BHIVA/BASHH guidelines on the use of PrEP

Final round of comments from BHIVA Executive Committee, Guidelines Subcommittee and BASHH

	Name	Comments	Writing group response
1.	Adrian Palfreeman	I have re read v 11 as well as all the comments received. It ticks all the boxes on our guideline checklist and is a fantastic piece of work.	Thank you – we're grateful for the positive feedback
2.	Laura Waters	Well done to the PrEP writing group! THe guidelines layout is very clear and all the responses to the consultation comments look fair to me. My only specific comment is re conflict btw FSRH and PreP GL wrt DMPA - agree with PrEP authors & the imminent BASHH/BHIVA/FSRH GL for SRH in people with HIV also state the same. Well done again y'all!	Thank you – we're grateful for the positive feedback
3.	Paul Clift	Many thanks to the writing group. An impressive job, not least in view of the Buying Generics section – well done! Will there be a patient-friendly summary at some point or do we leave that to i-base?	We decided not to produce a patient friendly summary as there are already many excellent resources available (e.g. I Want PrEP Now and i-base) and we agreed we would, instead, refer to these
4.	Ann Sullivan	Thank you, this is an extremely well written, comprehensive guideline. I have three comments. I do not believe there is evidence to recommend HCV testing for all individuals eligible for PrEP; there is for MSM, PWID and migrants from countries with intermediate/high prevalence (as per WHO definition) but not necessarily all others I am not convinced the evidence base exists for recommending 6 monthly testing of renal function for everyone apart from those under 40 and with an eGFR>90. I personally do not feel (iPrEx) Ole warrants a 1B given it is an open label extension. Overall (from higher quality studies) there were <1% ppts experiencing significant changes in renal function; in Partner PrEP no difference was seen between study and placebo group and more than 75% of abnormal renal results (rise in Cr/fall in eGFR) were not confirmed on repeat testing. The changes in Ole, while statistically significant, were unlikely to be clinically important, with the largest falls seen in those with highest baseline Cr, and again only <1% affected in total. Of note all 9 of those with a fall of eGFR to <60 (ie potentially of clinical significance) started with a baseline less than 90 and 8 were over aged 50. I believe the findings of Ole should be highlighted but my personal take on this evidence would be that it is not possible at this point to make a strong recommendation and more evidence is required. This has significant implications for service delivery and cost, although clearly that shouldn't be the primary driver it is an important factor if making such a strong	We have provided more detailed feedback to Dr Sullivan's comments – please see below

		recommendation. This leads to my final point which is that although this has an excellent cost effectiveness section it does not address the potential service and financial implications of implementing this GL in the UK context, and the significant potential barrier this may present to commissioning and spread. Whilst GL should give gold standard recommendations and services then need to determine what can be delivered in collaboration with their commissioners the BASHH GL guidance is that these factors need to be addressed specifically with in the guidance and BHIVA includes it as the final point on their checklist, so I think it needs addressing in some detail. One very minor technical point under Point 8 GPP it should read the clinician needs to ensure the generic is labelled as containing….not ..to ensure it does contain both drugs	
5.	Saye Khoo	Excellent document, very clearly written, will be very helpful. Ann's points are well-taken.	Thank you – we're grateful for the positive feedback
6.	Alan Tang on behalf of BASHH	The CEG group confirm it has no further comments and BASHH has had adequate representation on the writing group. BASHH is therefore happy for the guidelines to progress to the processes required for the guidelines to be published.	Thank you – we're grateful for the positive feedback

BHIVA / BASHH PrEP guideline writing group - Response to Dr Sullivan's comments

I do not believe there is evidence to recommend HCV testing for all individuals eligible for PrEP; there is for MSM, PWID and migrants from countries with intermediate/high prevalence (as per WHO definition) but not necessarily all others
It wasn't our intention to suggest HCV testing for all. We can see that there is some inconsistency in language and lack of clarity in the guidelines. We will edit the document to clarify that baseline and on-going testing for HCV is only for MSM and those at risk (as per national guidelines).
I am not convinced the evidence base exists for recommending 6 monthly testing of renal function for everyone apart from those under 40 and with an eGFR>90. I personally do not feel (iPrEx) Ole warrants a 1B given it is an open label extension. Overall (from higher quality studies) there were <1% ppts experiencing significant changes in renal function; in Partner PrEP no difference was seen between study and placebo group and more than 75% of abnormal renal results (rise in Cr/fall in eGFR) were not confirmed on repeat testing. The changes in Ole, while statistically significant, were unlikely to be clinically important, with the largest falls seen in those with highest baseline Cr, and again only <1% affected in total. Of note all 9 of those with a fall of eGFR to <60 (ie potentially of clinical significance) started with a baseline less than 90 and 8 were over aged 50. I believe the findings of Ole should be highlighted but my personal take on this evidence would be that it is not possible at this point to make a strong recommendation and more evidence is required. This has significant implications for service delivery and cost, although clearly that shouldn't be the primary driver it is an important factor if making such a strong recommendation.
The issue of renal monitoring was probably the most contentious amongst the writing group. We noted the conflicting evidence from different studies and did discuss the clinical significance of the changes seen in iPrEX Ole. Whilst we agree it is not possible to make a strong recommendation and we agree that more evidence is required, the majority (but not all) of the writing group felt that, until we have more evidence, we should err on the side of caution. Although the reductions in creatinine clearance in iPrEX OLE were small, the declines were

greater in those aged over 40 and we felt we had to reflect this in the guidance – and the average decline (albeit small) was not much different between those aged >40 and those aged >50 which is why, when deciding on an age cut off for recommended increased renal monitoring, we decided on 40 and not 50. We did note in our discussion that in iPrEXOLE that 8/9 people whose eGFR fell to <60 were all over 50 but decided to use 40 as the cut off for more frequent renal monitoring based on the greater % reduction in creatinine clearance. We accept that this may result in over testing but felt that, until more data is available, we should have a lower threshold for renal monitoring. This was supported by feedback from the public consultation and discussion with HIV / renal physicians. We agree that it makes sense to lower the grade of the recommendation from 1B to 2B. It should be noted that other national guidelines (e.g. CDC and Australian) recommend 6 monthly renal monitoring for all and more frequent testing for those with risks
This leads to my final point which is that although this has an excellent cost effectiveness section it does not address the potential service and financial implications of implementing this GL in the UK context, and the significant potential barrier this may present to commissioning and spread. Whilst GL should give gold standard recommendations and services then need to determine what can be delivered in collaboration with their commissioners the BASHH GL guidance is that these factors need to be addressed specifically with in the guidance and BHIVA includes it as the final point on their checklist, so I think it needs addressing in some detail.
At the beginning of the PrEP guideline writing process it was agreed that we would work to BHIVA's guideline writing guidance (as referenced in the guidelines – page 8) and not the BASHH guidance which does seem to be more explicit about the need to state cost of recommendations. The relevant section for BHIVA guideline development in terms of cost effectiveness is given below (Section 3.12) and outlines that the cost effectiveness of any intervention should be considered (although probably refers more to treatment rather than prevention interventions). This is what has been undertaken in the PrEP guidelines. We took the view that this was appropriate as guidelines are based on review of existing evidence and are not to generate new evidence. We did not feel it was our role to conduct an in-depth analysis or make recommendations about the costs of implementing the full guidelines in the fragmented commissioning setting, which would require extensive modelling work and a full, separate costing study which is outwith the limits (and budget) of any guidelines group. The cost effectiveness section in the PrEP guidelines uses information based on 18 months of work as part of an NIHR funded programme grant which allowed the modelling of the UK epidemic in MSM to be developed and undertaken and the cost effectiveness of PrEP modelled in a number of scenarios. No other BHIVA guideline outlines the cost of implementing the guidelines and we propose leaving the section as is. We are not aware of the final point on the checklist that Anne refers to – if we've missed something please let us know. We are not aware of any other guideline (either BHIVA or BASHH) that have such detailed content on cost and commissioning implications ***"3.12. Resource implications of the guideline recommendations*** ***Management of HIV disease demands a relatively high level of healthcare resource and finance. The provision of HIV services has been limited by resource allocation in the past and resources are finite. The co-authors of each guideline should draft and agree the*** ***recommendations within each guideline based primarily on clinical effectiveness but the use of resources and cost effectiveness should also be taken into account.There are limited data on the relative cost effectiveness of various treatments in this field; however, the available data strongly support the case that HIV treatment is cost effective in terms of Quality Added Life Years (QALYs) vs. many other health interventions.The co-authors should produce recommendations to follow any specified management which on balance favours health gain/patient benefit over risk/harm where there is evidence of clinical effectiveness. At the same time the co-authors may produce no recommendations, or recommendations not to follow a specified management if clinical and cost effectiveness is in doubt. The guidance will always make recommendations not to follow a specified form of treatment when the risks/harms exceed the assessed health gain."***
One very minor technical point under Point 8 GPP it should read the clinician needs to ensure the generic is labelled as containing….not ..to ensure it does contain both drugs
We agree that we should edit this