# BHIVA/BASHH guidelines on the use of PrEP

Public consultation comments

**Compilation of all comments received via BHIVA and BASHH websites. The Writing Group thanks everyone who replied to the consultation. The guidelines have been revised in light of the comments unless otherwise stated.**

[Pick the date]

| | Name | Affiliation | Comments | Writing group response (The guidelines have been revised in light of the comments unless otherwise stated.) |
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| 1. | Dr Abraham Kowo | Sexual Health Project for Africa's Key population | African migrants and refugees MSM need access to the PrEP trial. It will help reduce the cumulative community viral load .<br><br>How can this community be recruited into this PrEP study? | Unfortunately this is outwith the scope of the guidelines |
| 2. | Sanjay Bhagani | Royal Free Lonon NHS Trust | These are timely guidelines and the authors and co-chairs need to be congratulated for this comprehensive document.<br><br>There are a couple of specific issues that I think need further discussion.<br>With regards to hepatitis B, iPREX showed the possibility of using TDF/FTC in patients with chronic HBV, and more importantly, ability to stop PrEP safely in patients without cirrhosis and without the occurrence of significant hepatic flares (JAIDS 2016; 71: 281-286)<br>a) May I suggest that the recommendation for daily PrEP and assessment by a specialist in viral hepatitis/co-infection for those with evidence of chronic HBV with regards to continuing therapy or safety of stopping therapy, be put down as a specific recommendation (number 24?)<br>The recommendations around HCV testing, particularly in MSM/Trans individuals with chemsex risk behaviour needs further consideration.<br>The issue of HCV testing in HCV-Ab positive individuals has not been addressed. As seen from the Amsterdam cohort, a substantial number of HIV-negative MSM accessing PrEP are HCV-infected. Clearly many will have had their HCV treated pre-PrEP.<br>a) For HCV-IgG+ indiviuduals who have cleared HCV, HCV-testing would specifically need to be HCV RNA or HCV-cAg testing every three months<br>Furthermore, three-monthly anti-HCV testing would miss patients with early/acute HCV, and therefore, an opportunity to offer early treatment and risk-reduction counselling/intervention.<br>I would suggest, specifically for MSM/Transgender individuals involved with chemsex practices who are HCV-IgG negative<br>a) At the quarterly visit, offer ALT testing as well as anti-HCV testing. In those with abnormal ALT, re-call for HCV RNA/HCV-cAg testing (as per local guidleines) | |
| 3. | frances keane | Royal Cornwall Hospital trust | Very comprehensive -thank you. Only comment would be that an exec summary of all the key "blue box" recommendations at the beginning would be a useful addition -allowing a quick reference guide rather than ploughing through the entire document | |

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| 4. | sophie Forsyth | swindon Sexual health, great western hospital | Very useful guidelines. would it be useful to use urinary PCR in monitoring or dipping urine for protein on day of attendance? Do we need to test for Hep C regularly as not recommended in BASHH guidelines as part of routine screening for MSM unless they are HIV+, chem sex etc | |
| 5. | Dr Amy Evans | Leeds Sexual Health | Does the writing team feel able to make any consensus statement (even on lack of current consensus, given current data limitations) on Doxy-PEP or associated antibiotic propylaxis that some are now self-sourcing through the recommended prep for a? This would be most helpful I think to clinicians & third sector colleagues when advising patients. Many thanks | Thank you for your response to the consultation. Unfortunately this is outwith the scope of the guidelines. |
| 6. | David White | Umbrella Sexual Heatlh Birmingham | Although the current guidelines do present the facts as they are evidence in the studies I feel that they could be more nuanced. The evidence for very high efficacy for daily dosing with high adherence is presented and since this is consistent across studies I feel that this is supportable. However the evidence for Event Based dosing relies only on the IPERGAY (including OLE) and to a lesser extent from the Adapt studies. Although I have seen the very elegant subanalysis of <15 doses per month dosing presented at IAS from Ipergay I feel that the guidelines do not make it sufficiently clear that the evidence is less robust for EBM than daily dosing especially for infrequent episodes of medication cover and especially for short pre-exposure dosing. Arguably this should be looked at as risk reduction rather than the 97% efficacy of daily dosing (see CIs presented for <15 monthly doses in Paris). Otherwise the guidelines are a monumental and wonderful achievement. Thanks to everyone for their hard work. | |
| 7. | Dr Nurul Huda Mohamad Fadzillah | Oxford University Hospital | Please include explicit guidance for partner of HIV elite controller/long term non progressor who are not on treatment | |
| 8. | Emma Wainwright | The Florey, Royal Berkshire Hospital | The comment regarding Depo-provera is at odds with the FSRH guidance regarding HIV risk:<br>FSRH: there is no reason to advise against use of DMPA even for women at 'high risk' of HIV infection<br>PreP guidance: women at risk of HIV acquisition should be offered an alternative form of contraception if available. | The writing group disagrees with FSRH on this point as there are several more recent studies showing women using DMPA are at higher risk of HIV infection, including the 2016 updated systematic review by Polis et al, which that |

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| | | | | shows an increased risk of HIV acquisition in women using DMPA when compared to other forms of contraception or non-use. |
| 9. | Emily Clarke | Solent NHS Trust | In the MSM section you recommend daily or event based PreP where as in the 15-25yrs old section you only recommend daily PreP for young MSM. | |
| 10 | Dan Bradshaw | Chelsea and Westminster Hospital | Many thanks for this clear document.<br><br>I had one query in the 'viral hepatitis' section.<br><br>Is it worth a comment that screening with HCV RNA should be performed if there is a high suspicion for acute HCV, given that anti-HCV may be negative in this setting. An alternative is screening with HCV core antigen, although this is less sensitive than HCV RNA especially at low HCV viral loads. Delayed diagnosis of (often asymptomatic) acute HCV may have implications for onward transmission especially in the context of multiple partners.<br><br>Reference: EASL HCV guidelines 2016 | |
| 11 | Fiona Lyons | GUIDE clinic, St. James's Hospital Dublin | Well done to all - you've thought of absolutely everything! Only question is around POCT blood testing and whether or not it should be 4th gen POCT and if so should that be explicitly stated.<br><br>Thanks all | |
| 12 | Yusef Azad | National AIDS Trust | BHIVA/BASHH guidelines on the use of HIV pre-exposure prophylaxis (PrEP) 2017<br><br>Consultation response from NAT (National AIDS Trust)<br><br>NAT is the UK's HIV policy and campaigning charity. NAT has for a number of years been campaigning and working for the routine provision of PrEP and believe clinical guidelines will play an essential role in equitable and evidence-based access. We congratulate the Guideline writing group on an excellent draft. We have only a few comments.<br><br>3.2.3 – This has already been brought to the attention of the writing group but we also mention it for the sake of completeness. Aidsmap have recently reported a BMJ paper which identifies increased risk of still birth and early infant death amongst pregnant women taking tenofovir and emtricitabine ( http://www.aidsmap.com/page/3171862/). This clearly has implications for the Safety section in relation to pregnant women and to later prescribing recommendations. NAT recommends that further and more detailed discussions take place with women living with HIV and at risk of HIV to identify the most appropriate recommendation on PrEP for pregnant women, | |

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| | | | if these results on further investigation appear convincing.<br><br>3.3 – We note the lack of UK evidence on PrEP amongst people who inject drugs. The same, however, is also true of PrEP in heterosexual populations and cannot of itself be a reason not to recommend provision if similar biological efficacy can reasonably be assumed. It is the case though that HIV incidence remains low in this group, apart from specific outbreaks such as that recently in Glasgow. We would, however, warn against complacency and in particular against the assumption that needle and syringe programmes (NSP) and opioid substitution therapy (OST) are readily available everywhere in the country. A substantial number of people who inject drugs are not accessing OST and cuts to public health funding have made provision of both OST and NSP patchy in many places and not adequately accessible. We accept adherence may be an issue for this group and believe further studies in the UK of PrEP for people who inject drugs should be undertaken as soon as possible. At recommendation 7, it will be important for the clinician to assess not just the theoretical availability of OST and NSP but actual availability and access locally, bearing in mind the circumstances of the individual, and take this into account when considering whether PrEP might be an appropriate prevention option. NAT recommends the Guidelines are amended here to reflect this.<br><br>3.4 and 4.2.7 – There seems to be some inconsistency in the recommendation of PrEP regimen for trans women. At 3.4 and recommendation 9 it states that trans women having condomless anal sex should be offered 'daily oral TDF-FTC'. But at recommendation 17 within section 4 it states that 'PrEP with regular or event based oral TDF-FTC is offered to MSM and TGW at elevated risk of HIV acquisition through recent and ongoing condomless anal sex'. (And see also recommendation 33 and text at 6.3). We would add that the meaning of 'regular' is unclear. Is that the same as 'daily'? Or does it also include regular, intermittent dosing? NAT recommends amendment to ensure consistent recommendations for PrEP regimen for trans women.<br><br>5.2.1 – in relation to STIs the emphasis in the guidelines seems to be very much on testing. This is of course paramount. But we believe the Education section should include clear information that PrEP does not protect against other STIs (possibly it is assumed in the text this will be communicated), as well as information on transmission routes for the most relevant STIs and how to avoid their acquisition.<br><br>5.2.2 – in relation to drug use and chemsex it would be useful in the Behavioural support section to make reference to the Neptune project and guidelines. Neptune recommends that all clinical staff and health advisors in sexual health clinics are able to provide a brief information intervention around drug use and this recommendation should be referenced and replicated here.<br><br>At 5.2.3 where adherence support is discussed we welcome the references to particular groups who might need extended or elevated support. Given the references earlier in the evidence section to the significantly lower adherence of MSM on the event-driven regimen for PrEP we believe that group should also be referred to here as possibly requiring particular attention around adherence support.<br><br>5.6 – Given the recommendation that tenofovir alone can be considered for heterosexual women and men, what are the recommendations around frequency of dosing and lead in periods? Are they the same as for TDF-FTC? If so, and in any event, | |

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| | | | there should be explicit reference to frequency of dosing and lead-in periods for a regimen using tenofovir alone.<br><br>6.4 – the flowchart should be amended in the Baseline testing section, first bullet to read, 'HIV testing using 4th generation (plus POCT if same day initiation is preferable)' i.e add 'plus', to avoid cursory reading inferring that POCT can substitute for the 4th generation test.<br><br>Table 6.5.1 – there is a recommendation for an HIV test at one month from PrEP commencement if there was risk in the four weeks prior to starting PrEP. Is the assumption that delivery of this HIV test would involve a face-to-face consultation? If that is the case, then it might be worth stating explicitly at section 6.3 that a face-to-face consultation and HIV test is needed at one month for those who report risk in the four weeks prior to starting PrEP.<br><br>6.5.3 – we are unsure of the rationale for a different STI screening recommendation for heterosexuals from that for MSM. For those taking PrEP because they have a long-term regular partner who is HIV-positive and not virally suppressed we can see why routine 3-monthly STI screens are not required. But for other heterosexuals deemed at high risk of HIV, NAT believes the reasons for their eligibility for PrEP will almost always also be relevant to STI risk and so the 3-monthly screening recommendation should be the same.<br><br>4.1 and 6.5.8 – there is reference at 6.5.8 to heterosexuals at high risk of HIV as 'others whose risk of HIV may be greater than or equal to 2% per annum'. This is a reference to the GUMCAD code information provided at Appendix 1 and developed by Public Health England. We appreciate this definition is not that of the writing group and that it is important to reflect accurately the content of the codes. The reference to risk of 2% or above does, however, come as a surprise at this point in the Guidelines, when no reference was made earlier to that as a criterion for eligibility. NAT does not believe the 2% definition of equivalent high risk is a useful one to apply to assessments which are by definition case-specific and where no information of such statistical detail is available. This should be taken up with PHE.<br><br>NAT believes the content at Table 4.1.1 is the suitable and preferable way to assess risk of HIV which might make someone eligible for PrEP under the terms of the IMPACT trial within the 'equivalent risk' category. This raises the question of whether the Guidelines are accurate and helpful in describing such case-to-case assessments as being of 'Medium risk'. This unnecessarily unmoors the BHIVA/BASHH recommendation from eligibility criteria for the IMPACT trial and quite probably for any routine commissioning of PrEP to follow. We accept of course that clinical guidelines cannot be drafted within the constraints of separate commissioning decisions. But here NAT thinks it better for Table 4.1.1 to work on the assumption that all those offered PrEP have been judged to be at high risk of HIV acquisition (accepting there is a spectrum to that concept) and remove the phrases 'High risk' and 'Medium risk' in the relevant rows so that they simply state 'Recommend PrEP' and 'Consider on a case by case basis', respectively. | |
| 13 | Leena Sathia | Gilead Sciences | Gilead welcomes the opportunity to provide feedback on the consultation version of this Guideline on the use of HIV Pre Exposure Prophylaxis. The guideline provides a comprehensive review of the evidence supporting the efficacy, safety and tolerability of Truvada for PrEP in appropriate high risk populations. The pragmatic approach to HIV risk assessment, monitoring on PrEP, and provision of proformas will prove useful in clinical practice. | |

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| | | | We would appreciate the guidelines writing committee considering referencing the Truvada SPC (June 2017), available at https://www.medicines.org.uk/emc/medicine/15826 particularly in regard to the following points:<br>• The licensed dosing schedule of Truvada for PrEP is one tablet, once daily. The evidence supporting the use of on-demand PrEP in high risk MSM has been presented clearly, and non-daily dosing schedules may well be a preferred option for some PrEP recipients, however it should be highlighted this is an unlicensed dosing schedule.<br>• Renal monitoring recommendations in this guideline(Section 6.5.5) differ from renal management in PrEP detailed in the Truvada SPC | |
| 14 | Ian Green | Terrence Higgins Trust | Terrence Higgins Trust welcomes the draft guidelines for the use of HIV pre-exposure prophylaxis. We have reviewed the consultation document and have no specific observations to make. We are conscious the THT is represented on the Guideline writing group so have already had the opportunity to engage in the process. We are aware of recent concerns surrounding the use of PrEP in pregnancy and would request that these concerns are addressed within the guidelines. | |
| 15 | sophie candfield | Mortimer Market Centre | I don't personally think there is enough evidence to say that on demand PREP "is highly efficacious in preventing HIV infection in MSM". The MSM in the IPERGAY study were shown to have frequently used PREP 4x/week (median tablets per week by my calculations is 3.38), which as per IPREX data means it should have been equivalent, or close to, OD dosing. I think that a potentially increasing interest will emerge for PREP, and with that, on demand PREP, especially as it becomes more normalised in MSM communities and its use feeds into lower risk groups. I worry that lower risk MSM, ie those having UPAI infrequently, do not have enough evidence from IPERGAY to justify a strong recommendation for on demand PREP in that group. Sophie Candfield, SpR sexual health and HIV Mortimer Market | |
| 16 | Laura Waters | CNWL Mortimer Market Centre | Well done to all involved - a well-written and very comprehensive piece of work.<br><br>My only comment is related to the lack of urinalysis at baseline - I appreciate the rationale to not necessarily perform urinalysis regularly (including lack of tubulopathy in trials and poor PPV for creatinine rise) but:<br>1) Some trials (eg Partners PrEP) excluded individuals with protein+ urine dip at baseline, iPreX excluded individuals with renal disease at baseline<br>2) Trial participants were young (27 in iPreX, 33 in Partners PrEP) but real-life PrEP users may be older (e.g Kaiser Permanente cohort average age = 37)<br>3) Individuals with CKD are at elevated risk of TDF-related renal toxicity; the NICE definitions of CKD include proteinuria<br>4) Absence of urinalysis at baseline makes any subsequent renal impairment (including potential relatedness to PrEP) difficult to assess - in the absence of much/any real-life experience with TDF-based PrEP use in the UK should we not exert caution wrt monitoring until we accumulate more evidence of safety?<br>5) The fact that urine protein has poor PPV for creatinine rise should not necessarily lead to urinalysis not being performed since creatinine elevation is not the sole manifestation of TDF renal impairment<br><br>So, on this basis, my view is that urinalysis should be performed:<br>1) In ALL at baseline as a comparator for any future findings and as part of baseline renal function assessment to determine | |

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| | | | need for ongoing monitoring<br>2) Annually in those with existing renal disease, on nephrotoxic meds or with other renal risks<br>3) As part of the investigation of creatinine rise should this occur (as standard basic renal work-up) | |
| 17 | Dr Nneka Nwokolo | Chelsea and Westminster Hospital NHS Fdn Trust | A well thought through and pragmatic guideline.<br>It's helpful that the guidance for groups other than MSM are non-specific enough to be applicable to a diverse group of people on a case by case basis. I have concerns that many people from BME and trans groups will not come forward themselves; it's crucial, therefore that healthcare professionals are able to identify individuals at risk and offer PrEP to them.<br>Specific comments below:<br>Contents<br>Section 4.2.4 People with HIV-positive partners who are not on suppressive therapy – should this read "People with HIV-positive partners whose viral loads are not suppressed on therapy"?<br>Section 5.5 Other considerations<br>5.5.1 Pregnancy or trying to conceive –this sounds quite "lay" – I wonder if "Women who are pregnant or trying to conceive" might sound better<br><br>Body of guideline<br>Transwomen<br>Section 3.4.3.4 Interaction with female hormones page 31<br>The University of Liverpool (www.hiv-druginteractions.org) has responded to a request to clarify that there is no interaction between TDF/FTC and ethinylestradiol; concerns about co-administration relate to VTE risk not to drug-drug interactions<br><br>In 5.5.2 Bone health<br>5.5 Other considerations: Recommendations<br>29: We suggest that if an individual is pregnant when starting PrEP or becomes pregnant while on PrEP, we suggest continuation of PrEP during pregnancy…… etc.<br>"We suggest" is repeated<br>6.5.4 Viral hepatitis<br>Is it worth saying something about hepatitis B in non- responders to vaccination here?<br><br>7 Buying generics<br>There are no peer reviewed papers on this subject. See below:<br>Wang, X., Nwokolo, N., Korologou-Linden, R., Hill, A., Whitlock, G., Day-Weber, I., McClure, M. and Boffito, M. (2017), InterPrEP: internet-based pre-exposure prophylaxis with generic tenofovir disoproxil/emtricitabine in London – analysis of pharmacokinetics, safety and outcomes. HIV Med. doi:10.1111/hiv.12528<br><br>Guideline Might be easier if the references were all at the end. They could be ordered according to section but I think it would make the document easier to read | |

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| 18 | Bridie Howe | Newcastle upon Tyne Hospitals NHS trust | This is a comprehensive, informative and readable guideline, thank you. Just a couple of minor points:<br><br>1) I would like to recommend moving the summary to the start to make it easy to find as a quick reference.<br><br>2) EC90 – on page 40 – is it supposed to be IC 90?<br><br>3) Box 3.5 p80 and p36: for consistency "TGW women" could be shortened to "TGW" as in the rest of the document.<br><br>4) Abbreviations to add to the list:<br>AUC – area under the concentration-time curve<br>CASI – computer assisted interview<br>CI – confidence interval<br>DEXA – dual-energy x-ray absorptiometry<br>DMPA – depot medroxyprogesterone acetate (contraceptive injection)<br>FTC/FTC-DP – emtricitabine/emtricitabine disophosphate<br>IC 90 – Concentration at which 90% of organisms inhibited<br>ICER - incremental cost effectiveness ratio<br>IQR – interquartile range<br>PWID – people who inject drugs<br>POCT – point of care test<br>QALY – quality adjusted life years<br>SSA – sub-Saharan Africa<br>TDF – tenofovir disoproxil fumarate<br>TGW – transgender women<br>TGM – transgender men<br>TFV-DP – tenofovir diphosphate<br>TZM-bI - ? | |
| 19 | Diarmuid Nugent | The Mortimer Market Centre | These guidelines give very clear, practical advice and will be invaluable for use in clinical practice. I wanted to point out the conflicting advice regarding event based PrEP dosing in TGW. Sections 3.4 and 5.6 make it clear that event based dosing is not recommended in TGW even if their risk of HIV acquisition is through anal intercourse, whereas section 4.1 states that MSM and TGW can be offered event based dosing if they are at risk through anal intercourse. I am not sure I understand the biological rationale not to offer event based dosing in TGW who have not undergone gender re-assignment surgery and whose risk is from anal intercourse only. | |
| 20 | Matthew Hodson | NAM | The team at NAM believe that this is a comprehensive, sensible and practical set of guidelines, though inevitably handicapped by being issued at a time when the IMPACT trial is imminent. This will probably influence PrEP commissioning and prescribing, so guidelines may have to change again relatively soon.<br>There are a few relevant studies and data that have come out since these were written that may need inclusion. | |

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| | | | One point we'd particularly like to highlight, so have lifted it out of the detailed notes below:<br>Given our understanding of trans* people's risk of HIV, and also of anal sex between men and women in heterosexual sexual relationships, whether we should stop talking about efficacy in MSM versus heterosexuals and instead talk about efficacy in anal versus vaginal sex. We appreciate most studies are not done that way, but it would be good to at least look at the evidence for sexual practice, not sexual orientation, and also to make it clear that gender orientation is separate from both of those. We also know pretty much nothing about HIV infection via penile tissue and PrEP's effect for insertive men (not just heterosexual ones) and insertive trans women.<br>This does not just apply to the section we have drawn attention to, but applies throughout the whole document, and it might be going through it to see if, when you say "heterosexual", you actually mean "vaginal" and when you say "MSM" you actually mean "anal".<br><br>Detailed notes<br>Page 6, paragraph 2. "The literature review was from January 2004-May 2016". I presume this is a typo as you reference papers from 2017.<br>Even so, this will miss out important data from:<br>• New South Wales, Australia (see http://www.health.nsw.gov.au/endinghiv/Documents/q2-2017-nsw-hiv-data-report.pdf)<br>• The Kaiser Programme in northern California (see Marcus JL et al. Redefining HIV preexposure prophylaxis failures. Clinical Infectious Diseases, 2017. See https://doi.org/10.1093/cid/cix593<br>• And the latest diagnosis figures from San Francisco: https://www.sfdph.org/dph/files/reports/RptsHIVAIDS/Annual-Report-2016-20170831.pdf<br>• The recent US cost-effectiveness study: McKenney J et al. Optimal costs of HIV pre-exposure prophylaxis for men who have sex with men. PLOS ONE, 12(6): e0178170. 2017. Full text here.<br>• The recent review of tenofovir/emtricitabine risk in pregnancy – see Siemieniuk R et al. Antiretroviral therapy in pregnant women living with HIV: a clinical practice guideline. BMJ Open 358: j3961, 2017. And related papers.<br>• The Ipergay analysis of study subjects who had less than the average amount of sex: Antoni G et al. On-demand PrEP with TDF/FTC remains highly effective among MSM with infrequent sexual intercourse: a sub-study of the ANRS IPERGAY trial. 9th International AIDS Society Conference, Paris, abstract number TUAC0102, July 2017.<br>• And of course the latest UK data from Dean St etc.<br>I think there may be others I've missed, but these seem most relevant.<br><br>Page 10, last sentence. Re Ipergay (see ref above): The finding of 50% of men taking either a suboptimal dose or no dose at all, despite apparent PrEP effectiveness, begs the question of whether men were selectively not taking PrEP if they judged that their partner was not an HIV risk, and presumably doing so quite accurately. This may be evidence of 'viral sorting' i.e. not taking PrEP with HIV-positive partners known to be virally suppressed. We don't have evidence for this, but it may be worth noting as a further research topic.<br>Page 11, re ADAPT study: "The study demonstrated similar coverage of sex acts for daily and non-daily regimens". It didn't in Harlem. In Aidsmap's report, we say "In Harlem, the daily regimen protected 66% of sexual acts, the twice-weekly regimen protected 47% and the event-driven regimen protected 52%." This was highly significant (p=<0.0001 for daily versus time- or event-driven). See<br>http://pag.ias2015.org/PAGMaterial/PPT/2239_11079/Harlem%20HPTN%20067%20IAS%202015presentation%20updated%2 | |

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| | | | 0071815%20LB.pptx<br>Page 16, section 3.2 (reiterated from above)<br>Given our understanding of trans* people's risk of HIV, and also of anal sex between men and women, we believe it would be valuable to stop talking about efficacy in MSM versus heterosexuals and instead talk about efficacy in anal versus vaginal sex. I appreciate most studies are not done that way, but it would be good to at least look at sexual practice, not sexual orientation. We also know pretty much nothing about HIV infection via penile tissue and PrEP's effect for insertive men (not just heterosexual ones).<br>Page 19, section 3.2.2<br>Here, and I think also in 3.2, you quite rightly stick to the RCTs as your main evidence. But I think it is also important to mention the tissue absorbance and time to steady-state studies here (I know you cover them in section 3.6, but you should refer to that section here). It's an important caveat that PrEP adherence may need to be higher in women than men (and trans men who have vaginal sex).<br>Page 21, section 3.2.2.5<br>We support the general message that there needs to be a clear programme of education and information for non-MSM about PrEP.<br>Page 27, section 3.3.2<br>Bangkok Tenofovir Study: Given that adherence was at least 84%, much of it directly-observed, but effectiveness only 50%, this casts considerable doubt on the efficacy of PrEP for parenteral infection.<br>Page 28, 3.3.4.1<br>The Chemsex Report (Sigma / LSL) provides limited data that suggests that the HIV risk for people into chemsex is (probably) overwhelmingly sexual.<br>Page 29, 3.4<br>3rd bullet point, replace "to be" with a comma.<br>Thanks for trying to summarise the evidence for trans people.<br>Page 33, 3.5<br>And for young people!<br>Page 43, section 4.1.<br>Title: Is there a better word than "target"? We are not over-fussy about language but it carries overtones of blame, exposure or coercion. What this section is about is not 'targeting' but simply identifying those at risk.<br>Also, we believe it should be 'those at risk of HIV infection?' "Transmission" is a risk run by people with HIV.<br>Possibly replace "Population-level indicators" with "Demographic indicators"<br>Table 4.1.1<br>Transgender women are at high, not medium risk. The evidence we have suggests at least 50% more risk than MSM.<br>We would suggest having had a rectal bacterial STI in the previous year was high risk. It's included as a criterion in itself in a lot of PrEP studies/programmes.<br>We also think repeated nPEP course is an indicator of high risk too. Also included in some PrEP programmes, e.g. in France.<br>Perhaps the language of "medium risk" is unclear. Would this group be better as "Risk to be assessed on a case-by-case basis"?<br>Page 46, section 4.2.6 autonomy and networks<br>We suggest adding to the bullet pointed list (and to table 4.1.1), "Risks taken by the person's partner, outside of the primary | |

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| | | | relationship."<br>Page 47, section 4.2.7 Risk assessment.<br>You should include psychiatric/mental health assessment here. It always gets left out, yet psychiatric indicators ranging from depression to a history of child sex abuse are highly associated with HIV risk. EACS treatment guidelines on depression assessment are good (page 66 of the current edition) and they should be applied to PrEP assessment too. There is no point giving PrEP to someone too depressed to take it.<br><br>Also a social assessment too if there are indications of e.g. poverty, homelessness, undocumented residency status, domestic violence, etc.<br>However we welcome that section 4 is broad and flexible in its thinking.<br>Page 49, Section 5<br>I think you have to have some mention of the IMPACT trial here and what it includes in its protocol.<br>Page 50. Section 5.2.1 "Useful Resources". Please include www.aidsmap.com here for our PrEP news and consider www.prepineurope.org.<br>Page 51 5.2.3.1 Adherence interventions.<br>Although it's much broader than the measures you list here, psychological and social support are likely to produce improvements in adherence too in those needing them.<br>Page 53, good practice points<br>One other bullet point that could be added here is to remind clinicians to ask the person seeking PrEP if they foresee adherence difficulties, and if so why.<br>Page 56, recommendation 24<br>Shouldn't the hep C screening recommendation be specific to MSM?<br>Page 58, recommendation 29<br>Delete "We recommend that" at the beginning of the sentence.<br>Page 60, table<br>This is very helpful.<br>Page 61, recommendation 33<br>The wording of the second bullet point under 33 is unclear. Suggest: "MSM and TGW should be advised that daily PrEP may provide benefit so long as at least four doses are taken per week" or "MSM and TGW should be advised that daily PrEP is likely to be ineffective if fewer than four doses are taken per week"<br>Page 68, recommendation 37<br>Delete "is recommended" towards the end of the sentence.<br>GPP on bone health: no routine monitoring for PrEP users with no BMD risk factors, but what are you recommending for PrEP users who do have BMD risk factors??<br>Page 69, section 6.6, indications for stopping PrEP.<br>Some consideration might be given here to the question of following-up people who've stopped PrEP and not returned to clinic. Clearly it is not as crucial as it is in treatment and people will in general probably stop PrEP for good reasons, but I think it's good practice to follow-up patients who seemed very vulnerable on assessment and who disappear.<br>Page 71, section 7, generics<br>A good practice point relating to duty of care would be helpful. For example: "Individuals obtaining their own PrEP | |

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| | | | medications should be provided with monitoring to help them take PrEP safely."<br>Page 74, section 8, cost-effectiveness.<br>As I say above it would be a good idea to include the US cost-effectiveness study here (MacKenney et al.) as it's the first one published based on US models for some time.<br>Page 92, coding examples<br>An example or two using the O60 transgender code might help remind clinicians to use it.<br>Page 95, proforma<br>Two-step gender questions might help correctly record trans people's identity. CliniQ uses the following:<br>1. Please tell us how you see your gender<br>• Male (including trans male)<br>• Female (including trans female)<br>• Gender queer / non-binary<br>• Prefer not to say<br>2. Is this the same as the gender given at birth?<br>• Yes<br>• No<br>• Prefer not to say | |
| 21 | Louis Macgregor | University of Bristol | Dear Consultation Team,<br>I am an infectious disease modeller at the University of Bristol and have been working on HIV and Hepatitis C co-infection within men who have sex with men. I am currently working on how PrEP may impact Hepatitis C infection and as part of this I have completed a hepatitis C screening analysis aimed at PrEP users. Although not currently at the stage of a cost analysis I have looked at the changes in hepatitis C prevalence that could be achieved over a range of assumptions. I would very much like to send my preliminary work to be considered when looking at the PrEP guidelines in your consultation, to see if you view it as beneficial to screen PrEP users for hepatitis C as part of routine 3-monthly health check-ups. Is there a way I can attach or send my work for your consideration? | |
| 22 | Hannah Loftus | Sexual Health Sheffield | I wanted to clarify regarding renal screening in those under 40 with normal eGFR at baseline. In the text it would suggest that after starting, no further eGFR is needed until 1 year. In the flow chart it suggests that the patient is followed up at 1 or 3 months after starting PrEP for serum creatinine and eGFR (and HIV/STS screen, adherence check). Could this be clarified?<br><br>On page 38, the time to clinical protection for anal sex with double dose TDF-FTC is discussed. With no evidence about time to clinical protection for single dose TDF-FTC should all patients be advised to take a double dose for the first dose even if they are on daily dosing? | |
| 23 | John Saunders | Public Health England | Public Health England welcomes the thorough and practical guidelines on pre-exposure prophylaxis. Public Health England has been involved in the development of the guidelines through involvement in the writing group. Our virology colleagues are providing a separate response to the consultation. We would like to take the opportunity to provide some responses to the guidelines through this consultation. | |

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| | | | 1. Section 4.1 of the guidelines on p43 entitled 'How to target those at risk of HIV transmission' provides guidance on risk behaviours and vulnerability factors that increase the risk of HIV to be taken into consideration when considering eligibility for PrEP. Whilst this guidance is welcome where there is lack of an evidence base, there are certain indicators included in the 'medium risk' category that are not associated with a high risk of HIV in the absence of other risk factors, and we believe that this could be made even clearer in the guidelines. For example, the 2017 report of the Unlinked anonymous HIV and viral hepatitis monitoring among PWID found that the HIV prevalence among PWID was 0.85% overall; the prevalence of HIV among heterosexual black African men and women varies considerably based on country of origin; people who report sex work or transactional sex may only have an elevated HIV risk in the presence of additional risks such as condomless sex with partners from a population group or country with high HIV prevalence.<br><br>PHE have conducted additional analyses of GUMCAD surveillance system data to inform a risk analysis table for PrEP, in line with the table in section 4.1 of the guidelines and we would be happy to share this with the guidelines group once it is finalised. We have used an incidence of 2% per annum as a guide for recommending PrEP based on transmission data within serodiscordant couples. Where this incidence is greater than 2% per annum prescribing PrEP is recommended. If the incidence approaches 2% or is unknown, then we suggest that PrEP should be considered alongside additional potential risk factors.<br><br>2. In section 4.2.7, the risk assessment is closely aligned with the BASHH 2013 UK national guidelines for consultations requiring sexual history taking. This is includes a record of number of sexual partners in the last 3 months, and number of new partners in the last 3 months. A link to this guidance should be clearly highlighted. These variables are included in the new specification for the GUMCAD surveillance system which is currently being reviewed by NHS Digital. The technical specification which was piloted is available here: https://www.gov.uk/guidance/genitourinary-medicine-clinic-activity-dataset-gumcadv3-pilot. | |
| 24 | Louis Macgregor | University of Bristol | BHIVA PrEP guidelines consultation: modelling based projections of the impact of screening for hepatitis C in PrEP users<br><br>Authors: Louis Macgregor1, Natasha K Martin2,1, Ford Hickson2, Peter Weatherburn2, Matthew Hickman1, and Peter Vickerman1<br><br>Affiliations: 1School of Social and Community Medicine, University of Bristol 2London School of Hygiene and Tropical Medicine 3Division of Global Public Health, University of California San Diego<br><br>Summary: We examined the impact of PrEP on hepatitis C (HCV) and HIV infection patterns within men who have sex with men (MSM), using a joint HIV and HCV dynamic co-infection compartmental model. We made use of data from the European Men's Internet Survey to parametrize our model as well as extensive literature. We used our data in line with the PrEP eligibility criteria given by NHS England; resulting in eligibility of 13.2% of the HIV negative or HIV undiagnosed MSM population in the UK, assuming 43-86% efficacy of PrEP at reducing HIV transmission. We assumed current HIV prevalence of 5.9%, HCV prevalence within HIV positive MSM of 9.9% and HCV prevalence within HIV negative MSM at 1.2%.<br>Our results indicated that Screening PrEP users at increasing frequency resulted in significant reductions in HCV infection, not | |

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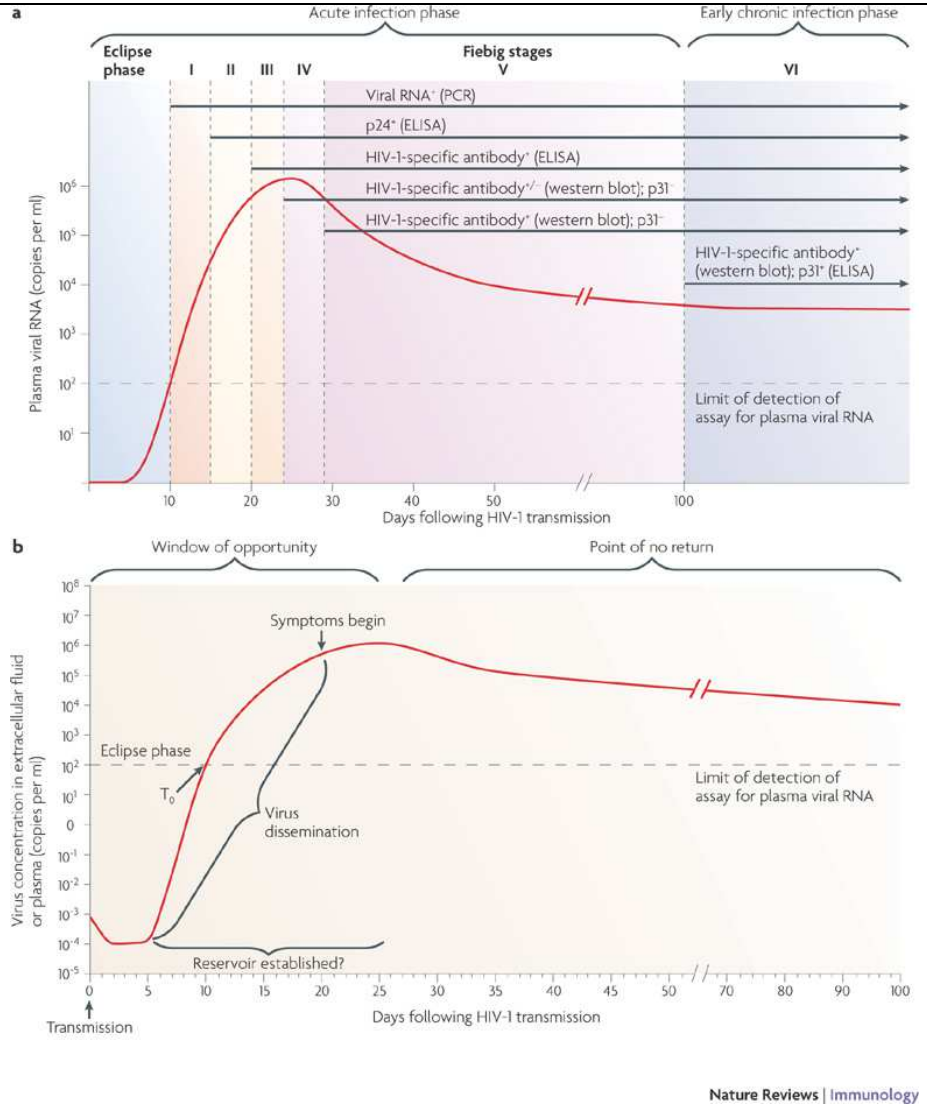
| | | | only for PrEP users themselves, but for HIV positive MSM. With no extra screening of PrEP users beyond current levels, after 10 years of steady PrEP coverage we projected 1.6% overall HCV prevalence within MSM, 2.59% within PrEP users and 9.53% in HIV positive MSM. However with annual screening, we projected 1.38% (13.5% reduction) in overall HCV prevalence in MSM, 1.45% (44.1% reduction) within PrEP users and 8.93% (6.3% reduction) in HIV positive MSM compared to no extra screening. What is more, with quarterly screening, we projected 1.31% (18.2% reduction) in overall HCV prevalence in MSM, 1.10% (57.3% reduction) within PrEP users and 8.69% (8.8% reduction) in HIV positive MSM compared to no extra screening. Our projections were not sensitive to the efficacy of PrEP (which we varied from 0-100%), but were sensitive to the level of PrEP coverage (which we varied from 0-25%). At 5%, 13.2% and 25% PrEP coverage, with 3-monthly screening of HCV, we projected 1.61%, 1.31% and 1.02% in overall HCV prevalence in MSM, 1.27%, 1.10% and 0.92% within PrEP users and 9.72%, 8.69% and 7.79% in HIV positive MSM respectively.<br>We also ran our model under assumptions of changing behaviours due to PrEP, specifically (1) Any partnership involving a PrEP user has condom use decrease from the current average of 68% to 13%, (regardless of partner HIV status); (2) Instead of mixing by HIV status, PrEP users no longer preferentially mix by HIV status and HIV diagnosed MSM mix preferentially with PrEP users as well as other HIV diagnosed MSM; (3) both scenario 1 and 2 combined. In all cases, screening for HCV in PrEP users 3-monthly, compared with no extra screening, provided a greater reduction in relative HCV prevalence than without changing behaviours. This shows that screening PrEP users for HCV may be an effective strategy as a pre-emptive intervention to reduce the negative impacts of risk compensations on HCV prevalence.<br><br>Contact: For full details of our model and projections (including graphs which could not be uploaded here), please email lm13381@bristol.ac.uk and I will be happy to provide our full analysis and model description. | |
| 25 | Colin Brown | Public Health England | **Section**:<br>'6.5.1 HIV testing HIV testing should be undertaken every 3-months with a laboratory 4th generation test or blood-based POCT. Further PrEP prescriptions should not be issued without repeat HIV testing every 90 days. Atypical testing results should be discussed with a regional expert, for possible further investigation for seroconversion.'<br>**PHE Response**:<br>The Fiebig stages of acute HIV infection are covered in the European AIDS Society guidelines but not BHIVA testing or monitoring guidelines: this covers the development of antibody and antigen responses such as partial or complete western Blot criteria for HIV infection, alongside appearance of p24 antigen and detectable RNA (see chart below {Michael JA et al. The immune response during acute HIV-1 infection: clues for vaccine development. *Nature Rev Immunol* 2010;10:11-23.}). | |




The particulars of the Feibig stages are soon likely to be surpassed by new staging criteria currently in development.
The PrEP draft guidelines highlight that 'atypical results' should be discussed with regional experts, however does not detail what such results may entail, or comment further about who may be a regional expert. There is increasing evidence from a variety of groups, particularly those who test large volumes of blood donors, and from existing data from PrEP trials, that PEP, PrEP and early ART initiation in acute infection can cause blunting of the HIV-1 antibody response, with both non-reactive HIV

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| | | | serology and non-progressive Fiebig profiles seen, in a setting where viral load is also likely to be undetectable.<br>We therefore recommend that this section includes more clarity of what is meant by an 'atypical' result. These definitions should include:<br>1) static unchanging reactivity on two or more consecutive samples (conceptually considered as 'discrepant' reactivity), which does not fit with a pattern usually associated with confirmed positivity, and<br>2) capturing 'discrepant' reactivity which changes over time, including 'any change in a combined antibody/antigen test reactivity while remaining on PrEP, with or without repeat testing on a separate assay'.<br><br>Both of these patterns will occur in the absence of molecular evidence of HIV infection. We use the term 'combined antibody/antigen test' throughout, given the development of '5th generation' assays that can differentiate between HIV-1 and HIV-2 antibodies.<br>We recognise that the cponsequences of these 'atypical' or 'discrepant' tests results for an individual may have little impact at a public health level. However, the scale-up of PrEP at a national level is an important time to clarify what is happening to these individuals to inform their management. We agree best practice would be for them to get followed up with advice from a 'regional expert', however we would appreciate if this latter term was clarified. We would recommend that these experts are a small group of 'laboratory or clinical professionals with significant expertise in the interpretation of equivocal or discordant HIV results having access to reference laboratories with experience of diverse methods for detecting evidence of HIV infection', who will work together and deliver harmonised advice and data collection. Therefore there could be four or five identified regional experts (with additional support from PHE Colindale and an additional expert for each of the devolved administrations), who would have a proforma for data collection and created a database for a core set of clinical and laboratory data. This would include information on which platforms the tests were 'atypical', signal-to-cutoff values, and local testing protocols. These data could be linked to the GU clinic number in order for linking to their prior clinical history within the GUMCAD surveillance system. It is likely that PHE, BHIVA and BASHH would want to be made aware of such cases, and enhanced surveillance of such cases should be considered.<br>For your information, PHE and Imperial College have established a new tertiary national referral clinic for patients with 'discrepant' HIV results, the IDRIS (indeterminate retrovirus infection service) clinic, looking at patients whose results leave diagnostic uncertainty regarding whether they have:<br>• established HIV infection with high level elite control i.e. HIV-1 infected persons who do not have detectable HIV-1 RNA in plasma by commercial assays, and with an equivocal serological diagnosis<br>• or complex non-specific cross-reactivity i.e. HIV-1 serology tests are repeatedly positive but confirmatory tests are inconclusive and molecular tests are negative and it is thought they remain uninfected.<br><br>An expanded panel of tests will be performed to assess surrogate and molecular markers of infection, however the first clinic is going to run in October, and any emergent information is unlikely to inform these guidelines.<br>For those people who develop 'atypical' or discrepant antibody reactivity and remain on PrEP there should be:<br>• agreement about how to investigate them further, for example on whether to discontinue PrEP for a period of 1-2 months and test off treatment, acknowledging that if these are true incident infections this will likely result in a viral | |

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| | | | burst resulting in an increased reservoir , with some heightened potential for adverse effects of primary HIV infection, and ensuring by barrier protection for sexual partners during the drug holiday<br>• more clarity about what is expected in terms of further testing, such as 'such individuals should undergo a panel of tests including multiple testing on at least two separate combined antibody/antigen generation commercial assays, alongside Western Blot or InnoLia testing, and molecular tests including extended primer sets, for a full assessment of likelihood of infection' (the use of ultrasensitive standalone p24 assays may be incorporated in the future).<br><br>There is considerable uncertainty in this area – for example, are people infectious with 'atypical' or discrepant antibody profiles, should they remain on PrEP, how should they be tested, how should they be followed up, and are the different test algorithms appropriate for 'event-based' and 'daily' PrEP regimens. This will likely be an iterative process that will change with more experience with different testing platforms and evolving international understanding, and at present there is no consensus. In particular the testing algorithm will evolve over time, and PHE is very willing to provide expert guidance into this.<br>Though we recognise that these issues will affect a very small number of people on PrEP, we think it is important to investigate affected persons and collate relevant data given the implications for resistance and transmission. Alllowance should be made for details to change over time e.g. the guidelines could reference the BHIVA website for 'current best practice' and 'list of regional experts' given the guidelines may last for up to five years. There could also be comment that communication through BASHH and BHIVA will occur as more data become available and consensus develops.<br>**Section:**<br>'6.5.2 Management of HIV seroconversion. HIV seroconversion should be considered in any individual presenting with symptoms suggestive of primary HIV infection and investigated with an HIV viral load in addition to a 4th generation HIV test.'<br>**PHE Response**:<br>In this or the above section, or indeed a separate section entitled 'uncertainties around negative results' or something similar, we recommend that reference should be made to caution of negative test results while people remain on PrEP and in any 'washout' period following its discontinuation, given the evolving literature on delayed antibody responses with PrEP (e.g. Partners PrEP){Donnell D et al. The effect of oral preexposure prophylaxis on the progression of HIV-1 seroconversion. *AIDS* 2017 Sep 10;31(14):2007-16.} and early ART initiation (e.g. HPTN 052){Fogel JM et al. Brief Report: Impact of Early Antiretroviral Therapy on the Performance of HIV Rapid Tests and HIV Incidence Assays. *J Acquir Immune Defic Syndr* 2017 Aug 1;75(4):426-430}. This may largely involve Western Blot profile development rather than initial antigen or antibody detection, but we would therefore recommended that the 'high risk' testing window from the BASHH/EAGA position statement on 4$^{th}$ generation testing should be used for follow-up testing. This would allow for testing at both 4 and 8 weeks following discontinuation to allow for any such blunting of primary infection and antigen detection, and subsequent development of antibody response.<br>Consideration should also be given to what it means to have an 'atypical' or 'discrepant' result and then a negative result off PrEP, and what any 'atypical' or 'discrepant' result may mean for restarting PrEP. The guideline writing group may wish to think about this in detail. If an 'atypical'or 'discrepant' result is first detected when off PrEP, then we advise no further PrEP should be prescribed until a definitive consensus is reached on how to best manage such patients.<br>Finally, it would be useful to have some comment on the information that any form submitted with a sample for HIV viral load testing or antibody/antigen testing should now include whether the patient has been taking either PEP or PrEP, and if so when | |

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| | | | and for what duration. Without this information is it impossible to comment on the significance of static or evolving indeterminate reactivities.<br>. | |
| 26 | Sophie Strachan | Sophia Forum | An excellent guideline, seeing the age groups categorised very helpful, and the equality statement<br>I have one point to make,<br>Baseline risk assessment - medium risk based on individual assessment, population markers- can you not include women at risk of CSE or trafficking, that would then identify those at risk beyond black African men and women ?<br>also the language around gender reassignment implies surgery or that only through surgery is gender congruent with ones felt sense/known sense of self.. this is not true and I wonder f this can be re visited regarding language used. | |
| 27 | Nigel O'Farrell | Ealing Hospital | Laudable as these guidelines are, STI clinics are being closed particularly in London where the incidence of HIV is highest in the UK. Patients are being turned away in droves and delays in access to STI healthcare are worsening almost on a daily basis. Paradoxically, Family Planning services are being increased and many such clinics are erroneously calling themselves sexual health clinics whereas in fact they provide minimal services to high risk clients. To roll out any program will therefore need to include nurse education about this specific issue if any sense of equity is to be maintained. There is little point in many subjects trying to obtain PREP from many STI clinics if staff are thin on the ground and they be better off going to Family Planning clinics that are calling themselves Integrated Sexual Health<br>It is also unfortunate that BASHH have not sought to raise the spectre of what is happening to a higher political agenda. Already this has resulted in delays to the Impact study because Directors of public Health can see that the study might make things worse before they get better. The guidelines should therefore give some riders to answer such issues which will strengthen the case for better access to provision of STI care<br>These points are relevant when the amount of details asked for are reviewed. For example, what is the point of asking for details of all partners in the last 3m (page 95)? This is part of a normal sexual history and such repetition is unnecessary and time-consuming. Similarly questions about chemsex are put of the sexual history except here the questionnaire tries to justify the question with a “Please”. If someone is planning a study of these data, this should be made clear in the guidelines.<br>It is surprising that these points are not addressed. Perhaps this reflects the make up the panel who may not be aware of the problems currently faced by clinics outside of a teaching hospital setting. | |
| 28 | rosalind coleman | UNAIDS | Thank you for such a seriously comprehensive piece of work. I appreciate its range of inclusiveness .<br><br>As an overall comment, I missed the community voice. The importance of engagement with a well informed population is well known and shaping clinics to be user friendly also.<br><br>Here are mainly minor points and I cannot claim to have read every word.<br>Box 3.1 pt 2 We recommend that PrEP with on-demand or daily oral TDF-FTC should be offered to HIV-negative MSM having condomless anal sex with partners who are HIV positive, unless it is a monogamous relationship and the partner has<br><br>P 20 As with Partners PrEP, efficacy was dependent on adherence to medication, as assessed by measure of plasma drug concentrations with non-seroconversion drug levels of 30.5 ng/mL for TDF and 103.3 ng/mL for 3TC.<br>Anal sex for women is probably covered as well. | As these are clinical guidelines they do have a more formal tone. There was a great deal of community involvement in their writing and this has been emphasised in the Introduction |

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| | | | Chapter 4 page 43 Target in the title is rather strong and does not reflect the rest of the document's emphasis on joint decision making.<br>P43 Table 4.1.1 mention monogamous relationships<br>Table 4.1.1 insert 'be' Condomless vaginal sex should only be considered<br><br>Can there be a comment Table 4.1.2 that these prevalences are means and that within each demographic group there will be a range of prevalence/incidence/risk factors<br>The information in section 4.2.1 is very important and could have better impact if presented in a table.<br>Section 5.1 context of a comprehensive<br>Provision of PrEP should be preceded…Is this the right word….? It implies that these other prevention strategies should be tried before PrEP is started. While this might be entirely appropriate for some people, for others an earlier move to PrEP will be the right decision. Suggest 'accompanied by' or similar.<br>Table 5.6.1 7 days please add before condomless sex<br><br>Chapter great to see generics addressed! Section 7.2 Other tenofovir formulations are becoming available; it seems that the abbreviation TDX is used to cover this.<br>Could this be mentioned as something to be aware of as it seems likely that more TDX/FTC will arrive on the generic web sites<br><br>Chapter 8 Please add some guidance around ways to increasing cost effectiveness of PrEP services include having a partnership with a well-informed public, strong adherence support and rapidly implementing lessons learned. Watch out for stigmatisation as risk assessment and the offer of PrEP becomes more refined. | |
| 29 | Rochelle Keenaghan | RCP | The RCP is grateful for the opportunity to respond to the above consultation.<br><br>We have liaised with our JSC in Genitourinary Medicine and fully support the development, and implementation of the BHIVA/BASHH PrEP guidelines. | |