not address specific switches for toxicity and we felt that acknowledging the role of LPV/r in the text was sufficient – this was echoed at the community consultation In Section 7.3.2.3 (First-line treatment failure on a ritonavir-boosted protease inhibitor-based two nucleoside reverse transcriptase inhibitor regimen with or without protease inhibitor resistance), there is the statement "Where PI/r mutations exist, DRV/r is the preferred agent (unless resistance is likely) and inclusion of an INI, ETR, or maraviroc (if R5 tropic virus) as one of the additional drugs should be considered." Following this statement we believe it is important to reiterate that if DRV/r resistance is likely then LPV/r may be an important option. This would ensure consistency with the recommendations in Section 5 mentioned previously and would ensure readers would not have to refer back to that section. Thank you - we have added a sentence to emphasise that where DRV/r is not an option, other PI including LPV/r and TPV/r may be considered Thank you.
14.	Simon Collins from HIV i-Base	Please find the following comments relating to sections 1-7, plus two of the appendices. Timeline for comments Given the lengthy process for this update - over three years - to limit the comments period to three weeks and to have a deadline immediately prior to a major HIV conference. There was a 4 week consultation and, for UK-CAB members this was 5 weeks, consistent with BHIVA guidelines procedure

		This is especially important given the significant changes in withdrawing the CD4 criteria treatment from previous 350 based, until now, on a press release from the START study that itself has no peer review process. Acknowledged but there was a caveat that if the START results led to any significant change in the guidelines the consultation would be repeated. The impact of the START study - dependent on full results to be presented at IAS - having implications throughout the whole draft guidelines. Agree – all sections should have been revised and this will be double-checked during the consultation review process The current draft has only been change to result the START results in the most obvious sections discussing CD4 criteria. Many other sections, including discussions on the approach to starting treatment - likely to have been written prior to the START results - have not been thought through for the implications of the results and the new BHIVA recommedations. This jumps out in quite a few places. The whole guideline has been reviewed to ensure consistency – where there remains emphasis on particular conditions this is to emphasise where immediate, as opposed to 'when ready' ART would be indicated and the conditions where, if NHSE do not support ART at all CD4, ART is recommended regardless Other research at IAS, including HPTN 052, might be just as important to consider. Thank you - this was reviewed at the post-consultation community consultation and writing committee meeting and other than START no other IAS studies were deemed of significant importance to add at this stage Format for draft It is a standard requirement that guideline updates clearly highly all changes. This is not part of the BHIVA guideline development manual – we are very happy to review this process prior to the next update. By not doing this, the process on commenting on changes is made considerable more difficult. More importantly, it becomes difficult to see at a glance where important key issues either have or have not been changed. Acknowledged – for review In my opinion, this limits the validity of the consultation and comment exercise. As above Timeline for update The length of time taken for the update - approaching three years - and the various missed deadlines for draft versions has been a community concern since the first guidelines were produced in 1998. The guidelines are updated every 2 years and there was an interim update in Nov 2013. There had therefore been a one year delay – this has also been raised a concern by the community reps, and others, on the writing panel and we propose a review of the writing

		process prior to the next update to address this. Even if the full guidelines are not reviewed annually, additional statements could be added to reflect important changes form key research and new drug approvals in closer to real time. We agree which is why there was a 2013 update on RPV and EVG/COBI The previous guidelines stated that this should have been in 2014 and it is unclear why BHIVA don't employ a part-time freelance medical writer/research to support the writing group. As above – has been suggested by the community reps on the writing group already and will be discussed at meeting outlined above Although the 2015 draft says a future update will be in 2017, it wold be helpful to have a statement that the guidelines group will comment promptly on any newly approved drug - even if this is a qualifying document and not a full revision. This is in place – see section 1.2.6 General comments The opportunity to comment on this draft is appreciated. Overall these look like good guidelines with perhaps the most significant changes for ten years in respect to starting treatment and choice of drugs. Thank you Although considerable work has gone into updating some of these sections, there seemed to be a missing discussion on efavirenz. This will be how to balance no longer being first-line preferred combination with the potential cost pressure from use of generic efavirenz. In a similar way the FDC vs separate dose discussion is not resolved in the context of Atripla. This was discussed at length during the writing process for the draft and post-consultation – we reviewed the introduction where cost is discussed and, considering that we have emphasised that cost-effectiveness remains beyond the guideline remit at present, will not expand cost discussions further. We will continue to review this issue carefully Section 1.0 A global comment is to consider deleting "the Writing Group thinks/believes etc" form all recommendations for the whole document. As a term this is unnecessarily. The guidelines as a document are produced this group so everything is based n their views. Qualifying so many of the recommendations this way makes the document seem less professional. Thank you – this has been revised and the use of 'the writing group' minimised Section 2.0? This is missing from the online draft. If this is to be recommendations and auditable outcomes, they need to be available for comment as with other sections. This is a summary of all the recommendations and auditable outcomes

		and will be added. Section 3.0 It is good to see reference to impact of social and economic factors on clinical outcome. Section 4.0 4.1.2 - delete "our" - and throughout - to make this less personal. Agree, amended accordingly - Previous setting at 350 was based on evidence from RCTs including HPTN 052 and not just cohort data. HPTN052 was referenced in the 2013 guidelines only in the context of transmission, not when to start - Perhaps qualify that conflicting results from cohort studies was on whether or not earlier treatment had additional benefits and did not suggest that it might have additional risks. Reviewed and we did not feel that more discussion of the old guidelines would add to the new recommendations - More importantly, this section is likely to benefit from significant rewriting when results from START are presented, especially if they are also published in a peer reviewed journal. Given the GRADE system is based on quality of evidence and START is and RCT, the full results need to be evaluated for inclusion in the 2015 BHIVA guidelines. The section has been reviewed post-publication of START and no major changes deemed necessary 4.1.3 Refs will need to be updated to include START and HPTN post IAS. START updated, HPTN052 update not considered necessary at this stage 4.3.1 - Primary infection Here - and throughout - the psychological impact of starting treatment is emphasised as a negative intervention in terms of stress (and not referenced) when in practice, from a community perspective, starting treatment is often a highly positive response to taking control. This is in addition to report that coping with a diagnosis is easier after achieving undetectable viral load that helps normalise HIV more quickly. The PHI section needs to be rewritten based on full results form START and its implications. The second para bullet list doesn't consistently relate to the introducing sentence for medical criteria. Many people actively want to start treatment and if anything current UK medical practice blocks this.

		References: Parsons V et al. UK clinicians' approach to ART in primary HIV infection; comparison with the BHIVA guidelines. 21st BHIVA, 21–24 April 2015, Brighton. Oral abstract O13. Parsons V et al. Attitudes, beliefs and acceptability towards early ART amongst men who have sex with men (MSM) recruited to a UK cohort of HIV seroconverters. 21st BHIVA, 21–24 April 2015, Brighton. Poster abstract P33. The pros and cons table needs to be balanced to equally represent various factor supporting early treatment in PHI. Given the expanded references for this section and the focus for potential benefits of very early treatment (especially within 3 months of diagnosis) - balanced by the recommendation of earlier treatment in chronic infection - it is disappointing that there is not an expanded narrative to discuss these areas. In the interest of space it is difficult to expand on all aspects here, there is clearly RCT data that for all individuals diagnosed HIV+ immediate ART has been shown to confer lob-term clinical benefit over deferral but specific factors around PHI support a more expedited ART initiation process, however these studies are small observational or RCT trials not powered to clinical endpoints or survival but to research reservoir evaluation endpoints which are of weaker evidence for clinical guidelines. I have added in this comment to the current draft This is a critical access issue in terms of patient choice. An additional UK ref for longer term benefits was presented at BHIVA 2015: Kinloch S. Enhanced immune reconstitution with initiation of ART at HIV-1 seroconversion (PHI). 21st BHIVA, 21–24 April 2015, Brighton. Oral abstract O7. Agreed and there have been many other presentations on this outcome too which have also been included in the references. The guideline could perhaps highlight that ongoing UK research includes studying treatment in PHI. The guidelines could also highlight the importance of referring pateints diagnosed within 6 months of infection to the UK HIV Seroconvertor's Register. Simon, thank you for these comments the table and text have been amended to incorporated this and the references added 4.4 TasP Consider changing the first bullet to two separate points. The rational fro this is that come UK doctors are using their

		evaluation of current risk of onward transmission to impact the offer of earlier treatment. (see earlier ref: Parsons V et al. UK clinicians' approach to ART in primary HIV infection; comparison with the BHIVA guidelines. 21st BHIVA, 21–24 April 2015, Brighton. Oral abstract O13.) This has an impact in terms of someone's future social response. Amended – reference not added at this stage – will e considered in next literature search 4.4.1.1 - Please delete "indefinitely" from bullet 4. Removed - Please use "serodifferent" consistently though the guidelines - the last bullet here reverts to serodiscordant. Amended, thank you - Perhaps includes a few more positive bullets points about treatment, including that it is relatively easy to modify treatment if there are side effects etc. Thank you – clinical benefits, low risk adverse events and option to switch have been added 4.4.2 para 4 - these were "gay couples" not MSM I have scoured the paper and the supplementary appendix and cannot find MSM nor 'gay couples', so I have changed the sentence so state that 97% were heterosexual para 5 - perhaps reword that condoms are recommended "if there is a concern about STIs or pregnancy". If there are not these concerns then there is no medical reason to use condoms. After lengthy discussion at the community consultation the wording has been amended and agreed at the writing committee meeting para 5 - reference a study from 2007 for mean time to viral suppression is not good enough. This section should reflect faster suppression with integrase-based combinations -especially as these are now strongly recommended for first line therapy. Thank you – this has been reviewed and new references added Globally, the guidelines should check fro similarly archaic references that are there for historical reasons but that have been updated by more recent data. This approach to relevant references is important Thank you – references have been reviewed Section 5.0 - What to start 5.1 - Overall - the significant changes to preferred first combinations based on better efficacy results with more recently

		approved drugs, including integrase inhibitors is welcomed. Thank you - delete references to "the Writing Group" as qualifications for recommendations. Everything in the guidelines is "in the view of the writing group". If it is needed for methodological reasons then there is no need to capitalise. As per previous response - It perhaps needs to be clearer that ABC//3TC is a preferred backbone when used with dolutegravir. However resolved in the text and table, It does not seem appropriate for this to be a footnote in the table. ABC/3TC is not a preferred backbone – with DTG the baseline VL caveat does no apply but ABC/3TC remains an alternative 5.3.1 - as above, clarifiy that ABC//3TC is a preferred backbone when used with dolutegravir. It is not that the caution dosen't apply, the data supported actively prescribing these RTIs. The table has been amended but ABC/3TC is not a preferred backbone regardless of 3rd agent – it is alternative based on the GRADE analysis – the difference with DTG is that baseline VL is not an issue 5.3.4 - Given the 12 references for the discussion about 3TC vs FTC it is surprising that this section reaches an opposite conclusion to the analysis from Ford et al in commentary to ATHENA results in CID. Ref: Ford N et al. Comparative efficacy of lamivudine and emtricitabine: comparing the results of randomised trials and cohorts. Clin Infect Dis. Advance access 3 November, 2014., http://cid.oxfordjournals.org/content/early/2014/11/03/cid.ciu767.full.pdf (PDF) This section has been reviewed in the light of this, and other, comments and the overall conclusion unchanged 5.4 - very supporting of the decision to drop recommendations to use older drugs that are not supported by efficacy and safety data compared to recently approved options. Thank you 5.4.3.7 The efavirenz results from D:A:D (ref 31) could perhaps be modified to reflect the conclusions from the study that emphasied that non-finding a link with suicide should not be interpreted as a lack of causative effect given this is well document - but more accurately, that health workers were appropriately managing this risk in prescription practice - ie alternative dosing to those at highest risk and effectively switching those who experienced symptoms. Sentence added

		6.0 support etc 6.1.2.1 This seems pretty disconnected form the current recommendations. What about integrase inhibitors etc. Thank you – amended 6.1.4 Final sentence should perhaps refer to low cost generics and not to their cost effectiveness if this hasn;t formally been studies. Thank you – amended accordingly Section 7.0 - treatment failure 7.5.1 - Good to see the reference to importance research. Several compounds in development could potentially be important for people with MDR HIV - especially with new classes - maturation, gp-120 inhibitors etc. Thank you Appendix - food chart - Great this is included. - Please could all drugs be treated similarly - see ATZ vs DRV. It would be more direct to always give approximate impact on drug levels rather than rely on general terms like "enhance" without giving data. - Atripla/efavirenz - concerned that this doesn't specifically reference high fat rather than just food. This is a important information for people taking treatment to understand. Taking with food has no impact on PK if this is low or zero fat content - and taking meds it something in your stomach helps. - Including a comment on the type of food, including when this makes no difference, would be a very helpful addition for all drugs with a food interaction. - Use of CAPS - if some words are going to be capitalised - "OR" - it might be clearer to use caps for WITH and WITHOUT as a global comment. - DRV - perhaps emphasise that food is required even with the boosting effect of RTV - also for ATZ. - Eviplera - that caution about taking without food could be stronger - ie "will" instead of "may". Also for Eviplera, I thought Gilead reported lower calorie count was needed for the FDC compared to when rilpivirine is taken as a single drug. Is this because food increases TDF levels?

		- Eviplera and rilpivirine should have similar text, if the food effect described is based on rilpivirine, unless the lower calorie requirement is being referenced. - Atripla and tenofovir should have the same text when referring to TDF. - Atripla and efavirenz should have the same text when referring to efavirenz Thank you – this has ben updated accordingly Appendix - renal dosing - Great this is included. - Comment on format - black writing on red background is unreadable on visually (access issue) and practically (on greyscale printouts. Please either reverse out text or use a different graphic solution. Thank you - changed
15.	Dr Peter Cowling from British Infection Association	The BIA is content with these guidelines Thank you
16.	Adyb BAAKILI from Medical BMS	Dear writing group, Thank you for the opportunity to submit the comment we may have. I want to inform the writing group that the European Commission (EC) decision for the Marketing Authorization of EVOTAZ (ATV/COBI) has been adopted 13 July 2015. EVOTAZ is indicated in combination with other antiretroviral medicinal products for the treatment of the HIV-1 infected adults without known mutations associated with resistance to atazanavir. EVOTAZ continues to offer the proven efficacy and safety of boosted-atazanavir, in the form of a once-daily, simplified dosing regimen. Additionally, Cobicistat (Tybost) has been recently commissioned by NHS England which provides an alternative booster to ritonavir. KR, Dr Adyb BAAKILI HIV Medical Manager BMS Thank you – we have added a section on cobicistat

17.	Rishender Singh from Janssen	Dear BHIVA guidelines writing panel, Janssen appreciates the opportunity to consult on the draft BHIVA guidelines for the treatment of HIV-1 positive adults with antiretroviral therapy 2015 and would like to commend the writing committee on the methodology employed that provides a transparent summary for health care professionals, patients and policy makers. Please see below for detailed comments by section: SECTION/PAGE: Section 5.0 what to start (page 22) BHIVA GUIDELINE COMMENTS: None JANSSEN COMMENTS: This section makes no reference to the accessibility of darunavir/cobicistat FDC (EMEA approval: 19/11/2014) and Janssen believes its availability should be highlighted given the bioequivalence data versus DRV/r to offer patients an additional option that reduces pill burden when taking DRV as a third agent. REFERENCE: Rezolsta SmPC. Kakuda et al. J Clin Pharmacol 2014. Kakuda TN, et al. Antivir Ther 2014. Kakuda et al. Cobicistat-boosted darunavir in HIV-1-infected adults: week 48 results of a Phase IIIb, open-label single-arm trial AIDS Research and Therapy 2014, 11:39 doi:10.1186/1742-6405-11-39 A section on cobicistat has been added SECTION/PAGE: Section 5.4.3.2 recommendations (page 28) BHIVA GUIDELINE COMMENTS: This section states: for the comparison between DRV/r and RAL in the three-arm ACTG5257 study [20], overall virological response was significantly higher for DRV/r (OR 1.83 [95% CI 1.16---2.89] at 96 weeks in favour of DRV/r; p=0.009). JANSSEN COMMENTS: Janssen believes this is incorrect and should read: When tolerability and virologic response are considered together, RAL-based therapy was superior overall to both PI-based therapies and ritonavir-boosted DRV was superior to

		ritonavir-boosted ATV. Apologies – we have double-checked the graphs and the OR is correctly quoted but RAL and DRV/r were the wrong way round on the graph. This comes from Lennox 2014, Figure 3 (ITT analysis) and the adjacent text: "The proportion of participants with an HIV-1 RNA level of 50 copies/mL or less at 96 weeks by ITT analysis (regardless of treatment status) was 88.3% for ritonavir-boosted atazanavir, 93.9% for raltegravir, and 89.4% for ritonavir-boosted darunavir (Figure 3, top)." The number of participants contributing data at 96 weeks (from figure 3) are: 515, 526 and 518. So numbers of patients with copies <50/mL at 96 weeks are: 455/515, 494/526 and 463/518. REFERENCE: (Reference: Lennox JL, Landovitz RJ, Ribaudo HJ et al. Efficacy and tolerability of 3 nonnucleoside reverse transcriptase inhibitor---sparing antiretroviral regimens for treatment---naïve volunteers infected with HIV---1: a randomized, controlled Equivalence trial. Ann Intern Med. 2014 Oct 7;161(7):461---71.) SECTION/PAGE: Section 5.4.3.3 recommendations (page 28) BHIVA GUIDELINE COMMENTS: This section states: in the FLAMINGO study - for important outcomes there were significantly more clinical serious adverse events in the DRV/r arm (OR 2.00 [95% CI 1.05---3.80; p=0.03]). JANSSEN COMMENTS: Janssen believes this is incorrect and should indicate that more clinical serious adverse events are seen in the DTG arm. Apologies, you are right and this has been corrected REFERENCE: Molina JM, Clotet B, van Lunzen J et al. FLAMINGO Once---daily dolutegravir is superior to once---daily darunavir/ritonavir in treatment---naïve HIV---1---positive individuals: 96 week results from FLAMINGO. J Int AIDS Soc. 2014 Nov 2;17(4 Suppl 3):19490. SECTION/PAGE: Section 6.3.2.2 switching rationale (page 47) BHIVA GUIDELINE COMMENTS: This section states: Switching in virological suppression to RVP from PI maintained suppression, was safe and with or

		without K103N, had a high response rate. JANSSEN COMMENTS: This should read RPV not RVP. Thank you - corrected REFERENCE: None SECTION/PAGE: Section 6.3.3 protease inhibitor monotherapy (page 50) BHIVA GUIDELINE COMMENTS: None JANSSEN COMMENTS: Janssen believes that data from the PROTEA study will be beneficial if included in this section. Thank you – PROTEA has been included REFERENCE: Week 48 efficacy and central nervous system analysis of darunavir/ritonavir monotherapy versus darunavir/ritonavir with two nucleoside analogues. Hill, Andrew M.; Antinori, Andrea; Clarke, Amanda; Svedhem-Johanssson, Veronika; Arribas, Jose; Arenas-Pinto, Alejandro; Fehr, Jan; Gerstoft, Jan; Horban, Andrzej; Clotet, Bonaventura; Ripamonti, Diego; Girard, Pierre-Marie; Moecklinghoff, Christiane. AIDS 2015. SECTION/PAGE: Section 8.6 Cardiovascular Disease 8.6.4.1 (page 89) BHIVA GUIDELINE COMMENTS: The section states BHIVA recommend ATV/r as the preferred PI in individuals with a high CVD risk. This has changed from previous 2012 guidelines which simply recommended against the use of LPV/r and FPV/r. JANSSEN COMMENTS: This appears to be based on the data from D.A.D. cohort where no association has been reported between ATV use and MI but not enough data exists yet to analyse a link with DRV.

		Furthermore the ACTG 5257 study showed no significant difference between ATV and DRV in terms of rise in plasma lipids. Whilst there was a difference in progression of cIMT between the two drugs, with ATV showing slower progression, BHIVA stated that it is unclear if this translates to a reduction in CVD risk. Janssen believes there is currently little evidence to exclude DRV as a favourable option in patients with a high risk of CVD. Reviewed –though there is no evidence of harm on DRV there is evidence of lack of harm on ATV so no change required REFERENCE: Monforte A, Reiss P, Ryom L, et al. Atazanavir is not associated with an increased risk of cardio or cerebrovascular disease events. AIDS. Jan 28; 2013 27(3):407–415. Ofotokun I, Ribaudo H, Na L, et al. Darunavir or atazanavir vs raltegravir lipid changes are unlinked to ritonavir exposure: ACTG 5257. In: Program and abstracts of the 2014 Conference on Retroviruses and Opportunistic Infections; March3-6, 2014; Boston. Abstract 746 Stein, J.H., H. Hodis, et al.(2014)."Prospective randomised clinical trial of the effects of three modern antiretroviral therapies on carotid intima-media thickness in HIV-infected individuals (aids clinical trials group study A5260S). "Journal of the American College of Cardiology 63(12SUPPL.1): A1322. SECTION/PAGE: Section 8.7 Women 8.7.3.2 Fetal safety (page 101) BHIVA GUIDELINE COMMENTS: This section states: “Approximately 200 or more reports need to be received for a particular compound before data are reported for that compound by the APR.....There are, so far, fewer than 200 prospective reports for DRV, RAL and RPV within the APR and hence no reports on these agents are yet available.” JANSSEN COMMENTS: Janssen believes this section should be amended to include DRV in the list of drugs with over 200 reports without a signal of increased risk of congenital abnormality. The most recently available interim report from the APR included safety data on DRV as there are now 314 reports of 1st trimester exposures to DRV. The APR interim report to the 31st January 2015 states “For abacavir, darunavir, didanosine, efavirenz, indinavir, and stavudine, sufficient numbers of first trimester exposures have been monitored to detect at least a two-fold increase in risk of overall birth defects. No such increases have been detected to date.” Thank you and apologies for the oversight – this has been corrected

		accordingly REFERENCE: Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral Pregnancy Registry International Interim Report for 1 January 1989 through 31 January 2015. Wilmington, NC, Registry Coordinating Centre, 2015. Available at http://www.APRegistry.com (accessed July 2015). SECTION/PAGE: Section 8.10 Bone disease in PLWH in and antiretroviral therapy 8.10.4.2 (page 109) BHIVA GUIDELINE COMMENTS: This section states: Tenofovir (TDF formulation) and protease inhibitors have been associated with low BMD and bone loss in cohort studies [21-¬-25], and use of TDF and lopinavir/ritonavir or any protease inhibitor with and increased incidence of fractures [26, 27]. JANSSEN COMMENTS: DRV was not included in the analysis referenced here for any protease inhibitor. Janssen believe this would be worth stating in the guidelines. Section reviewed with this in mind REFERENCE: 26. Bedimo R, Maalouf NM, Zhang S, Drechsler H, Tebas P. Osteoporotic fracture risk associated with cumulative exposure to tenofovir and other antiretroviral agents. AIDS 2012; 26:825 31.27. 27. Womack JA, Goulet JL, Gibert C, et al. Increased risk of fragility fractures among HIV Infected compared to uninfected male veterans. PLoS One 2011; 6:e17217.
18.	Dr Alistair Paice from ViiV Healthcare	ViiV response to consultation on the draft “BHIVA guidelines for the treatment of HIV-1 positive adults with antiretroviral therapy 2015” On behalf of ViiV Healthcare Ltd we would like to thank you for the opportunity to comment on the draft 2015 BHIVA treatment guidelines. We recognise the complexities of assessing the available evidence and we fully support the 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, with particular focus on Section 5: What to Start.

		Section 4.0 When to start Section 4.1: Chronic Infection • The statement recommending that people with HIV start ARVs at any CD4 count is a significant step towards improving patient benefit. ViiV fully supports this approach. Thank you Section 5.0 What to start Section 5.1 Summary recommendations. • This table might be confusing to prescribing physicians. The recommendations on what to start require reference to several lines of footnotes, which may be overlooked or misunderstood. It is also not clear from the body of this table that DTG +ABC/3TC is an entirely appropriate regimen for naive patients at any baseline viral load, which is consistent with the recommendations in other major guidelines such as DHHS and EACS. As these guidelines present their recommendations as regimens, they are easier to interpret at a glance. We acknowledge this point and will review agent vs regimen based recommendations for the next update – we have clarified the table. ABC/3TC remains an alternative based on the CV risk, the only change is that the VL cut-off is not an exclusion when given with DTG. • It is unclear why ABC/3TC is in the alternative column, based on a statement around results with baseline viral load >100K relying on potentially inconsistent data, and indeed one that is not true for DTG + ABC/3TC. The indication for Kivexa in the Summary of Product Characteristics does not restrict use as a backbone by baseline viral load, although we acknowledge that there is a statement in section 4.4 (Warnings and precautions) in line with the findings of ACTG5202: "The risk of virological failure with Kivexa might be higher than with other therapeutic options." It is alternative based on the fact that VF may be higher (as per the SPC) AND the evidence for increased CVD risk • The stringency of the above approach to ABC/3TC seems at odds to that taken for RPV, which has a license prohibiting use above VL > 100K, but which still appears in the preferred column. This does not appear to be consistent. We make it very clear that RPV is NOT recommended >100,000. RPV was statistically superior to EFV when analyses confined to the <100,000 VL strata and there are no known safety concerns so far (unlike ABC and CVD) • We wonder whether it might be possible to address these issues using one of the following approaches: o ABC/ 3TC appearing in the preferred column, with an asterisk explaining that for baseline VL> 100K, use of DTG as a third agent is recommended, or No - for reasons above o Leaving the table as it is, but within the DTG box in the preferred column, inclusion of a further line stating that it can be used with either a TDF/FTC or ABC/3TC backbone As above – this would suggest that ABC/3TC is preferred, it

		is not Section 5.3 Which nucleoside reverse transcriptase inhibitor backbone Section 5.3.2 Rationale • SPRING-2, SINGLE and FLAMINGO data should contribute to the body of evidence in Section 5.3.2. The efficacy of DTG/ABC/3TC in HIV-infected, therapy naive subjects is based on the analyses of data from two randomized, international, double-blind, active-controlled trials, SINGLE (ING114467) and SPRING-2 (ING113086) and the international, open-label, active-controlled trial FLAMINGO (ING114915). In SINGLE, 833 patients were treated with dolutegravir 50 mg once daily plus fixed-dose abacavir-lamivudine (DTG + ABC/3TC) or fixed-dose efavirenz-tenofovir-emtricitabine (EFV/TDF/FTC). All the patients in the DTG arm received ABC/3TC as the NRTI backbone. In both SPRING-2 and FLAMINGO, the selection of the NRTI backbone was at the discretion of the investigator: the ABC/3TC backbone was used in approximately 40% and 33% of subjects in these studies, respectively. The NRTI backbone choice was non-randomised. In SINGLE backbone comparison are confounded by the difference in 3rd agent • Raffi (AIDS 2015;29:167–174) demonstrated no difference in the efficacy outcomes by backbone when DTG was used as the 3rd agent. In addition the Granier summary of summative results by backbone, using SPRING-2 and FLAMINGO and presented at CROI this year, demonstrated that TDF/FTC was comparable to ABC/3TC irrespective of the 3rd agent used (Granier C et al. 22nd Conference on Retroviruses and Opportunistic Infections, 23rd-26th February, Seattle, WA. 550). NRTI comparison non-randomised • In the analysis for GRADE within the body of the text for section 5.3.2, there was no difference in virological outcome by backbone at 48 weeks or 96 weeks. ACTG 5202 was excluded as reported 96 weeks only – ACTG 5202 drives the difference • The data from ACTG 5202 has methodological queries, such as early withdrawal, which have made the results difficult to interpret. This is clearly acknowledged and discussed in the text already • In summary, the overall evolving body of evidence does not appear to merit leaving ABC/3TC an "alternative" NRTI option. We disagree – based on GRADE analysis of critical outcomes Section 5.4 Which third agent Section 5.4.3.3 Dolutegravir • The wording around the SINGLE study design and results does not make clear that the DTG arm used the ABC/3TC backbone. This is key to understanding why the 'What to start' table recommends that baseline viral load is not an issue with use of ABC/3TC in combination with DTG. The DTG/ABC/3TC regimen demonstrated statistical superiority

		over the 'gold standard' EFV/TDF/FTC regimen at the primary endpoint (48 weeks) whatever the baseline viral load. This is more robust than the results of the post-hoc pooled analysis for RPV (see below) and we feel should be acknowledged. The bullet list of studies at the top of this section already clarified backbones for each study but the body of the text has been amended to further emphasise this. We have emphasised efficacy at all VL. • The statement around FLAMINGO and DRV/r is qualified by a statement about the open label design. This ignores the fact that the study was a fully powered, randomised RCT that demonstrated superiority at a pre-specified endpoint. Superiority and the randomised design are discussed – the lack of difference for other critical outcomes is the main driver for the conclusion and this has been explained in the text already Section 5.4.3.6 Rilpivirine • It is interesting to note that rilpivirine has been placed in the list of preferred agents. We note that: o There is an acknowledgement that in the text of Section 5.4.3.6 that in the three RCTs "there were significant differences in drug resistance and virological failure, both in favour of EFV" But not <100,0000 ie when the drug is used within licence o There is a statement "when analysis is restricted to individuals with a baseline VL less than 100,000 copies/mL there was a significantly better virological response to RPV compared to EFV" This is wrong and has been corrected, sorry ¾ We would question whether this post-hoc pooled analysis is of high enough quality by GRADE criteria to ensure that RPV should be deemed a "preferred" agent. StAR also supports efficacy of RPV at lower viral loads – RPV was superior to EFV at baseline VL <100k Section 6.1.6 Single tablet regimens • Minor typo "DOL". Corrected, thank you Overall, we would like to congratulate the Writing Committee on an important contribution to the management of HIV in the UK. The changes to section 4.1 will make a significant contribution to improving the outcomes for PLWHIV. Unfortunately, the criteria used for placing ABC/3TC in the "alternative" list, compared to placing RPV in the "preferred" list for example, do not appeared balanced. To date RPV has not been associated with an increased risk of CVD It is possible that prescribers referring to the table in Section 5.1 might not get a representative picture of what regimens would have the best outcomes for patients. Table has been amended – recommendations are unchanged We would like to thank you again for the opportunity to review and respond to the draft BHIVA guidelines. If you would like further clarification of any of the above comments, please contact us using the details provided with this

		commentary.
19.	Sarah Radcliffe from National AIDS Trust	Comments from NAT (National AIDS Trust) A. GENERAL COMMENTS NAT welcomes the opportunity to comment on the draft new treatment guidelines. BHIVA guidelines play a vital role in ensuring everyone living with HIV in the UK have access to testing, treatment and care services. Given the technical nature of the guidelines and the substantial changes to the 'when to start' section in particular, it is unfortunate that the consultation period is only three weeks– too short for many community stakeholders to engage fully with the draft. The draft was on UK-CAB website 5 weeks pre-deadline and there has been community engagement from the start of the process – we will review the guidelines process but currently the recommended period for consultation is 4 weeks NAT welcomes the commitment made to consult again if further updates are made in light of the complete START data. We would recommend that this second consultation be of a longer duration. No significant updates were made so a second consultation was not deemed necessary As with previous treatment guidelines, the structure of these guidelines is clear and the section headings use accessible language. Thank you It would have been helpful if the document highlighted or otherwise indicated all sections which have changed – this has made it harder for community stakeholders who are not clinical experts to make an informed and focussed response to the consultation. Agree – to discuss prior to next version The inclusion of the appendices is welcome, in particular the food chart which will be a useful resource for people living with HIV as well as those providing care. Thank you B. COMMENTS ON UPDATES TO THE GUIDELINES 4.1.1 – when to start NAT agrees that it was important for the draft guidelines to take into account the available information from the START study. However, it is important that the whole guideline is reviewed with a view to the full data from START, once these are available. The wording of recommendation 4.1.1 is very clear and strikes a balance between providing access to treatment that will benefit people living with HIV, and acknowledging that treatment commencement is ultimately a personal choice the individual has to make and commit to. Whole guideline was reviewed post-START

		and will be carefully reviewed again post-consultation 4.3.1 – primary infection Currently, the wording could be seen to imply that treatment commencement during primary infection is going to be a cause of additional stress to someone recently diagnosed with HIV. This will not necessarily be the case and so this should be made clear in the final guidelines. BHIVA guidelines will have an important role in helping clinicians have open and informed conversations with newly diagnosed people about treatment commencement – so it is worth revisiting this section when the full START data are available. Commented on below but this has now been incorporated into the table and text for this section reflecting this comment thank you 4.4.1 – prevention The recommendations made here are welcome. However, the order in which they are currently listed gives the impression that the clinician's assessment of risk of transmission takes precedence over the general principle that everyone with diagnosed HIV should be offered treatment if they wish to take it for prevention. The order should be revised to make this clearer. Thank you – amended accordingly NAT, July 2015
20.	Alison Sayer from Renaissance at Drugline Lancashire	We agree with the content of this consultation. It is very important that all aspects of the diagnosis, treatment and advocacy are tailored to holistically support the client. All services involved with the client should collaborate with each other to support the client to the utmost. Of course their domestic situation, relationships, benefits and support network affect their adherence and well being. Thank you
21.	Clive Blowes from Terrence Higgins Trust	Terrence Higgins Trust consultation response to BHIVA guidelines for the treatment of HIV-1-positive adults with antiretroviral therapy 2015 Terrence Higgins Trust (THT) is the UK's largest HIV and sexual health charity, with over 30 service centres across England, Scotland and Wales. THT is a membership and campaigning organisation that works with and advocates on behalf of people living with or affected by HIV. It is also a provider 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 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 and by creating a community forum topic thread on THT's 'myHIV' website. Terrence Higgins Trust broadly welcomes these revised guidelines and in particular • the recommendations for treatment at any CD4 count when the patient is ready • the recommendation for treatment in early primary HIV and the guidance about the pros and cons of such treatment • the recommendation that 'Treatment as Prevention' is offered to all • the addition of NICE guidance around adherence • the changes with regards to which 'third agent' to use. Thank you We would like to express our concern that this consultation is going ahead before the full results of the START study have been presented at IAS conference on 19 July. Our knowledge is currently limited to the headlines of this ground breaking study and thus we are not aware of the full implications of the research. We feel that this restricts our ability to respond comprehensively, particularly around when to start treatment. Acknowledged and addressed elsewhere Despite this, we have a number of comments on some aspects of the guidelines which are detailed below, by section. 3.0 Involvement of PLWH in decision-making We welcome the section on patient involvement within the guidelines but note that there appears to be minimal change in this section compared with the previous guidelines. With the onus now being on the patient being ready to commence treatment, we would like to propose that this section be expanded further. From our experience of working with individuals living with HIV, we believe that it is crucial that individuals starting treatment feel included in that decision. Thank you – section 3 reviewed and signposted in when to start section 3.1 Recommendations THT welcomes the recognition of the important role that community-based advocacy and peer support plays in helping patients be more involved in the decision-making process. We suggest that referral to treatment advocacy services and peer support becomes an auditable output. It is important to actively encourage people to access peer support and the offer should be repeated, especially at times of stress, such as when newly diagnosed, changing

		treatment, becoming pregnant or ageing. Agree - added 3.2 Rationale THT fully supports the recommendation that individuals are able to start treatment when they are ready, after discussion with a clinician. However, we would like more definition around what 'being ready' looks like and how readiness will be assessed by the clinician. Section 3 has been reviewed and in terms of when to start a sentence signposting to section 3 has been added We would like to see this section expanded to state that the clinician must make sure that all the key issues are fully explained to each person. We feel that basic information about how standard triple therapy regimens are configured, including an overview of backbone and third agents, should be given to individuals. This should be explained in the context of the practicalities of starting treatment, such as food requirements, pill burden, employment situation, job role, social life, lifestyle in general and informal support networks. Thank you – paragraph added These are crucial areas that many of our community forum members report are overlooked, and in some cases have resulted in difficulties with adherence and anxiety around whether to start antiretroviral treatment (ART). Food requirements and pill burden are often areas that some struggle with, which could lead to poor overall adherence or 'selective adherence'. Emotional well-being and the assessment of other psychiatric conditions is a key area that could be strengthened with additional good practice points clearly highlighted within the body of the text. This clearly ties in the section 5.0 and the recommendation 'We recommend people with HIV start ART at any CD4 count once they are ready to commit to taking therapy'. Assessment would be part of monitoring guidelines, not ART Many of our service users report difficulties in relation to their emotional well-being in the context of starting treatment, and there are examples where undiagnosed depression and anxiety have resulted in poor adherence, self belief that the decision to start was the wrong one and a questioning of the value that ART can bring to their overall wellbeing. With some of these difficulties in mind, and recognising the power imbalance that may exist between doctor and patient, we would like to recommend that disadvantaged groups, including women and black and ethnic minority groups, are given the option to access advocacy support to assist with decisions about when to start HIV treatment. It is essential that the patient is fully informed about the treatment and how it affects them individually. Discussed at length at community consultation and post-consultation writing group meeting – majority view was that, particularly now auditable outcomes are included, the section on peer support in strong enough; any individual may been additional support.

		4.0 When to Start 4.1 Chronic HIV Infection THT welcomes the decision to amend the current 'when to start' recommendation. This has received much support from our online service users. Thank you However, we are wary that there is no direction on the nadir at which ART should commence from a clinical perspective. We would not wish the phrase 'start ART at any CD4 count' to result in local commissioners/clinicians making decisions based on cost, rather than patient willingness and choice. At any CD4 has been removed to emphasises that we strongly recommend ART for all The comment 'the absolute risk of deferring ART was small in the study' could be interpreted by commissioners/clinicians that delaying treatment until the CD4 cell count is at a level of 350 is still within the remit of the recommendation. Acknowledged and amended Thus we wonder whether greater clarity of the lower limit where treatment should not be further delayed could be provided. Feedback from our community forum members tends to favour treatment earlier than the current position, and a recommendation that treatment should commence at a CD4 cell count of around 500, rather than the current level of 350. More detail from the START study may help to clarify this issue further. Discussed at length – the unanimous view from the community consultation and the writing committee meeting was that, particularly in the absence of association between CD4 and clinical outcomes in START, CD4 thresholds are no longer useful or appropriate – ART is recommended for all and the absolute risk as a given CD4 should form part of individualised decision making 4.3 Treatment Of Primary HIV Infection THT welcomes the recommendation for treatment in early primary HIV infection (PHI) and the guidance about the pros and cons of such treatment. Our online service has noted an increased awareness from a small cohort of individuals asking for information about treatment during primary infection yet little consensus or information being available from clinicians. This guidance will help in this matter. In particular, the inclusion of the following additional criteria is very much welcomed in the treatment of PHI: • PHI diagnosed within 12 weeks of a previous negative test • The pros and cons of early ART initiation with a view to long term therapy should be clearly and sensitively

		presented to any individual diagnosed with PHI. The change in this recommendation will provide a further opportunity for individuals to make informed decisions along with their clinicians, further strengthening the importance of patent involvement in decision about their treatment and care. Thank you 4.4 Impact of treatment on prevention of onward transmission THT strongly supports the recommendation that treatment as prevention is offered to all. This area is important to many of our service users, and it is encouraging that NHS England are providing funding for people living with HIV to commence ART to prevent onward transmission of HIV. Thank you 5.0 What to start 5.3 Which nucleoside reverse transcriptase inhibitor backbone In the 2013 comments to the writing group it was suggested that TDF / FTC and ABC / 3TC could be recommended on an equal footing as there is a common perception that TDF / FTC is the 'gold standard' with ABC / 3TC being somewhat inferior. ABC/3TC is alternative based on differences between the backbones by GRADE analysis and the selected critical outcomes Although the evidence suggests that TDF/FTC is superior from a virological failure perspective there appears to be little mention of the development of the chronic kidney disease (CKD) associated with TDF. Presenting at CROI2015, Mocroft et al (2015) have shown a cumulative increase in risk of CKD with ongoing use of TDF in persons with an initially normal estimated Glomerular Filtration Rate. Reference included, thank you THT would like to propose that this evidence is reviewed against the increased risk of myocardial infraction (MI) as a result of including ABC in the backbone regimen. With the impact of channelling those at high risk of both CKD or MI to the most appropriate NRTI backbone we would like to question whether there is an argument that both NRTI backbone regimens should be placed on an equal footing in these circumstances. ABC/3TC is alternative based on differences between the backbones by GRADE analysis and the selected critical outcomes 5.4 Which Third Agent Atazanavir Whilst it is acknowledged that atazanavir is comparable to EFV, DRV/r and RAL in terms of clinical endpoints (virological suppression, resistance and virological failure) the writing panel also acknowledges that the majority of treatment discontinuation seen with atazanavir is due to hyperbilirubinemia/jaundice.

		it is questionable whether this is 'a well-known, harmless complication' in the wider context as there are many instances where our service users have been concerned about the development of hyperbilirubinemia/jaundice and the impact this has had on their emotional well-being. Some individuals have reported loss of confidence, and self-isolation concerns about being asked about changes to their skin / eye colouration. We have added a line about potential distress and stigma – thank you The recent study by Mocroft et al. (2015) provides an interesting insight into the role atazanavir (and other ARVs) may play in the development of chronic kidney disease over time. Although the risk of developing CKD is low for people with normal kidney function, with fewer than 1% of patients in the large cohort studied developing it, the study found that the relative risk of developing CDK was increased by 320% after 6 years exposure to ATV/r. Reference included, thank you Given that atazanavir is often discontinued because of hyperbilirubinemia/jaundice, and the possible association with CKD, THT would like to ask whether the writing committee might consider a further review of atazanavir as an effective 'alternative' third agent. These were not considered critical outcomes – to be reviewed at next update Rilpivirine The inclusion of Rilpivirine (fixed dose combination Eviplera) as a 'preferred' third agent is welcomed, particularly in light the decision to change the efavirenz to a suitable 'alternative' treatment option. Thank you Dolutegravir Dolutegravir is also a very welcomed addition to the 'preferred' third agent listing as it provides individuals with a greater degree of flexibility as it can be taken with or without food in treatment-naïve individuals, without integrase inhibitor resistance. The practicalities of food requirement and treatment options is often commented upon by our community forum members as a real concern. Therefore both dolutegravir and raltegravir provide additional choice for patients where food requirement is an important consideration. Thank you Efavirenz THT also welcomes the downgrading of efavirenz to an 'alternative' third agent Community representatives have long been concerned about the suitability of efavirenz as a 'preferred' third agent. Out of all the first-line treatment options, efavirenz has received the most attention from our service users. Many of them have reported concerns about starting treatment including efavirenz, with several more reporting on-going sleep disturbance and changes in mood that have not been addressed by the clinical team. It is also welcomed that the writing committee has noted that 'for patients stable on EFV based ART we recommend a review of tolerability, sleep and mood at all visits'. Our service users often comment that whilst they experience

		difficulty tolerating an EFV-based regimen, they are reluctant to change, based on the perception that other more debilitating side effects become apparent with a different drug. Having a regular review with such individuals will be key in helping to alleviate these perceptions. Thank you 6.0 Supporting Individuals on therapy 6.1 Adherence THT welcomes the addition of NICE guidance around adherence. However, it would be helpful to make reference in this section to the value of community organisations, online and face-to-face peer support in supporting adherence. As with section 3.0, THT would like to recommend, or propose a good practice point, that individuals struggling with adherence are provided with a pathway into community advocacy groups and peer support to provide further practical support when struggling with adherence. There is some anecdotal evidence to suggest that these more informal networks of support may elicit further information about the practical implications of adherence outside the clinical setting. We would also like to propose that the writing committee considers the benefits of including nursing staff / pharmacists to also support patients to achieve high levels of adherence. THT believes that it is important to look at standardising new ways and models of ensuring adequate support at the point of initiation of ARV. Investment at this point could result in a greater likelihood of long term adherence Thank you – we have added a GPP as per your comments and added some test re nurses/pharmacists. We have not gone as far as to describe specific models due to wide variation in clinic size, staffing and patient need but could consider this for future guidelines. 6.2 Pharmacology THT recognises that this is a complex area but would like to ask whether the writing committee could provide clearer information about specific drug/drug interactions, including over-the-counter agents that reduce the efficacy of a particular ART. Dolutegravir and cobicistat are good examples of drugs that are impacted by over-the-counter medication . This issue may not always be clear to patients and these agents (such as multivitamins that contain minerals) are often not included in HIV drug interactions charts. Similarly attention should be paid with regard to the use of over-the-counter antacids together with the PPIs, elvitegravir, atazanavir and rilpivirine. We agree and BHIVA will explore, with HIVPA< developing a patient information leaflet with practical advice for PLWH – details DDI advice is beyond the scope of the general ART guidelines. 8.0 Special populations THT applauds the extension of this section and particularly welcomes section 8.7 for ART in women and the additional

		subsections relating to the modification of cardiovascular disease risk factors. Thank you 8.4 HIV-associated neurocognitive impairment THT recognises that neurocognitive impairment remains a significant problem for some people living with HIV. We would like to suggest that more guidance about what screening tests and/or questions should be used to best asses subtle neurocognitive changes and when neuro-psychometric testing should be undertaken. Beyond scope of the treatment guidelines – for monitoring guidelines to consider. 8.7 Women THT would like to suggest that more detail or links to Faculty of Sexual and Reproductive Health guidance on contraception and ARVs would be helpful in section 8.7. We need a better understanding of the issues surrounding contraception as some oral contraceptive medicines work well and some do not. There is the also the question raised by the Faculty's statement around Depo Provera and its potential impact on immunological responses, which may lead to HIV positive women who use Depo being more likely to transmit HIV. The section is very brief and it is a common issue. Acknowledged – will be addressed in SRH guidelines General Comment: For future consultations it would be useful to identify which changes were made to previous guidelines, using 'tracked changes' for example. Agree but the document can become very difficult to read throughout the multiple review processes prior to consultation – we will review the process prior to the next update Reference: Mocroft, A., Lundgren, J., Ross, M., Fux, C., Reiss, P., Moranne, O., … Ryom, L. (2015). Exposure to antiretrovirals and development of chronic kidney disease. Accessed from http://www.croiconference.org/sessions/exposure-antiretrovirals-arvs-and-development-chronic-kidney-disease-ckd Clive Blowes Research and Information Officer Terrence Higgins Trust
22.	Elizabeth Foley from BASHH	Thank you for the opportunity to review these guidelines for the treatment of HIV- 1 adults. Our review committee have no comments to make and support these guidelines. Thank you
23.	Silvia Petretti from UK-CAB	The UK-CAB is a national network of HIV treatment advocates our membership includes over 700 representatives with

		120 organizations. The UK-CAB welcomes this opportunity to comment on the BHIVA guidelines for the treatment of HIV-1 positive adults with antiretroviral therapy 2015 . However we are concerned that the consultation time was really short and it impacted on our ability to respond properly. Acknowledged but was on UK-CAB website for 5 weeks pre-deadline – we can review, with the community, what time frame would be preferred for next iteration We are also concerned that the consultation is going ahead before IAS conference where more detailed results from the START study will be presented. Until the findings are presented and published in a peer reviewed journal, our limited knowledge of the full implications of START affects our ability to fully comment on the guidelines. Acknowledged and addressed elsewhere Moreover the process of commenting on the changes was incredibly difficult because the parts that had changed were not highlighted. The community rep had asked for highlights to be included at an early meeting, and was told it was not possible. However it is possible if you pay somebody to do it. The whole process of writing the guidelines would be enhanced by having a medical writer and the UKCAB has already requested this. Acknowledged and addressed elsewhere Section 1 no comments Section 2 is missing. Will it be made available at a later date for comments? This is simply a summary if the recommendations and auditable outcomes that is added at the end when these have been finalised – the consultation often results in small changes in wording, emphasis and ordering Section 3 The UKCAB applauds BHIVA for the section 3.2 on the involvement of people living with HIV in decision making: We suggest that in this section there is a clearer definition of what 'being ready' to start treatment means. A new paragraph has been written – thank you Within the context of preparing people to treatment appropriate questions should be answered. Canadian AIDS Treatment Information Exchange (CATIE) developed a set of questions for patients to assess complementary therapy, but also equally valid set of questions for any medication : What am I hoping to get out of this therapy? Do other HIV positive people use it?

		Am I able to talk to any of these other people about their experiences? Is there any research or additional information about this therapy? What are the side effects, if any? What sort of commitment do I have to make to use this treatment? Where can I get this treatment, and will it be regularly available? How much of this treatment is too much and what are the early signs of taking too much? Can this treatment will interact with over the counter medicines, recreational drugs, vitamin and mineral supplements and herbal remedies'. How much does it cost? http://www.catie.ca/en/practical-guides/complementary-therapies/5-doing-your-own-research The section on patient involvement should spell out the process of making an informed decisions. • People with HIV should be given non judgmental information about treatment • Treatment is the individual's choice, not the healthcare provider's • Choice should be over whether or not to take medication • Choice should then be over which medication to take • The individual is offered time to think through options and discuss with others before making a decision We applaud BHIVA for making a very strong case for peer support and peer advocacy in relation to starting, and adhering to treatment. We suggest that referral to treatment advocacy services and peer support becomes an auditable output. It is important to actively encourage people to access peer support and the offer should be repeated, especially at times of stress (newly diagnosed, starting treatment, changing treatment, onset of comorbidities, getting pregnant, end of relationship, retirement, etc.). A clear pathway for additional support signposting re: peer mentoring, mental health and social concerns with follow up at next clinical meeting should be part of it . Thank you – we have added auditable outcomes The phrase "Community advocacy and peer support are helpful..." should read "Community advocacy and peer support including clinic-based peer support are helpful..." to include the various initiatives at a small but hopefully increasing number of centres. Being clinic-based and therefore 'on call' is hugely helpful to patients and to doctors

		alike. Agree – we have amended accordingly The phrase: "A number of factors may affect adherence..." should include 'social and cultural beliefs' along with the current list of factors affecting adherence, and indeed affecting actual uptake of the treatment offer. Agree – we have amended accordingly In order to facilitate people's involvement in their care, doctors, including GPs should give clear guidance as to whether there is significant interaction after looking at http://www.hiv-druginteractions.org. Women should be given clear guidance about contraception and HRT without having to grapple with the significance of percentage changes in the area under the curve (AUC). See http://www.hiv-druginteractions.org/data/ExtraPrintableCharts/ExtraPrintableChartID13.pdf Agree - the BASHH SRH guidelines WILL include a patient information leaflet about contraception options – this is not the remit of the ART guidelines There is a clear need for rolling training or a support network to be formed to help people who finding it difficult to communicate with all health providers involved in their care. As well as learning to navigate and understand how health/social/public services work. We agree and have added auditable outcomes to emphasise the importance of peer support Section 4 4.1.2 This section is likely to benefit from significant rewriting when results from START are presented, especially if they are also published in a peer reviewed journal. Given the GRADE system is based on quality of evidence and START is and RCT, the full results need to be evaluated for inclusion in the 2015 BHIVA guidelines. Duplicated comment addressed elsewhere 4.3.1 Here - and throughout - the psychological impact of starting treatment is emphasised as a negative intervention in terms of stress (and not referenced) when in practice, from a community perspective, starting treatment is often a highly positive response to taking control. This is in addition to report that coping with a diagnosis is easier after achieving undetectable viral load that helps normalise HIV more quickly. PHI table corrected to address this References: Parsons V et al. Attitudes, beliefs and acceptability towards early ART amongst men who have sex with men (MSM) recruited to a UK cohort of HIV seroconverters. 21st BHIVA, 21–24 April 2015, Brighton. Poster abstract P33. The summary table of pros and cons for primary infection is unhelpful, and some members believed it should be scrapped. The only difference between pros and cons of starting treatment in primary infection vs. any other situation is the preservation of immune response from treatment immediately after getting HIV and therefore the benefits this

		may bring in the future. 4.4 TasP Consider changing the first bullet to two separate points. The rational fro this is that come UK doctors are using their evaluation of current risk of onward transmission to impact the offer of earlier treatment. (see earlier ref: Parsons V et al. UK clinicians' approach to ART in primary HIV infection; comparison with the BHIVA guidelines. 21st BHIVA, 21–24 April 2015, Brighton. Oral abstract O13.) Agreed and amended accordingly This has an impact in terms of someone's future social response. 4.4.1.1 these are duplicates of earlier comments so have been addressed - Please delete "indefinitely" from bullet 4. Review - Please use "serodifferent" consistently though the guidelines - the last bullet here reverts to serodiscordant. - Perhaps includes a few more positive bullets points about treatment, including that it is relatively easy to modify treatment if there are side effects etc. Review 4.4.2 these are duplicates of earlier comments so have been addressed para 4 - these were "gay couples" not MSM Review para 5 - perhaps reword that condoms are recommended "if there is a concern about STIs or pregnancy". If there are not these concerns then there is no medical reason to use condoms. Review para 5 - reference a study from 2007 for mean time to viral suppression is not good enough. This section should reflect faster suppression with integrase-based combinations -especially as these are now strongly recommended for first line therapy. Globally, the guidelines should check fro similarly archaic references that are there for historical reasons but that have been updated by more recent data. This approach to relevant references is important. Section 5 5.1 these are duplicates of earlier comments so have been addressed - Overall - the significant changes to preferred first combinations based on better efficacy results with more recently approved drugs, including integrase inhibitors is welcomed. - delete references to "the Writing Group" as qualifications for recommendations. Everything in the guidelines is "in

		the view of the writing group". If it is needed for methodological reasons then there is no need to capitalise. - It perhaps needs to be clearer that ABC//3TC is a preferred backbone when used with dolutegravir. However resolved in the text and table, It does not seem appropriate for this to be a footnote in the table. 5.3.1 these are duplicates of earlier comments so have been addressed -as above, clarifiy that ABC//3TC is a preferred backbone when used with dolutegravir. It is not that the caution dosen't apply, the data supported actively prescribing these RTIs. 5.3.4 these are duplicates of earlier comments so have been addressed - Given the 12 references for the discussion about 3TC vs FTC it is surprising that this section reaches an opposite conclusion to the analysis from Ford et al in commentary to ATHENA results in CID. Ref: Ford N et al. Comparative efficacy of lamivudine and emtricitabine: comparing the results of randomised trials and cohorts. Clin Infect Dis. Advance access 3 November, 2014., http://cid.oxfordjournals.org/content/early/2014/11/03/cid.ciu767.full.pdf (PDF) 5.4 these are duplicates of earlier comments so have been addressed -very supportive of the decision to drop recommendations to use older drugs that are not supported by efficacy and safety data compared to recently approved options. 5.4.3.7 these are duplicates of earlier comments so have been addressed The efavirenz results from D:A:D (ref 31) could perhaps be modified to reflect the conclusions from the study that emphasied that non-finding a link with suicide should not be interpreted as a lack of causative effect given this is well document - but more accurately, that health workers were appropriately managing this risk in prescription practice - ie alternative dosing to those at highest risk and effectively switching those who experienced symptoms. 6.0 these are duplicates of earlier comments so have been addressed 6.1.2.1 This seems pretty disconnected from the current recommendations. What about integrase inhibitors etc. 6.1.4 Final sentence should perhaps refer to low cost generics and not to their cost effectiveness if this hasn;t formally been studies.

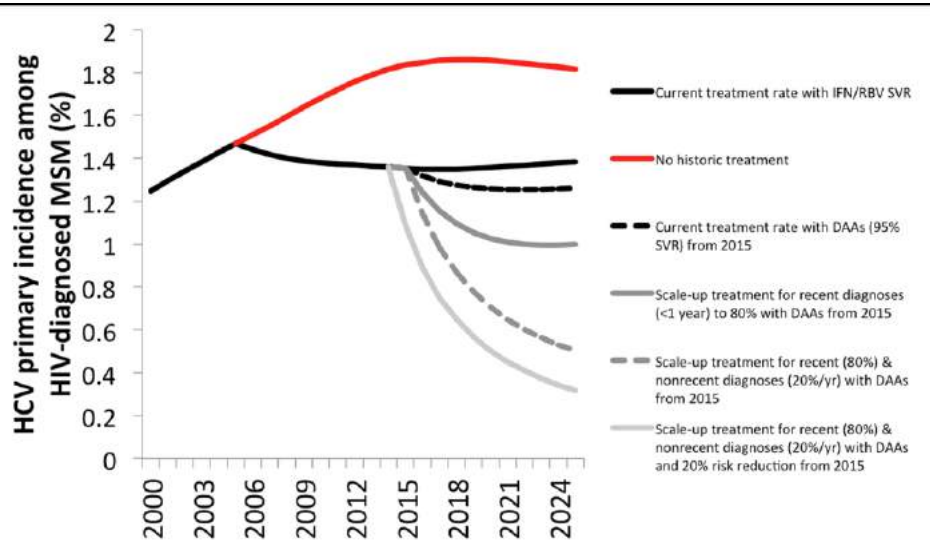
		Section 7.0 these are duplicates of earlier comments so have been addressed 7.5.1 - Good to see the reference to importance research. Several compounds in development could potentially be important for people with MDR HIV - especially with new classes - maturation, gp-120 inhibitors etc. Section 8.7 UK-CAB applauds BHIVA for addressing women as a special population. We are relly pleased that the lack of gender specific data and concerns with drug toxicities and adherence have been acknowledged. Thank you We have held a consultation in collaboration with Positively UK with a group of women living with HIV who have confirmed that there are many issues with side effects even when VL is undetectable. Women also have questions about gynaecological issues, contraception , changes in body shape, menopause and access to information and support around those issues; this can have an impact on the ability to adhere to treatment. Women have also expressed that they find it difficult to communicate with doctors, especially BME women, who culturally perceived doctors as people in authority that shouldn't be challenged. Women have concerns around food and nutrition and would like food recommendations with ARV's to be culturally appropriate and include African foods We have suggested a separate piece of work involving the community, HIVPA and DHIVA Some women also stressed that social issues such as extreme poverty and destitution, combined with high prevalence of domestic violence affect their mental health and ability to take HIV treatment, and their confidence to communicate with the healthcare team. As women living with HIV experience high levels of mental health problems it is crucial that women's mental health is regularly checked, not just at diagnosis and appropriate referrals to professional mental health services and peer support are made . The women living with HIV we consulted with would like the guidelines to recognise the need for women centred psyco-social support, including referral to women peer advocates and access to women only peer groups and treatment advocacy. Thank you – we have added a paragraph to this section Appendix - food chart Great this is included. It would be great to include examples of African foods that can be taken with medications We agree and will be addressed in a proposed food information leaflet, thank you The remainder of these comments are duplicates of earlier comments so have been addressed - Please could all drugs be treated similarly - see ATZ vs DRV. It would be more direct to always give approximate

		impact on drug levels rather than rely on general terms like "enhance" without giving data. - Atripla/efavirenz - concerned that this doesn't specifically reference high fat rather than just food. This is a important information for people taking treatment to understand. Taking with food has no impact on PK if this is low or zero fat content - and taking meds it something in your stomach helps. - Including a comment on the type of food, including when this makes no difference, would be a very helpful addition for all drugs with a food interaction. - Use of CAPS - if some words are going to be capitalised - "OR" - it might be clearer to use caps for WITH and WITHOUT as a global comment. - DRV - perhaps emphasise that food is required even with the boosting effect of RTV - also for ATZ. - Eviplera - that caution about taking without food could be stronger - ie "will" instead of "may". Also for Eviplera, I thought Gilead reported lower calorie count was needed for the FDC compared to when rilpivirine is taken as a single drug. Is this because food increases TDF levels? - Eviplera and rilpivirine should have similar text, if the food effect described is based on rilpivirine, unless the lower calorie requirement is being referenced.. - Atripla and tenofovir should have the same text when referring to TDF. - Atripla and efavirenz should have the same text when referring to efavirenz Appendix - renal dosing - Great this is included. - Comment on format - black writing on red background is unreadable on visually (access issue) and practically (on greyscale printouts. Please either reverse out text or use a different graphic solution.
24.	Allan Anderson from Positively UK	Positively UK is the leading providing of peer support for people living with HIV, providing support around every aspect of living with HIV, emotional well-being and practical support to over 1,000 people every year. We provide specialist support to women, gay men, heterosexual men, young people, the African community and young people transitioning care. Independent evaluation of our peer support services found that peer support can improve well-being and support understanding and adherence to medications http://positivelyuk.org/improving-well-being/ 3.0 Involvement of People Living with HIV in decision-making

		As a peer-led and peer support organisation, Positively UK welcomes the involvement of people living with HIV in decision making. In Section 3.1 there are two recommendations – involvement in decision making and involvement of community resources such as peer support. However 3.1.1 then makes an auditable outcome for only the first point – involvement in decision making. We urge BHIVA to include an auditable outcome regarding access to information and peer support. Positively UK makes reference to the need for such auditable standards in our Positive Change report http://positivelyuk.org/positive-change/ Auditable outcomes added, thank you This measure could be framed within the development of Patient Reported Outcome Measurements building upon work undertaken on this to date by BHIVA and Public Health England. review 4.0 When To Start We welcome the in new guidelines the incorporation of the results of the START study and the recommendation to commence treatment at an earlier stage, particularly the recognition that this is 'when [people] are ready to commit to taking therapy'. Thank you However as with other colleagues in the sector we are disappointed that the deadline for responses to consultations is the week prior to IAS and the launch of the details results from the START study. Without access to the full findings of the START study we are unable to provide informed comments on this or any issues that may be noted in the findings. Acknowledged and addressed elsewhere 4.4 Impact of Treatment on Prevention of Onward Transmission We welcome the new guidelines addressing the Impact of TaSP and notably the involvement of people living with HIV in making this decision. We strongly endorse the auditable measures which address concerns around coercion and ensuring there is informed consent; while recognising choice and the importance for people in sero-discordant relationships. Thank you However we also raise concerns that although TaSP is now recognised Positively UK continues to receive feedback and directly come into contact with clinical staff in HIV clinics, who are not making people aware of this, and in some cases acting as a barrier to people starting treatment even when requesting this for prevention purposes. While some of these issues may be resolved with the recommendation to start treatment earlier, we recommend that the auditable measure record that ALL patients have had discussion regarding TaSP. The recommendation has been strengthened to state ALL - NHSE have not approved TasP (this points has been added to the first paragraph) so any patient denied TasP should complain 6.0 Supporting individuals on therapy In terms of 6.1 Adherence the guidelines rightly note that there are a range of barriers to people adhering to

		treatments. There is also the auditable outcome of the offer of 'treatment support'. We recommend that there is a definition of what represents 'adherence support' and this includes referral to community and peer support which, as noted earlier Added, thank you We recommend that a definition of 'ready to commit' is identified and fully shared across health and social care providers. The section on patient involvement should spell out the process of making an informed decisions. See section 3 Positively UK welcome the identification of the needs of women as a specific population. Positively UK held a consultation in collaboration with UKCAB with a group of women living with HIV to inform our response to the treatment guidelines. Participants confirmed there were many issues with regards to side effects even when viral load is undetectable. Women also have questions about gynaecological issues, contraception, impact on body shape, menopause and access to information and support around those issues; this can have an impact on the ability to adhere to treatment. Women have also expressed that they find it difficult to communicate with doctors, especially women from black and minority ethnic communities, who culturally perceive doctors as people in authority and an authority that should not be challenged. The women living with HIV we consulted with would like the guidelines to recognise the need for women centred psyco-social support, including referral to women peer advocates and access to women only peer groups and treatment advocacy. Thank you – this comment has been duplicated elsewhere so has been addressed
25.	Roy Trevelion	The BHIVA antiretroviral (ART) guidelines 2015 – HIV and hepatitis C (HCV) coinfection We support these comments about HCV treatment and will pass on to the hepatitis writing committee The rationale from Page 74 of the draft for consultation is: • HIV has an impact on HCV infection. • Individuals with HCV coinfection have higher HCV viral loads. • The thickening and scarring of liver tissue – fibrosis – progresses faster. • There is increased risk of cirrhosis compared to people with HCV alone. Cirrhosis is a chronic disease of the liver marked by degeneration of cells, inflammation and fibrous thickening of tissue. • End-stage liver disease, liver cancer and liver-related death occur more frequently, at an earlier age and within a shorter time period, with risks of cancer and death increasing as the CD4 count declines. • The efficacy of pegylated interferon (PEG-IFN) lessens as the CD4 count declines, but PEG-IFN-free regimens seem not to be affected by HIV markers.

		• And although ART slows the progression of liver disease it is still likely to be faster than in HCV monoinfection. The guidelines make recommendations for starting ART at CD4 counts above 500. They say that Individuals with a CD4 count greater than 500 who defer HCV treatment should be given the option to commence ART. But are individuals being given the option to commence or defer HCV therapy? The guidelines say that the new direct acting antivirals (DAAs) are not being considered as an alternative option to PEG-IFN. This is despite DAAs being highly effective in curing HCV infection with fewer difficult-to-manage side effects. Researchers at UK CHIC have applied treatment-as-prevention to see if it would halt the HCV epidemic in HIV-positive gay men. Their projected figures for the next ten years show a decline in HCV infection: At the moment, around 8% of gay men living with HIV in the UK also have HCV. Without treatment as prevention, double this number would have HCV in ten years' time. But if 80% of men were treated within a year of acquiring HCV. And 20% of men who've had HCV for longer went on treatment, researchers say that fewer than 3% of HIV-positive gay men would have HCV by 2025. Not only would early treatment stop the rise in HCV coinfection, but it would also prevent individuals from becoming seriously ill before therapy is started. It is unacceptable that treatment is not on offer until the patient has serious liver damage which might well progress to organ failure and death. The Health and Social Care Act called for more competition in the NHS. Are individual pharma companies unwilling to share their successes with others? How many individuals will die because of lack of access to treatment? I've attached a pdf of the UK CHIC slide: Treatment as prevention in HIV/HCV (from N Martin et al 2015 submitted)

		
26.	Robin Jakob, Treatment Advocate and Information Officer, HIV i-Base	General. The process of commenting would have been easier if, as has been done in the past, changes and new sections had been highlighted. The drawn out process of updating these guidelines is a concern. This update should have come in 2014. BHIVA could employ a medical writer to assist in the work. Section 3. The decision to include a section on the involvement of people living with HIV in decision-making should be applauded. It would benefit from a clearer description of what patient involvement and informed decision-making would look like. This could take the form of a checklist or list of recommendations that help ensure key choices are made collaboratively. Section 4. Within this section the psychological impact of starting treatment is described negatively. This of course may sometimes be the case but people often described the process of starting treatment as helpful within coming to terms with their diagnosis and 'taking control' of their HIV. This is not acknowledged in this draft

		Section 5. The changes to this section are generally welcome, particularly the inclusion of dolutegravir as a preferred third agent. The dropping of older meds inc. d4T is also very welcome. The downgrading of EFV to alternative agent is warranted. It should be noted that EFV will come of patent soon and its status as alternative rather than preferred should not be price dependent when it inevitably becomes very cost-effective. Perhaps a statement to this effect could be included in this section. Section 8. BHIVA should be applauded for including women as a special population. While statistically a small group BHIVA could also include trans* people. Trans* people have unique social and often medical challenges, even before they become HIV positive. A variety of treatment issues are important to highlight. This includes potential drug interactions between hormone therapy and ARVs. Linkage to and retention in care is particularly important for this group. Relevant services like CliniQ at 56 Dean Street in London could be highlighted. Thank you for your comments
27.	Dr. Eilish McCann, Senior HTA & EBM Manager Dr. Bryn Jones, Medical Advisor From	Dear BHIVA, MSD welcomes the opportunity to consult on the draft BHIVA guidelines for the treatment of HIV-1 positive adults with antiretroviral therapy (2015). MSD supports the development of evidence-based guidelines and consequently welcomes the inclusion of the START study findings within the guideline; it is hoped that the full data will be incorporated in the guideline when available. Please see below for detailed comments by section. Thank you Kind regards, Dr. Eilish McCann, Senior HTA & EBM Manager Dr. Bryn Jones, Medical Advisor

Section	Page	Guideline text	MSD comment
1.3	7	At a population level, ART is likely to be important in reducing the incidence of HIV infection.	This statement needs to be supported with references to reflect the existing body of evidence (and ongoing trials such as HPTN 071 – PopART) e.g. Vandormael *et al*.

			demonstrated within a population in KwaZulu-Natal that antiretroviral coverage was significantly associated with reduced transmission of HIV . HPTN 071 has not presented any results so cannot be included. The population impact of ART is very dependent on the nature of the HIV epidemic in a given region and it is likely that TasP has greater impact on a population level where epidemics are characterised by predominantly heterosexual transmission from chronically infected individuals – the impact may be less where most transmission is driven by undiagnosed HIV (as in UK MSM). In the absence of good evidence that TasP has a population impact in the UK we will not reference this point at present.
1.4	8	The BHIVA Writing Group recognises that cost of drugs is an important issue in the choice of ART regimens.	The guideline could acknowledge that in addition to drug acquisition costs there are other costs/resources that should be considered i.e. multidisciplinary team meetings, additional tests required when switching, management of drug-drug interactions/comorbidities etc. Thank you – we have added a line to this effect
1.4	8	The Writing Group recognises and supports that commissioning arrangements and local drug costs will and should influence ART choice where outcomes, across a range of clinical measures, are equivalent between individual drugs in the treatment of defined populations.	It is not clear how the Writing Group defines equivalence in outcomes i.e. the measures used or thresholds used to define equivalence. The term equivalent has been replaced – this was confusing, thank you for highlighting
1.4	8	Typically however, improvements in treatments are deemed to be cost-effective if the cost of an additional QALY is <£20–30,000.	The guideline acknowledges that incremental cost-effectiveness ratios (ICERs) are not commonly utilised in HIV decision-making (in comparison with other areas of the health economy); it may therefore be appropriate to remove this statement or to accompany the statement with a brief explanation of an ICER to aid comprehension. We have removed the sentence on QALY and after discussion do not feel any additional discussion on ICER is warranted at this stage
3.2	10	HIV-positive individuals should also be screened for anxiety and for cognitive impairment.	It would be helpful for the guideline to state here what services should be available for patients that are identified to have anxiety and cognitive impairment; screening alone may not be helpful without appropriate follow-up. Similar comment to

			paragraph regarding alcohol. Beyond scope of ART guidelines – please refer to BHIVA standards and BHIVA monitoring guidelines
4.0	14	N/A	It would be helpful for this section to contain 'signposting' to state that information on 'when to start' within special populations is included later in the document. This has been added
4.1.1	14	N/A	MSD suggests that this section could be supported by an 'auditable measure' similar to following sections in order to drive best practice. One has been added
4.1.2	15	The absolute risk of deferring therapy may be one that an HIV-positive individual is, reasonably, prepared to accept in the short term.	This statement would benefit from being supported with appropriate references as the evidence base is not clear. This has been removed
4.3.1	16	ART should be started only when the individual feels ready to do so.	MSD fully recognises the importance of patient choice in commencing therapy but suggests that guidelines also need to be fully evidence-based. We feel that the findings of the recent START study should be reflected in this statement. Removed from recommendation – importance of readiness and individualised decision making remains in text
4.3.1.1	17	The proportion of patients presenting with PHI where the pros and cons of starting ART are discussed at diagnosis.	In addition to discussing the 'pros' and 'cons' of starting ART the auditable measure could also record the proportion of patients who initiated ART (or who did not initiate ART) following this discussion. Added – thank you
4.3.1 (table)	17	Ambivalence to ART at a time of emotional challenges can risk poor adherence and the development of drug resistance. Individuals with recently diagnosed PHI may be in a particularly vulnerable psychological state, and thus ill-prepared to commit to starting long-term	Our interpretation of this table is that although these 'cons' may reflect the experience and perception of some patients, equally a proportion of patients who are newly-diagnosed with HIV may be comforted and supported by the knowledge that they have initiated ART and are actively managing their condition. We would suggest that this section needs to reference available data on patient perception of treatment, or the proportion of patients who have this perception etc. Incorporated these sentiments into the redraft of the PHI section to express that

		treatment.	whilst ART initiation may confer added stress to some individual's initiation of immediate ART with the knowledge of personal clinical benefit in light of START trial results and HPTN052 may also be comforting. (also in response to similar comments elsewhere).
4.4	20	N/A	MSD believes that it would be beneficial for this section to also refer to the START study (in the context of earlier treatment impacting on transmission). Thank you - benefit of ART' has been added as a point for discussion when discussing TasP
5.3.2	24	ABC-3TC is an acceptable alternative option in individuals with a baseline VL <100 000 copies/mL (other than in combination with DTG when ABC-3TC can be initiated regardless of baseline viral load), but must only be used after ensuring HLA□B*57:01 is negative.	MSD suggests that in patients with high viral load (>100,000 copies per ml), raltegravir may be considered as an alternative third agent in patients starting ABC/3TC. This was discussed and we do not believe that SPRING-2 supports this. Other data on ABC/3TC/RAL are limited This position is based on the SPRING-2 96-week data reported by Raffi *et al*., who stated that "Subgroup analyses of virological non-responders (snapshot) that combine baseline viral load strata and backbone NRTI, however, showed similar numbers of virological nonresponders between groups."[ii] In addition, the IAS 2014 guidelines state that raltegravir combined with abacavir/lamivudine may be used in patients with a viral load >100,000 copies: "No evidence that abacavir/lamivudine performs less well at HIV-1 RNA levels >100 000 copies/mL when taken with raltegravir."[iii] As above
5.4.3.1	27	Similarly, there was a higher risk of developing resistance at virological failure on RAL compared with ATV/r in ACTG5257 (OR 2.04 [95% CI 0.91-4.57; p=0.08] at 96 weeks).	The risk of developing resistance at virological failure is not described by Lennox *et al*. in the main publication describing the results of ACTG525[7] [iv]. What is described is the proportion of patients developing resistance in relation to the overall number of patients in each study group. Thank you – we have reviewed the data and disagree. The data come from table 2 in Lennox 2014 and Lennox 2014 (p468) states: "Overall, virologic failure with resistance occurred in 3.0% of study participants randomly assigned to raltegravir (2 of whom developed intermediate-

			level resistance to dolutegravir) and in 1.5% or fewer of those in either boosted PI group." These percentages relate to % of total study groups and these are the data that generated the OR quoted. We have therefore left this statement unchanged To quote the odds ratio of resistance between the treatment groups is potentially confusing when numerically virological failure was observed least frequently in the raltegravir group (n=85 for raltegravir, n=95 for Atz/r, n=115 for Drv/r). The study authors stated that "Antiretroviral resistance at the time of virologic failure was rare but more frequent with raltegravir." As above, we do not think people reading the guidelines will find an OR confusing but for clarity we have added the % failing with resistance in the RAL sub-section. MSD therefore suggests that the number of patients failing and the proportion failing with resistance (3.0% raltegravir, 1.5% Atz/r, 0.67% Drv/r) would provide a better summary of these results. MSD also notes that it could be misleading to present an odds ratio which does not appear in the original publication. Consistent with guidelines methodology we use OR throughout that may not be quoted in the original papers, this does not makes those OR invalid and would suggest MSD contact the BHIVA guidelines subcommittee if they think this should be reviewed. We have received no other comments questioning the use of independently generated OR for this nor the previous version of the guidelines since utilising GRADE methods and Forest plots. Consistent with MSD's request we have added the % failures to the RAL sub-section.
5.4.3.1	27	…the majority of discontinuations from ATV/r were for hyperbilirubinaemia /jaundice, a well-known and harmless complication.	MSD acknowledges that jaundice is a well-known complication, but does not agree that it is harmless; it can impact patients and yield higher discontinuation rates (as in ACTG5257[iv]). This was not considered a critical outcome by the Writing group and will be reviewed again at the next guideline update – we have rephrased the discussion, removed the word harmless and emphasises the potential distress and stigma and visible side effect can cause In addition, a significant number of patients in ACTG5257 discontinued within the

			Atz/r group due to gastrointestinal toxicity (N.B. it is not known whether these discontinuations were patient or clinician-driven). Numbers small and this difference was not considered clinically significant
5.4.3.2	28	For the comparison between DRV/r and RAL in the three-arm ACTG5257 study [20], overall virological response was significantly higher for DRV/r (OR 1.83 [95% CI 1.16-2.89] at 96 weeks in favour of DRV/r; p=0.009).	Lennox *et al*. stated that "The cumulative probability of virologic failure by 96 weeks was 12.6% in the ritonavir-boosted atazanavir group, 9.0% in the raltegravir group, and 14.9% in the ritonavir-boosted darunavir group." The confidence interval for the difference in virological failure between Drv/r and raltegravir was 5.6% (1.3% to 9.9%)[iv]. Lennox et al used 97.5% CI, not the 95% CI we utilise for analysis of the data, hence the difference. We have kept our original figures based on guidelins methodology MSD suggests that the odds ratio of 1.83 quoted in the draft guideline may be confusing and does not clearly reflect the published results from the ACTG5257 study. The OR is calculated from the published results therefore does reflect the published results but favoured RAL, not DRV/r which we have corrected. The OR is derived from Lennox 2014, Figure 3 (ITT analysis) and the adjacent text: "The proportion of participants with an HIV-1 RNA level of 50 copies/mL or less at 96 weeks by ITT analysis (regardless of treatment status) was 88.3% for ritonavir-boosted atazanavir, 93.9% for raltegravir, and 89.4% for ritonavir-boosted darunavir (Figure 3, top)." The number of participants contributing data at 96 weeks (from figure 3) are: 515, 526 and 518. So numbers of patients with copies <50/mL at 96 weeks are: 455/515, 494/526 and 463/518. We have added the % at MSD's request but kept the OR as is.
5.4.3.3.	28	Overall virological failure rates at 48 and 96 weeks were not significantly different; although there was a significantly lower rate of treatment success on RAL at week 96 in those with a baseline viral load greater than 100,000 copies/mL (OR 2.10 for virological success favouring DTG; 95% CI 1.17-3.75; p=0.01), SPRING-2 was not powered for this comparison.	Although this statement is caveated MSD suggests that the current draft guideline places too much emphasis on the results of a subgroup analysis (viral load strata) at a secondary analysis time point. Wording amended

5.4.3.5	29	RAL was compared to ATV/r, DRV/r and DTG In studies outlined in 5.4.3.1, 5.4.3.2 and 5.4.3.3, respectively. RAL was non-inferior to EFV In STARTMRCK…..	Typo - STARTMRCK should read STARTMRK. Thank you - corrected
5.4.3.6	29	Pooled analyses by the investigators of the two RCTs showed the risk of virological failure with RPV was highest in participants with a baseline VL >100000 copies/mL [17] and when analysis is restricted to individuals with a baseline VL less than 100,000 copies/mL there was a significantly better virological response to RPV compared with EFV.	The statement that virological response was significantly better in the rilpivirine group compared with the efavirenz group in patients with a viral load of <100,000 copies per ml is not clearly supported by Nelson [v] *et al*. Agree, corrected The authors stated that "virologic response at week 96 was also analysed across 3 baseline HIV-1 RNA strata; results indicated that RPV+FTC/TDF was non-inferior to EFV+FTC/TDF in those with baseline HIV-1 RNA ≤100,000 copies/mL (83% RPV vs 80% EFV; 95% CI, -3.9 to 9.1)." This confidence interval would not generally support a statement of significance if a statistical test were performed. Agree, corrected and and added a reference with an analysis specific to the <100k population
6.1.3	36	For ART regimens, a meta-analysis of once-*vs.* twice-daily ART regimens found that in the subgroup of treatment-naïve trials, once-daily ART was associated with a significantly improved adherence and virological outcome [36]. Therefore, once-daily dosing is a reasonable intervention to reduce unintentional non-adherence to ART.	Further evidence should be considered within this section, specifically relating to dosing and antiretrovirals. ACTG5257 was a large randomised controlled trial that compared treatment regimens in an open-label fashion [iv]. Within the study dosing requirements differed by group i.e. BD in the raltegravir group vs. OD in the boosted protease inhibitor groups. Therefore these results could be considered here. Revised The study concluded that the group taking raltegravir (as third agent) was equivalent to Drv/r and Atz/r in terms of virological efficacy. Raltegravir was equivalent to Drv/r and superior to Atz/r in terms of tolerability failure. Furthermore, in the combined pre-planned endpoint raltegravir was superior to both PIs and Drv/r was superior to Atz/r. Further studies, specified below in relation to section 6.1.4, should also be considered. Revised

6.1.4	37	In summary FDCs support adherence to treatment, and this may well reduce the risk of virological failure. However, the size of this effect is yet to be defined.	This statement could be reworded to "FDCs support adherence to treatment but their impact on virological failure is yet to be fully demonstrated" Review as it is not clear which evidence supports the current wording. In a recent meta-analysis of randomised controlled trials Nachega *et al*. reported that "…average adherence was modestly higher in once-daily regimens than twice-daily regimens (weighted mean difference [WMD] =2.51%; 95% confidence interval [CI] 1.20 to 3.83; p=0.0002). Patients on once-daily regimens did not achieve virologic suppression more frequently than patients on twice-daily regimens (relative risk [RR] = 1.01; 95% CI 0.98 to 1.03; p=0.57).[vi]" Revised MSD suggests that these figures be quoted to help quantify the impact of dosing on adherence and outcomes.
6.1.6	39	Potential advantages of using STR are improved adherence, reduced selective adherence, patient preference and improvement in quality of life [5, 6]. Randomised studies demonstrating these advantages are scarce and among cohorts and observation studies results are varied.	Andrew Hill recently presented a meta-analysis of randomised controlled trials at the 2015 BHIVA conference (http://www.bhiva.org/documents/Conferences/2015Brighton/Presentations/150422/AndrewHill.pdf). Within his presentation he stated that "In STRATEGY-PI and A12663 trials, [there is] no difference in Quality of Life (SF-36 score) between STR and control treatment." Thank you, we have referenced this analysis and added a line re negative QoL findings
6.2.4.2	44	Although formal pharmacokinetic data are not available, switching EFV to RAL should not lead to clinically significant consequences, as co-administration of EFV with RAL led switch but the degree of this reduction is unlikely to be clinically meaningful [24].	It appears that there is a typographical error in this sentence as the meaning is not clear. Thank you – corrected to complete sentence
6.3.2.2	47	With the exception of a small, single arm TDF/FTC + RAL to Stribild switch study (50 subjects all of whom maintained virological suppression with minimal impact on renal and lipid markers) [6] there are no integrase inhibitor within class switch studies.	In addition to highlighting the small size of this switch study, the guideline should also highlight that there are no switch studies to support a switch within class to dolutegravir. We have already stated that there are no other within class integrase switch studies and feel this is sufficient
6.3.2.	47	One RCT assessed switching from PI to ELV/c in people with viral suppression, finding suppression is	It should be noted that the study examining switch from PI to elvitegravir/cobicistat excluded patients with a history of resistance to tenofovir/emtricitabine and those

2		maintained and regimen is well tolerated [28].	with a history of virological failure. Thank you - added
8.2.1 (table)	73	Start ART before HCV treatment commenced (1C); acceptable to defer if CD4 >500. Discuss with HIV and viral hepatitis specialist.	It is not clear whether this recommendation can be supported in light of the START study findings. This was discussed again – it continue to be considered acceptable by the writing committee to defer ART if HCV treatment is planned in individuals with CD4 >500
8.2.3.1	74	We recommend HCV be considered an additional factor supporting ART in individuals with CD4 >500 who are uncertain about commencing ART (2C).	Again, it is not clear whether this recommendation can be supported in light of the START study findings. Discussed – the ART benefits in terms of HCV related fibrosis are an additional reasons to start ART
8.6.2.2	88	For the purposes of these guidelines, individuals with an elevated CVD risk are those with established atherosclerotic CVD; diabetes mellitus type 1 over the age of 40 years…	Is 'diabetes mellitus type 1' supposed to read 'diabetes mellitus type 2'? No, diabetes mellitus type 1 is correct
8.6.5.2	90-93	N/A	There is some inconsistency in the way that lipid outcomes are reported between trials. In some instances the lipid levels are reported and in others only one group is reported, accompanied by a comment stating 'higher'. This may reflect the availability of published data however it would be helpful to state which group was 'higher' in order to aid interpretation. Thank you – the table has been amended accordingly
8.7.3.2	99	N/A	This section appears to be lacking data from ACTG5257. The published data state that "Some evidence of differential treatment effects for tolerability by screening HIV-1 RNA level was apparent for ritonavir-boosted atazanavir versus raltegravir ($p<0.036$) and by sex for ritonavir-boosted darunavir versus raltegravir ($p<0.047$). A greater tolerability benefit of raltegravir compared with ritonavir-boosted atazanavir was observed among participants with a baseline HIV-1 RNA level less than 100 000 copies/mL; similarly, a greater tolerability benefit of raltegravir over ritonavir-boosted darunavir was observed in women. No other differential treatment effects were apparent ($p<0.128$)."[iv] Reviewed: the study was not powered to detect gender differences and therefore this is a post-hoc sub-

			analysis. Moreover, it comes to no different conclusion than the overall result (that is, RAL better tolerated than DRV/r) - which we refer to in the 'what to start' section ACTG5257 also has added importance as the proportion of women included within the study was higher than in many other previous studies (n=424 or 24% of those in the study). We agree that 24% women in a study is better than many other clinical trials but don't think this warrants amphasis

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