BHIVA/BASHH/FSRH guidelines for the sexual & reproductive health of people living with HIV

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Abstract

These guidelines are an update to the 2007 UK guidelines for the management of sexual and reproductive health (SRH) of people living with HIV infection (PLWH). The writing group have utilised updated BASHH guideline methodology, notably using the GRADE system for assessing evidence and making recommendations. We have made significant changes to the recommendations which are summarised below.

Keywords

HIV; reproductive; sexual health; conception; contraception; transmission.

Important changes in the 2017 guidelines

- Cervical screening update
- Practical guidance regarding conception advice and fertility screening
- Undetectable = uninfectious
- Pre-exposure prophylaxis for conception
- Contraception considerations
- Menopause
- Intimate partner violence
- Sexual dysfunction

Methods

The guidelines writing group utilised the updated version of the BASHH Framework for Guideline Development accessible at http://www.bashh.org/documents/2015%20GUIDELINES%20FRAMEWORK.pdf. This includes use of the GRADE system for assessing evidence (http://www.gradeworkinggroup.org/index.htm).

The writing group included: representatives of BASHH, BHIVA and FSRH, clinicians with expertise who applied or were invited to join the writing group, members of the broader multi-disciplinary team (nursing, pharmacist, health advisor, psychology and trainee representatives) and a community representative elected by UK-CAB.

The writing group determined the PICO questions which then formed the basis for literature search:

PICO

- P = patient population = adults with or at risk of HIV considering reproductive/ contraceptive options
- I = interventions = options for conception (UPSI, PrEP, sperm washing etc)

other assisted reproduction options including surrogacy and adoption, contraceptive options, sexual dysfunction and fertility

- C = no intervention, different interventions
- O = outcomes = good sexual & reproductive health, no onward HIV transmission

Keywords were identified by the Writing Committee and the electronic database searches were set up by the information Scientist based on a PI (population, intervention) framework (HIV AND all interventions). A combination of index headings (where available) and text word searching

was used and details can be found in the database search protocol in the online appendix to the guideline.

- The following keywords were used for the conference website/ abstract book: conception conceive fertility subfertility infertility sperm washing contraceptive contraception IVF reproduction insemination surrogacy donor egg UPSI.
- The results of the searches were sifted by reading the titles and /or abstracts and potentially relevant papers obtained in full text if available and reviewed. Relevant papers were then appraised

The following sources were searched for published peer-reviewed studies:

- Medline and Pre-Medline
- Embase
- The Cochrane Library

The following conferences were also searched for 'grey literature' (oral and poster presentations):

- IAS HIV Pathogenesis and Treatment
- World AIDS
- CROI
- EACS
- BHIVA/BASHH
- HIV Drug Congress (Glasgow Meeting)
- FSRH

Study types searched for were systematic reviews, clinical trials and observational studies:

- Date parameters for the database search were January 2004 to December 2015 and the last three years for conference abstracts. Searches were conducted during March & December 2015 with limited additional searches undertaken December 2016-August 2017
- Animal studies, case reports, letters and editorials and comments were excluded
- Results were limited to English language

Stakeholder involvement, piloting and feedback

The draft guidelines recommendations were presented at the British HIV Association Autumn conference 2016. The document was reviewed by the Clinical Effectiveness Group of BASHH, and their comments incorporated. The draft guideline was placed on the BASHH website and any comments received after 8 weeks were reviewed by the authors and actioned appropriately (appendix XX – to be added post-consultation). The writing group included a community representative.

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Introduction & general issues

The number of people living with HIV (PLWH) continues to rise in the UK [1], a function of increasingly normal life expectancy for those diagnosed and on treatment [2] and new diagnoses annually [1]. HIV should not be a barrier to healthy and fulfilling sex life, particularly now there is good evidence to support a zero risk of HIV transmission from antiretroviral treated individuals with sustained viral suppression [3-5]. Access to appropriate, up-to-date advice about transmission risk is an essential element of holistic HIV services. Likewise, PLWH should expect the same standards of reproductive, preconception, fertility and antenatal services as their HIV-negative counterparts. The risk of HIV transmission from a woman living with HIV (WLWH) if diagnosed in a timely manner and managed appropriately, is very low [6]. The British HIV Association (BHIVA) standards for PLWH include recommendations for access to appropriate sexual health screening, treatment and advice, as well as reproductive health services; they also highlight, however, that the impact of living with HIV, a potentially stigmatising condition, and associated sexual dysfunction and psychosexual morbidity, must not be underestimated. In addition, rising rates of sexually transmitted infections (STI) amongst men who have sex with men (MSM) emphasise the importance of open and rapid access to STI screening, treatment, partner notification and risk reduction advice.

Who are these guidelines for?

All people involved in the provision of services or advice related to the sexual and reproductive health of PLWH and their partners including: HIV clinics, sexual & reproductive health services, primary care, obstetrics, gynaecology & fertility services, community and peer-led organisations, and appropriate commissioners.

What is not covered in the 2017 guidelines?

A number of relevant issues may be mentioned but are covered in more detail by other guidelines accessible on the BHIVA, BASHH and FSRH websites, including:

- Human papilloma virus (HPV) vaccination [BHIVA vaccine guidelines]
- HPV-related malignancy screening & management [BHIVA malignancy guidelines]
- Viral hepatitis screening/vaccination [BHIVA hepatitis & BASHH hepatitis guidelines]
- STI screening & management [BASHH guidelines]
- Sexual history taking & STI screening [BHIVA monitoring guidelines]
- Post-exposure prophylaxis [BASHH PEP guidelines]
- Pre-exposure prophylaxis [BHIVA/BASHH PrEP guidelines]

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6. http://www.bhiva.org/documents/Guidelines/Pregnancy/2012/BHIVA-Pregnancy-guidelines-update-2014.pdf accessed 19th September 2016.

Sexually transmitted infections

Recommendations:

- To follow BHIVA monitoring guidelines for STI screening in PLWH (GPP)
- To follow BHIVA monitoring plus BHIVA hepatitis guidelines for viral hepatitis screening in PLWH (GPP)
- Sexual history review at all routine clinic appointments (GPP)
- Provision of appropriate verbal, written or online information about risks and recommended screening for STI and viral hepatitis (GPP)

2016 BHIVA monitoring guidelines are summarised below. We recommend following the BHIVA monitoring guidance with regards to STI screening although highlight that not all acute hepatitis C is associated with a raised ALT and individuals who have had a high risk potential exposure to HCV within 6 months should be offered RNA or antigen testing regardless of ALT level.

Of note, the BHIVA monitoring guidelines state that hepatitis and STI screening should be available within HIV clinics. We strongly support this recommendation, particularly in an era of service fragmentation secondary to divided commissioning arrangements, service reviews and tendering exercises.

BHIVA 2016 monitoring guideline recommendations for STI and hepatitis screening

Baseline

- We recommend a full STI screen is offered to all PLWH at baseline, to be directed by the sexual history. The screen should include syphilis serology for all, vulvo-vaginal swabs for chlamydia and gonorrhoea Nucleic Acid Amplification Tests (NAAT) for all women, urine testing for chlamydia and gonorrhoea NAAT for men, and pharyngeal and rectal swabs for chlamydia and gonorrhoea NAAT for MSM and heterosexual women with a history of oral or anal sex (1B).
- Hepatitis A virus IgG (or total)
- Hepatitis B tests:
    - Surface antigen (HBsAg)
    - Anti-core total antibody (anti-HBc)
    - Anti-surface antibody (anti-HBs)
- Hepatitis C virus antibody
    - If positive test RNA (at least twice if initially negative)

Annually

- Screen for gonorrhoea and chlamydia all exposed sites if partner change since the last test (self-taken swabs if asymptomatic);
- Syphilis serology if partner change since the last test;
- Hepatitis B (for infection or immunity) and C screening (in at-risk patients).

Three-monthly

We recommend 3-monthly screening for STIs if the patient has high risk factors for acquisition, e.g. MSM with frequent partner change or chemsex/IVDU with chaotic lifestyle/CSW/patients who frequently use intranasal cocaine/recent tattoo abroad/recent blood transfusion abroad/other risk (1B)

- We recommend that in such patients the following will be performed (1B):
    - Screen for gonorrhoea and chlamydia at all exposed sites;
    - Syphilis serology
- Also consider at least annually in patients with high risk:
    - Hepatitis B surface antigen or core antibody if not known to be core antibody positive or vaccinated with an adequate surface antibody response (>10 MIU/mL);
    - Hepatitis C antibody (HCV antigen or RNA if ALT abnormal).

The BHVA hepatitis guidelines recommend those without immunity should have an annual HBsAg test or more frequent testing if there are known and ongoing risk factors for HBV acquisition. Their recommendations with regards to hepatitis C testing are:

- HCV antibody at baseline and at least annually if not in risk group requiring more frequent testing
- Anti-HCV and HCV-PCR if raised transaminases or recent high-risk exposure to an individual known to be HCV positive. If prior spontaneous clearance or successful treatment HCV-PCR only should be performed
- We recommend the HCV-PCR should be repeated after 1 month if initially negative and if any potential exposure
- We recommend patients who have repeated high-risk exposures but persistently normal transaminases are screened with anti-HCV and HCV-PCR, or HCV-PCR alone if previously successfully treated for or spontaneously have cleared infection and are HCV antibody positive, at 3–6-monthly intervals

Cervical screening

Recommendations

- Current National Health Service Cervical Screening Programme (NHSCSP) UK guidelines recommend that women with HIV be screened annually between the ages of 25 and 65 and we endorse these recommendations
- The clinical reason for annual smears must be documented on the sample request form (ie the woman is HIV positive) or the sample may be rejected by the laboratory
- Multifocal intraepithelial neoplasia is commoner in women with HIV than those without. Symptom enquiry and external ano-genital examination is advised when taking a cervical cytology sample
- For women diagnosed with HIV after the age of 25, particularly those with previous cervical abnormalities or a long interval since last screening, colposcopic evaluation as well as cervical cytology should be offered where resources permit
- Challenges regarding invitation for annual screening for WLWH who do not wish to disclose their HIV status to primary care should be discussed

Cervical cancer is common globally, almost always associated with human papilloma virus (HPV) infection – HPV types 16 and 18 account for over 60% of cases – and is more common in WLWH [1,2]. WLWH have an increased risk of high-risk HPV (hrHPV) infections compared with their HIV-negative counterparts [3].

In the UK, adolescent females are offered vaccination against HPV at the age of 12-13 as part of the NHS Childhood Vaccination Programme. This is free of charge and in 2015-16, 85% of eligible female adolescents received the full course of vaccination via this programme [4]. The longer term impact of vaccination on CIN and cervical cancer rates has yet to unfold. Currently, no change is suggested with respect to cervical screening in the UK regardless of whether or not a woman has been previously vaccinated against HPV.

The age at first cervical screening invitation via the NHS programme is currently 25 years across the whole of the UK (Scotland and Northern Ireland have devolved NHS programmes but these are in line with England and Wales). There is no differentiation for women with or without HIV infection with respect to age at first invitation.

The increase in age of first invitation for cervical cytology to 25 years has created some controversy both within and further afield from the UK. Indeed, Scotland only recently (June 2017) increased the age of first invitation to 25 from 20 years. There is now general consensus, within the UK at least, that starting screening below the age of 25 confers greater risks than benefits. A full discussion of the summary evidence and references can be found within the NHSCSP Guideline [5]. Samples sent to NHS laboratories before a woman reaches the age of 24 years and 6 months without good clinical reason (i.e. not as a screening test in an asymptomatic woman alone) will be discarded by the laboratory and not processed.

Age of first invitation/recommendation for cervical cytology in the UK is at variance to that of the USA. For WLWH, US CDC guidelines currently recommend cervical screening from 1 year after sexarche, regardless of age at HIV diagnosis. There is no national co-ordinated programme of HPV vaccination for adolescents in the USA. CDC guidelines also recommend that after three consecutive normal annual cervical smears, screening interval can be extended to 3 years, a 2B recommendation. Further, CDC guidelines recommend that where Pap smear is normal and

hrHPV negative, the screening interval of 3 years can be applied after a single normal/negative result. This recommendation is based on evidence from two trials:

1) The Women's Interagency HIV Study (WIHS) recruited 855 WLWH (mean age, 36 years) and 343 HIV-negative women (mean age, 34 years) with normal baseline cervical cytology during 1994-1995 and performed semi-annual Pap smears for a median of 7 years. This study demonstrated, for women with a negative HPV test, similar cumulative rates of cytological abnormalities in WLWH with CD4 greater than 500 (6%) and HIV-negative women (5%), however cumulative incidence of cytological abnormalities was higher in women with CD4 <200 or 200-500 (19% and 14%, respectively) [6].
2) A second WIHS analysis enrolled 420 WLWH and 279 HIV-negative women with normal cervical cytology at baseline over 1 year (10/2001 to 09/2002) with follow-up through to 04/2011. Pap testing (and cervical biopsy if indicated) and HPV testing were performed semi-annually. The 5-year cumulative incidence of high-grade cytological and histological abnormality was similar in HIV-positive and -negative women with negative cytology and oncogenic HPV at enrolment. There was numerically higher cumulative incidence of any squamous intraepithelial lesions (SIL) in HIV-positive women with a CD4 <350 (25% vs 11% in women with CD4 350-499 and >500 and 6% in HIV-negative women) but rates of CIN-2 were low (5% in both groups) with no difference by CD4 count [7].

EACS guidelines recommend a cervical screening interval of 1-3 years but do not specify in whom the interval can be lengthened nor on what evidence this recommendation is based [8]. A Belgian cohort demonstrated reduced risk of persistent cervical hrHPV infection in WLWH women with sustained viral suppression for at least 40 months and sustained CD4 >500 for at least 18 months [9], In an, as yet unpublished, study the same group demonstrated a lower risk of cervical dysplasia in women with a CDd4 >350 compared to those with lower CD4, but there was no comparison with HIV-negative women [10].

Data suggest is that it may be time to revise the recommended interval of screening in WLWH who have a negative cytology result and whose CD4 count is maintained above 500. However, this recommendation should be made via the NHSCSP with appropriate supporting evidence and incorporated into the algorithms for screening and cytology management. If changes to any part of the cytology programme are made outwith the input of this overarching body, it is likely that coverage and appropriate screening of this particularly vulnerable group of women (WLWH) may be reduced or missed rather than improved.

There is evidence that in HIV positive women there is an increased risk of false negative cytology [11]. This may be ameliorated by the addition of HPV testing for HIV positive women, even if their cervical cytology is negative. This would be outside the current practice in the UK for the processing of cervical cytology where only samples showing borderline or low grade abnormality are further tested for HPV. Again, this should be something for the NHSCSP to consider and make appropriate recommendation to ensure translation into practice and consistency across the population.

<u>Multifocal disease</u>

Women with HIV are more likely to have multifocal disease (HPV related intraepithelial neoplasia of multiple areas the ano-genital tract) than their non-HIV positive, immune-competent counterparts [12]. It is therefore especially important to enquire of WLWH whether they have any symptoms which might indicate multifocal disease (itch, irritation, soreness of the

anogenital region) and to inspect all of these areas at the time of cervical cytology sampling. Visible changes that may indicate intraepithelial disease include discoloration of the skin (darker or lighter than the surrounding skin), raised lesions especially if warty or having an irregular surface in appearance and these may warrant colposcopic examination and/ or anoscopy. It should be noted that women will not necessarily have a history of receptive anal sex even if there are disease changes towards the anal margin. Anal cancers may develop in WLWH and anoscopy may be required. Anal screening is still in the development stage but anal cytology may be considered in specialist settings.

Summary

- We recommend annual cervical cytology from the age of 25 unless there is clinical concern (as per standard guidelines for age of first smear in HIV negative women); this may be revised in the near future with stratification according to CD4 count.
- UK advice regarding cervical cytology in WLWH is not aligned with that of the CDC in the USA but there are other significant variations in practice with respect to cervical cytology and the management of abnormal cervical cytology in the USA regardless of HIV status, not all of which are driven by the same evidence and motivators as in the UK.
- For women diagnosed with HIV after the age of 25, particularly those with previous cervical abnormalities or a long interval since last screening, colposcopic evaluation as well as cervical cytology should be offered where resources permit.
- Caring for WLWH can be complicated by reluctance to disclose HIV status, particularly to GPs where the majority of cervical screening takes place. Without the relevant clinical information on a cervical cytology request, a sample which appears to be outwith the normal screening interval may be rejected by the laboratory. If women are reluctant to divulge their HIV status, for whatever reason, to their GP then this may create additional vulnerability with respect to cervical screening. This should be flagged up with WLWH as an additional encouragement to inform their GP if they are reluctant to do so. As more restrictions are placed on hospital services with respect to provision of services to HIV positive people this becomes ever more important.

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Pre-conception advice & conception

Recommendations

- Persons living with HIV should have access to accurate information and support around safe conception for themselves and their partners, involving their partners where appropriate to do so (GPP)
- Where a PLWH has not disclosed their HIV status they should be encouraged and supported to do so such that the best advice and management can be offered (GPP)
- We recommend documented discussion of reproductive plans in all PLWH with reproductive potential at baseline assessment & annually where appropriate (GPP)
- We suggest all services/networks have a named health care professional responsible for reproductive advice & signposting (GPP)
- We recommend pre-conception health promotion consistent with general guidance (GPP)

The marked improvement in the life expectancy of PLWH and low risk of vertical transmission mean fertility desires amongst PLWH are high, the majority expressing a desire to achieve pregnancy and have biological children [1-4]. Despite this, communication between patients and health providers about childbearing and safe conception is often inadequate and pregnancies amongst women are often unplanned [5-9]. HIV can itself be an important factor influencing HIV-affected women's reproductive choices [10].

There is a need to understand the reproductive and parenting choices made by people living with HIV. WLWH may have concerns regarding the risks of HIV transmission, delivery method and feeding options. One study identified two variables with a strong association with fertility desire: age less than 30 years and being childless [11]. In another cross-sectional study, the desire for pregnancy was associated with increased rates of intercourse, partner concurrency and unprotected sex with a non-concomitant partner, decreased condom use, and a high number of previous STIs [12]. The prevalence of unintended pregnancies is higher amongst this group and in a case note review of teenagers with HIV in London, 82% of pregnancies were found to be unplanned, with 65% of women reporting no contraception use, and an overall vertical transmission rate of HIV of 1.5% [13].

A lack of correct information and knowledge on safe conception coupled with a high desire to have biological children can reduce the practice of safer sex amongst couples affected by HIV, potentially risking transmission to HIV-negative partners or superinfection of HIV-positive partners [14]. However, the HPTN 052 [15], PARTNER [16] and Opposites Attract [17] trials demonstrated no onward transmissions to HIV-negative partners when the HIV-positive partner was on suppressive ART. These studies should be discussed with all patients at an early stage to maximise their chance of achieving a successful and safe pregnancy. Serodifferent couples (i.e where one partner is la PLWH and the other is HIV-negative) where the HIV-positive partner is on suppressive ART can be counselled that conception through timed unprotected sexual intercourse (UPSI) is an appropriate and safe option. Where the HIV-positive partner is not on ART or not suppressed, this should be reviewed, ART offered/optimised as appropriate and the risks of onward transmission to the negative partner discussed.

Some studies have demonstrated an inverse association between HIV and fertility [18,19] which may increase the demand for fertility treatment in PLWH. A study of WLWH undergoing IVF demonstrated lower success rates in WLWH than HIV-negative controls due to a reduced

response to ovarian stimulation [20]. However, no difference in IVF outcome was noted in WLWH undergoing ovum donation, suggesting an impact of HIV on ovarian response and reserve rather than implantation. Retrospective data from Sub-Saharan Africa [21,22] and prospective data from the UK suggest an increased incidence of tubal infertility in WLWH [23]. For these reasons, couples trying to conceive should be referred for fertility evaluation if they have not conceived within 6-12 months of self-insemination or UPSI. Earlier referral should be made if there is a history of pelvic inflammatory disease or they are over 35 years of age.

Some PLWH may face negative attitudes regarding their choice to become a parent. Challenging stigma, both in the community and amongst some healthcare professional is an ongoing concern [24]. Reproductive counseling should be an integral part of modern HIV care and should be provided routinely to all PLWH in order to assist independent and safe reproductive decision making. It is recommended that every HIV clinic has a dedicated clinician available to discuss matters in detail with patients and provide them with appropriate advice and guidance in a timely manner.

Pre conception advice

All couples who wish to conceive where one or both partners are HIV-positive should receive detailed reproductive counseling prior to attempted conception or fertility treatment. This is to facilitate an informed choice about their reproductive options, the inherent risks and costs of any treatment that might be required and the likely chances of success.

The main objectives in offering reproductive advice to couples affected by HIV are to assist them in achieving a successful pregnancy while minimising the risk of viral transmission to the uninfected partner and future child.

Methods of Conception

The preferred method of conception may vary according to:

- HIV status of couple:
    - Sero-different
    - Both HIV-positive
- Treatment status of the person living with HIV
    - If not already on treatment, PLWH should commence Treatment as Prevention (TasP) (see below), even if both members of the couple are HIV-positive.
- The HIV viral load of PLWH
    - If suppressed (below limit of detection) for at least 6 months and there is no evidence of a sexually transmitted infection, timed (with ovulation) condomless sex may be recommended; see later discussion on pre-exposure prophylaxis for Conception (PrEP-C)
    - If detectable HIV-RNA despite optimal ART and partner HIV-negative, consider PrEP-C, self-insemination or assisted conception (including sperm washing) as appropriate
- The fertility of both members of the couple
    - If either member of the couple has reduced fertility, assisted reproduction techniques may be required to achieve pregnancy

Different conception options will be discussed further in section in the following section.

Pre-pregnancy health

Folic acid supplementation (400mcg daily) should be commenced ideally prior to conception or as soon as pregnancy is achieved. If the mother is on folate antagonists such as co-trimoxazole, or has other indications as per NICE guidelines [25] folic acid should be given at an increased dose of 5mg and continued throughout pregnancy. Health care professionals should also be aware of other current guidelines relevant to pre-pregnancy health including general advice [26] and vitamin D supplementation [26]

Lifestyle advice regarding alcohol consumption, smoking, use of recreational drugs and ideal weight should be given prior to conception to both prospective parents or as soon as the pregnancy is known. Sexual health screens are also recommended for both the partners prior to any attempts at conception.

Women who need antiretroviral treatment for their own health, should be commenced on a regimen that is most suitable for them. In women with very low CD4 counts (<200), it is preferable to defer pregnancy until virological suppression and immune reconstitution are attained to minimise exposure to drugs used to treat and prevent opportunistic conditions and to reduce the risk of the mother developing HIV-related complications during pregnancy. The subsequent improvement in the general health of the HIV infected woman is also likely to increase chances of conception and a successful pregnancy.

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Antiretroviral therapy: impact on transmission & conception

Recommendations: Treatment as Prevention

- It is recommended that all individuals diagnosed with HIV should commence treatment with antiretroviral therapy (ART) as per BHIVA Adult Treatment Guidelines
- The evidence that treatment with ART lowers the risk of transmission should be discussed with all PLWH, and an assessment of the current risk of transmission to others made at the time of this discussion (GPP)
- We recommend that heterosexual PLWH with sustained viral suppression (at least 6 months) and high adherence to ART can be advised there is no risk of onward transmission of HIV to others (1A)
- We recommend that when serodifferent heterosexual couples wish to conceive the HIV-positive partner be on fully suppressive ART (1A)
- We recommend that MSM living with HIV with sustained viral suppression (at least 6 months) and high adherence to ART can be advised there is no risk of onward transmission of HIV to others (2A)
- If the decision to start ART is being driven primarily by transmission risk it should be the HIV-positive individual's choice and must not be due to pressure from partners or others. High and consistent adherence to ART is required to maintain viral suppression and minimise transmission risk (GPP)
- It is recommended that the plasma viral load should be suppressed for ≥ 6 months before timed condomless sex to achieve conception is undertaken (GPP).

Recommendations: ART in women

- We recommended WLWH start ART in line with BHIVA treatment guidelines (1A)
- We recommend women wishing to conceive be offered ART if not already on a suppressive regimen (1A)

Treatment as prevention

The initial evidence base for treatment to reduce transmission was based on a number of cohort studies that found that transmission between heterosexual couples where the HIV-positive partner had an undetectable or low viral load on treatment was very rare or did not occur [1-5]. This was followed by high quality evidence from a randomised controlled trial (HPTN 052) [6] demonstrating a 96% reduction in the risk of onward HIV transmission to negative partners when the HIV-positive person received ART. HPTN 052 is supported by the secondary outcomes of the earlier Partners in Prevention trial [7] that demonstrated a 92% reduction in onward transmission with effective ART. It is important to note that 97% of the couples in HPTN 052 and all participants in Partners in Prevention were heterosexual so are highly relevant for couples wishing to conceive.

More recently, the PARTNER study demonstrated a protective effect of viral suppression in serodifferent couples where the PLWH is on suppressive ART (viral load < 200 copies/mL). Among serodifferent heterosexual and MSM couples followed for 1238 couple years in which the HIV-positive partner had viral suppression on ART, during which time there were 58,000 condomless sex acts, there were zero incidences of within-couple HIV transmission. The estimated rate of transmission was thus estimated to be zero (upper 95% confidence limit 0.3 / 100 couple years of follow-up) [8]. More recently the Opposites Attract study amongst MSM in

Australia, Thailand and Brazil demonstrated no cases of HIV transmission in serodifferent partnerships where the positive person was on suppressive ART [9]. Combining the PARTNER and Opposites Attract results show no HIV transmission after more than 40,000 condomless anal sex acts in MSM where the positive partner is on suppressive ART.

PLWH should be informed that taking ART does not result in immediate viral suppression. Most individuals commencing ART achieve viral suppression by 3–6 months. PLWH should also be informed about the possibility of virological failure leading to transmission of HIV and the importance of adherence to ART.

Decisions on having condomless sex should always be based on a recent viral load test result and not on an assumption that taking ART implies non-infectiousness.

For heterosexual couples wishing to conceive, suppressive ART expands the choices available. Condomless sex around the time of ovulation (timed ovulatory condomless sex, TOCS) carries **no risk** provided the HIV-positive partner has a durably suppressed viral load. However, if couples have not conceived after 6 cycles of timed condomless sex we suggest referral to a fertility specialist.

ART and Women
Data on the impact of suppressive ART on fertility is conflicting. Prospective cohort data from the US suggests that ART is associated with a lower likelihood of conception whereas a large study of over 4,500 women in Africa reported higher pregnancy rates among women on ART (9.0/100 person years vs 6.5/100 person years) [10,11]. It is clear however that progression of HIV is associated with decreased pregnancy and live birth rates [12]. Therefore, in women with CD4 counts <200 cells/mm^3 who have previously declined treatment with ART but who wish to conceive, commencing ART may increase the chance of conception and would be recommended.

Women starting treatment for HIV should commence standard suppressive ART as per BHIVA Adult Treatment Guidelines with preferential selection of ARVs with Antiretroviral Pregnancy Registry data supporting safety [13].

HIV Superinfection
Superinfection occurs when a PLWH is infected with a strain of HIV they do not already have. Superinfection may occur with wild-type or resistant virus but, based on data in serodifferent couples, is not a concern if both members of the couple are on suppressive ART [14,15]. For serosame couples attempting to conceive through unprotected intercourse, there are no conclusive data on the overall risk of superinfection. In fact, there is little data available to accurately predict the risk of superinfection in any PLWH but small cohort studies of MSM failed to show any evidence of superinfection although there is one report of an MSM on fully suppressive ART who was superinfected with a multiresistant strain of HIV [16].

Additional information on conception methods

<u>1. Natural conception – timed ovulatory condomless sex (TOCS)</u>
Conceiving through timed condomless sex (CS) was previously not recommended for conception in couples where one or both partners is/are HIV-positive. Based on HPTN 052 and PARTNER TOCS can be recommended if the HIV viral load of the positive partner(s) is <50c/ml for >6

months and their adherence is good, and there are no concomitant STI in either partner. It is important therefore to have an open discussion with the couple about the data that informs this decision.

2. Sperm washing

Sperm washing is the process where the HIV negative female partner is inseminated with the HIV positive partner's sperm, centrifuged first to separate spermatozoa from seminal fluid and associated non-sperm cells. It was first described in 1992 in Italy [17].

A recent systematic review and meta-analysis of forty single-arm open-label studies among HIV-different couples that underwent intrauterine insemination (IUI) or in vitro fertilization (IVF) with or without intracytoplasmic sperm injection (ICSI) using washed semen has shown zero HIV transmission in 11,585 cycles of assisted reproduction among 3,994 women [18-20]. Among the subset of HIV-infected men without plasma viral suppression at the time of semen washing, no HIV seroconversions occurred among 1,023 women after 2,863 cycles of assisted reproduction with the use of washed semen. Studies that measured HIV transmission to infants reported no cases of vertical transmission. Overall, 56.3% of couples (2,357/4,184) achieved a clinical pregnancy with the use of washed semen.

Sperm washing is only available in certain parts of the country and often requires additional funding requests (IFRs) for treatment to proceed; clinics should be aware of localservices and pathways. NICE fertility guidelines do not recommend sperm washing over timed condomless sex where the HIV positive male has a VL <50c/ml for at least 6 months and high reported adherence, unless there is coinfection with Hepatitis B or C. It may also be considered where the couple wishing to conceive are not partners.

3. Self-insemination

Where a couple are concerned that having TOCS may increase any risk of HIV transmission should sex be traumatic couples can be advised to time ovulation and to have protected sex using a nonspermicidal condom. Sperm can then be extracted from the condom using a syringe or pipette and inserted into the woman's vagina for release of sperm. For friends wishing to conceive naturally together the male is advised to ejaculate into a sterile cup from which sperm can be drawn as above and given to the female for release of sperm into the vagina.

4. Sperm donor for HIV positive women

This is an option for WLWH who wish to become a parent on their own, for those in a same sex relationship and for those whose partner has male factor infertility. The safest and most reliable way of obtaining sperm from a donor is via a clinic that is licensed, inspected and regulated by the Human Fertilisation and Embryology Authority (HFEA). The Authority is the UK's independent regulator of treatment using eggs, sperm and embryos. Baseline fertility tests in the woman planning to conceive could be considered especially if over 35 years of age.

5. Adoption

Adoption or fostering is an option for PLWH, which they may wish to consider on alone or with a partner. Although considered an undesirable factor, HIV does not automatically exclude one from being approved to be an adoptive parent, but as in the case of any other chronic illness, one's health and circumstances would need to be assessed to ensure the child's needs can be met. It is likely that the patient's HIV physician will be asked to produce a report commenting on the stability of the person's HIV infection and their presumed life expectancy.

	Positive Woman, Negative Man	Positive Man, Negative Woman	Positive Woman, Positive Man	Positive Man Negative Woman (not partner)
ART	Recommended but not essential if using AI	Recommended	Recommended for both	Recommended with AI
Timed Ovulatory Condomless Sex	Recommended only if VL <50c/ml	Recommended only if VL <50c/ml	Recommended unless one or both partner detectable HIV-RNA + discordant resistance	Not recommended
PrEP for Conception	Consider if HIV-positive partner's HIV-RNA not suppressed	Consider if HIV-positive partner's HIV-RNA not suppressed	Not recommended	Consider if HIV-positive partner's HIV-RNA not suppressed
Artificial insemination using non spermicidal condoms	Recommended	Not applicable	Not applicable	Recommended
Sperm washing	Not recommended	Not recommended unless detectable HIV-RNA (although suppressive ART first choice)	Not recommended	Consider
Sperm donor	Consider if male subfertility	Consider if male subfertility	Consider if male subfertility	Consider if male subfertility
Egg donor	Consider if female subfertility	Consider if female subfertility	Consider if female subfertility	Consider

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Pre-exposure prophylaxis (PrEP) and pre-exposure-prophylaxis for conception (PrEP-C)

Recommendations

- We do not recommend PrEP-C where the positive partner has been undetectable on HIV treatment for >6 months [1A]
- We suggest in exceptional situations PrEP-C may be used [GPP]
- PrEP-C may be discussed with heterosexual women or men whose partners have HIV infection (serodifferent couples) as one of several options to protect the uninfected partner during attempts to conceive [GPP]
- The potential risk and benefits of PrEP-C to mother and foetus should be discussed so that an informed decision can be made [GPP]

The evidence that effective treatment with ART lowers the risk of transmission to negligible levels is outlined in the section above. Despite all this evidence, it is currently not possible to state that the absolute risk of transmission when the plasma viral load is undetectable is **definitely zero**, although the data are very reassuring. The prospect for some individuals embarking on condomless sex for the purposes of conception, however, may cause anxiety, particularly when considering reports that genital tract viraemia can persist despite undetectable plasma viral load [1]. Some couples may request PrEP-C as an additional "safety net" but should be reassured that there have been zero transmissions from PLWH on suppressive ART and PrEP is not indicated.

Recent results from clinical trials have made it clear that PrEP is highly effective as part of a comprehensive package of biomedical prevention tools. Ten randomised controlled trials have reported on the use of pre-exposure prophylaxis, five providing evidence for the effectiveness of daily oral tenofovir-DF [2,3] or tenofovir-DF/emtricitabine [4,5,6] and one for tenofovir-DF/emtricitabine taken before and after sex (event-driven PrEP) [7]. Effectiveness for oral tenofovir-DF-based regimens has been demonstrated in MSM [4,5,7], heterosexual serodifferent couples [2], young heterosexual adults [6] and injecting drug users [3]. Two randomised placebo controlled trials conducted in women in Sub-Saharan Africa observed no benefit for daily oral tenofovir-DF, daily oral tenofovir-DF/emtricitabine or daily tenofovir-DF 1% vaginal gel [8,9]; the discrepant results for these trials are explained by low levels of adherence - less than a third of women on the active arms had detectable drug at the first study visit.

Tenofovir-DF-DF has been used in pregnant HIV positive women for more than 10 years and has featured on the Antiretroviral Pregnancy Registry since 2009 [10] with a reported foetal anomaly rate of 61/2779 first trimester exposures to tenofovir-DF (2.20%, 95% CI 1.68-2.82%) as of January 2016. Emtricitabine has a reported foetal anomaly rate of 48/2145 first trimester exposures (2.24%, CI 1.65-2.96%); tha background risk of abnormality is 2-3%. Data on the impact of PrEP on pregnancy incidence and outcomes is available from the Partners PrEP Study [2]. In this large study, in which 431 pregnancies occurred, daily oral tenofovir-DF or daily tenofovir-DF/emtricitabine were efficacious for HIV prevention. Differences in pregnancy incidence were not statistically different for women receiving tenofovir-DF alone or tenofovir-DF/emtricitabine compared with placebo at conception [11]. Birth outcomes (live births, pregnancy loss, preterm birth, congenital anomalies), and infant growth were measured and differences in women receiving PrEP compared with those receiving placebo at conception were not statistically different. Given that PrEP was discontinued when pregnancy was detected and that confidence intervals for the birth outcomes were wide, definitive statements about the safety of PrEP in the peri-conception period cannot be made.

It is important to note that PrEP-C is an unlicensed, experimental treatment within the UK. There are no randomised controlled trials to substantiate that this is a safe or effective method of preventing HIV transmission to the negative partner when trying to conceive in HIV serodifferent couples. In 2011 Vernazza *et al* [12] published data on 53 women receiving pre-exposure prophylaxis with oral TDF at the time of attempted conception. All women were HIV-negative three months after last exposure. Pregnancy rates were high and reached a plateau of 75% after six cycles. Data has also been published on the use of PrEP-C in UK clinics using a similar regimen to that utilised by Vernazza *et al*, again with no HIV transmissions [13]. There is, however, no evidence to show that when the HIV-positive partner is on suppressive ART there is any *additional* protective benefit from the use of PrEP-C.

A statistical model was developed to estimate the benefits of PrEP-C as an adjunctive HIV prevention method during attempted conception between HIV-negative women and HIV-positive men [14]. Variables included: whether the positive partner received ART, maternal age, fertility issues and use of PrEP-C. The model highlighted that in most scenarios PrEP provides little added benefit if all of the following are true: the HIV-positive man is receiving suppressive ART; unprotected sex is limited to the period of ovulation and STIs are diagnosed and treated in both partners.

Ideally couples who are planning to conceive should be seen by clinicians with a particular interest in HIV preconception. There should be access to and, where appropriate, referral to sexual health testing facilities, HIV clinical nurse specialists and fertility services as per BHIVA standards [15]. Couples seeking PrEP-C should be counselled extensively together and separately prior to embarking on PrEP-C to ensure both partners understand all the issues and are willing participants in the treatment. Couples should also be informed that PrEP-C does not guarantee that HIV transmission will not occur and clear documentation of this conversation should be made. It must be made clear that in the very unlikely event that male-to-female HIV transmission should occur during conception the onward risk of transmission to the foetus may be up to 18% [16]. Condoms should be recommended between the end of the fertile period and the next menses.

There are a range of dosing options for administering PrEP-C ranging from peri-conception Truvada which minimises antiretroviral exposure versus continuous daily Truvada, which will achieve higher drug levels but may have implications for cost and toxicity.

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Investigations in couples affected by HIV, trying to conceive through UPSI.

For those couples who decide on UPSI, a minimum of hormone analysis for the female partner to look into ovulatory function, and a semen analysis for the male partner is recommended before they have any attempts at unprotected sex. Along with these, it is recommended that they also have baseline STI screens and serology as following.

For the woman	For the man
Blood Tests 1. HIV 2. Hepatitis B 3. Hepatitis C 4. Syphilis 5. FSH, LH and Oestradiol days 2-5 of cycle 6. Progesterone 7 days before expected day of next period 7. Prolactin & thyroid function if history of amenorrhoea/oligomenorrhoea 8. Rubella serology	**Blood Tests** 1. HIV 2. Hepatitis B 3. Hepatitis C 4. Syphilis
STI Screen and Microscopy 1. Vulvovaginal chlamydia NAAT 2. Vulvovaginal gonorrhoea NAAT 3. Trichomoniasis (if symptomatic)	**STI Screen** 1. Urine chlamydia NAAT 2. Urine gonorrhoea NAAT

Couples where the female partner is < 35 years old, should be advised to try for 6 – 12 months and those in whom the woman is > 35 years old, for 6 months. If the couple fails to conceive after this time period, the patient should be referred to fertility services for further investigations, for example, in women, a pelvic ultrasound, and tubal patency tests and in men, semen analysis. Semen analysis is recommended above as a standard base-line test in any couple embarking on UPSI (If normal no need to repeat). If the semen analysis result is abnormal it should be repeated at least 3 months later to confirm abnormality (to allow time for spermatozoa formation). However, if there is a gross spermatozoa deficiency (azoospermia or severe oligozoospermia) the test should be repeated as soon as possible.

Following completion of these investigations, couples, in whom fertility treatment or sperm washing is warranted, should be referred to the closest centre which offers such treatment to couples where one or more partner are HIV positive.

Contraception for Women with HIV

Recommendations

- We recommend all contraceptive options be discussed with WLWH (GPP)
- HIV infection per se is not a barrier to any form of contraception (GPP)
- We recommend taking a contraceptive history at every visit (GPP)
- We recommend that where ART is a barrier to the optimal method of contraception, due to the impact of drug-drug interactions on hormonal contraceptive efficacy, and reasonable ART alternatives exist, ART be switched (GPP)
- The efficacy of DMPA, LNG-IUS and Cu-IUD are largely unaffected by drug-drug interactions with ART, and offer very effective contraception
- Consistent condom use should be encouraged in conjunction with an additional contraception method for optimal contraception, STI prevention and prevention of HIV transmission depending on sexual history/HIV status of partner(s) and whether on suppressive ART
- For WLWH not on ART, all available contraceptive methods are suitable, although nonoxinol-9 spermicide should be avoided if partner(s) HIV-negative
- For women on liver enzyme inducing ART: a Cu-IUD is the recommended method of emergency contraception except in women ith a CD4 less than 200 and detectable HIV-RNA. If POEC is used, a doubling of the standard dose of Levonelle® to 3mg stat is recommended

Introduction

These contraception guidelines are an adjunct to existing Faculty of Sexual & Reproductive Healthcare (FSRH) documents, which provide evidence based guidance on a variety of contraceptive methods (www.fsrh.org). In addition, the Clinical Effectiveness Unit of FSRH has produced the 2016 UK Medical Eligibility Criteria for Contraceptive Use (UKMEC)[1], an adaptation of WHO Medical Eligibility Criteria (WHOMEC), and classify a range of medical conditions (including HIV) into eligibility categories, by contraceptive type (See table 2). The UKMEC categories were updated in 2016, and recommendations for WLWH are summarised in tables 3 and 4. UKMEC recommendations are based on safety rather than efficacy, so it is important to consider that drug interactions with certain ART may reduce efficacy despite the contraceptive method being safe to use. Please check the FSRH website (www.fsrh.org) for updates.

Provision of contraception advice

WLWH requiring contraception should be given information, both verbal and written, about all methods of contraception and be supported to make an informed choice. They should be provided with the most effective suitable method of contraception that is acceptable to them. Counselling should be sensitive to cultural differences and religious beliefs. Women should be informed when contraceptives are used outside the product license and there should be clear written documentation in the notes as to why this is necessary.

Most available methods of contraception can be considered in WLWH and are safe and effective, however, special considerations need to be made in women on or about to commence ART due to the potential risk of drug-drug interactions that may impair contraceptive efficacy, or with CD4 count <200 cells/mm^3.

All women being considered for contraception should have an appropriate medical history taken as part of routine assessment and appropriate reference made to UKMEC criteria. Risk of transmission of HIV and other sexually transmitted infections (STIs) must also be discussed when recommending or prescribing contraception.

Barrier methods

Barrier methods include male condoms (latex or non-latex), female condoms (nitrile or latex), diaphragms (latex, silicone), cervical cap (silicone) and dams (latex, non-latex). Men and women requesting barrier methods should be given information on how to use the method correctly.

Condoms
The effectiveness of both male and female condoms in preventing pregnancy is dependent on correct and consistent use (See table 1) [1-3]. Pregnancy rates are similar for latex and non-latex male condoms [4-6].

The main spermicide available in the UK contains nonoxinol-9 (N-9). It is a mucosal irritant that can cause epithelial disruption and lesions in the vagina or rectum [7], which may in turn increase the risk of HIV acquisition/transmission. It offers no protection against other STIs and does not reduce pregnancy rates when compared to non-spermicidally lubricated condoms [8]. Condoms lubricated with N-9 are therefore not recommended [9].

Dual protection using both barrier and either hormonal or intra-uterine contraception is the most effective way to prevent both pregnancy and to reduce transmission of HIV but may not be required in the context of suppressive ART. Women using condoms alone should be aware of emergency contraception, and know how to access a supply in a timely manner; drug-drug interactions between ART and emergency contraception must be considered.

Diaphragm and Caps
Diaphragms and caps provide a physical barrier to sperm reaching the cervix. When used perfectly, diaphragms and cervical caps are estimated to be between 92% and 96% effective at preventing pregnancy. Diaphragms cover the cervix and part of the upper vagina, and caps cover only the cervix. Relatively large areas of the vaginal mucosa remain exposed with both methods, thus permitting potential viral transmission. In addition, caps and diaphragms are recommended to be used with N-9 [10], and as outlined above, this would not be appropriate in WLWH with HIV-negative partners or when women are at risk of HIV acquisition. Women should be made aware that there is little evidence that diaphragm or cervical cap reduces the risk of HIV transmission [11]. The risks of using these methods by women at high risk of HIV or living with HIV generally outweigh the benefits (WHOMEC Category 3).

Combined Hormonal Contraception (CHC)

CHC is highly effective (perfect use failure rate 0.3% in the first year, typical use failure rate up to 9% [3]) and prevent pregnancy through a variety of mechanisms including suppression of gonadotrophins, increased viscosity of cervical mucus and endometrial suppression [12,13].

There are three types of CHC:

- Combined oral contraceptive pill (COC): the most common method in the general population aged 16-49 years [14,15]
- Combined contraception transdermal patch (CTP): applied for 3 weeks followed by 7 days patch-free
- Combined contraception vaginal ring (CVR): inserted for 3 weeks then removed for 7 days

CHC is safe and effective for WLWH not on ART (UKMEC 1). However, a detailed history should be taken including other medical conditions, drug use, family medical history, and lifestyle factors such as smoking, in addition blood pressure and BMI should be checked prior to first prescription of CHC as per standard recommendations.

For women on ART a careful review of drug-drug interactions should be undertaken and, where there are interactions known or suspected to limit contraceptive efficacy, an alternative ART regimen or alternative method of contraception considered.

Progestogen-only Contraception (POC)

There are currently three POC methods available in the UK:

- Progestogen-only pill (POP)
- Progestogen-only injectable (POIC)
- Progestogen-only implant (IMP)

Progestogen-only Pill (POP)
POPs are taken without a pill-free interval and mainly work by thickening cervical mucus, and by a lesser effect on the endometrium; desogestrel works primarily by inhibiting ovulation [17].

If used consistently and correctly, POPs are more than 99% effective. Although there is a lack of robust data, the desogestrel POP may be more effective than traditional POP, as it suppresses the ovulation more consistently and has a longer missed pill window [18].

POP is classified as UKMEC category 1 for WLWH, not on ART. For women on ART a careful review of drug-drug interactions should be undertaken and, where there are interactions known or suspected to limit contraceptive efficacy, an alternative ART regimen or alternative method of contraception considered.

Progestogen-only Injectable Contraception (POIC)
Two POIC methods are available in the UK: Depot medroxyprogesterone acetate (DMPA) and norethisterone enantate (NET-EN). DMPA can be administered by intramuscular [19] or subcutaneous [20] routes; NET-EN is less commonly used and licensed for short-term use only [21]. POICs work primarily by inhivitong ovulation [22-24].

The failure rate of POIC is approximately 0.2% in the first year of use, if administered at the recommended dosing interval. With typical use the failure rate is approximately 6%.

DMPA may increase HIV acquisition in women at high risk (see next section for more detail).

POIC use is associated with a small loss of bone mineral density (BMD), which is usually recovered after discontinuation [25-26]; HIV infection may also be associated with reduced bone density [27] and initiation of ART is associated with an initial loss in BMD before being stabilised [28]. BMD considerations should be included in discussion about contraceptive method and re-evaluation of the osteoporosis risks and benefits should be carried out every 2 years in those who wish to continue POIC. NICE recommends vitamin D supplementation for women, who may be at an increased risk of developing osteopenia or osteoporosis [29]. There is no robust evidence to make recommendations on dual energy X-ray absorptiometry (DEXA) scanning in POIC users. Local protocols for referral criteria should be followed.

Progestogen-only subdermal implants (IMP)
IMP contains etonogestrel, suppresses ovulation and is licensed for 3 years of use. It is a safe and effective method of contraception for WLWH not on ART (UKMEC 1). See the next section for more detailed information on drug-drug interactions between IMP and ART; IMP should not be co-adminstered with efavirenz due to reports of contraceptive failure and the results of a pharmacokinetic study (see below).

Intrauterine Contraception (IUC)

IUC comprises two types:

- Copper-bearing intrauterine device (Cu-IUD)
- Levonorgestrel-releasing intrauterine system (LNG-IUS)

Copper Bearing Intrauterine Devices (Cu-IUD)
Cu-IUDs prevent fertilisation and inhibiting implantation and are licensed for 5-10 years use. They are a safe and effective method of contraception for WLWH with CD4 count ≥200 cells/mm^3, with no evidence of increased complications when compared to HIV negative women (UKMEC 2) [33,34]. However, initiation of Cu-IUD is UKMEC 3 for WLWH with CD4 count <200 cells/mm^3 due to potential higher risk of infection post procedure. UKMEC 2016 indicates that the initiation of Cu-IUD may be appropriate in some women with low CD4 counts who have an undetectable viral load. The decision is a matter of clinical judgment. Women with CD4 count <200 cells/mm^3 and a Cu-IUD already in situ may continue to use the method under category 2.

Levonorgestrel intrauterine system (LNG-IUS)
LNG-IUS devices contain different doses of levonorgestrel and are licensed for 3-5 years [35-37]; their main mechanism is via direct local effect on the endometrium, preventing implantation. WLWH with CD4 count ≥200 cells/mm^3 can be offered an IUS (UKMEC 2) but initiation in women with CD4 count <200 cells/mm^3 is classified as category 3 for reasons outlined above. Like the CuIUD, women with a CD4 <200 and a LNG-IUS already in situ may continue to use the method under category 2.

Emergency Contraception

Emergency contraception (EC), with Cu-IUD or oral pills, reduces the risk of unintended pregnancy following any unprotected sexual intercourse (UPSI) or when their usual method of contraception has failed.

The Cu-IUD is the most effective form of EC. All women presenting between 0 and 120 hours of UPSI or within 5 days of earliest ovulation (e.g. day 19 in a regular 28-day cycle) should be

offered a Cu-IUD as EC, if eligible. Use of a Cu-IUD for EC carries the same contraindications as routine Cu-IUD insertion [1]. However, the risk-benefit ratio may be different for the use of the Cu-IUD as EC compared to when it is used for routine contraception.

There are two methods of oral EC available in the UK. Ulipristal acetate (UPA) is a progesterone receptor modulator and is licensed for use within 120 hours of UPSI. Levonorgestrel EC (1.5mg LNG) is licensed up to 72 hours after UPSI or contraceptive failure. Like hormone-based methods, UPA may also be subject to drug-drug interactions with ART [38].

Table 1: Percentage of users becoming pregnant in first year of use of method, with perfect and typical use of the method[3]

Method	Perfect use	Typical
Combined Hormonal Contraceptives	0.3	9
Progestogen only oral	0.3	9
Progestogen only injectable	0.2	6
Progestogen only implant	0.05	0.05
Male condom	2	18
Female condom	5	21
Diaphragm	6	12
Copper IUD	0.6	0.8
Levonorgestrel IUS	0.1	0.2
Female sterilisation	0.5	0.5
Male sterilisation	0.1	0.15

Table 2: UK Medical Eligibility Criteria (UKMEC) categories[1]

UKMEC	Definition of category
Category 1	A condition for which there is no restriction for the use of the method
Category 2	A condition where the advantages of using the method generally outweigh the theoretical or proven risks
Category 3	A condition where the theoretical or proven risks usually outweigh the advantages of using the method. The provision of a method requires expert clinical judgment and/or referral to a specialist contraceptive provider, since
Category 4	A condition which represents an unacceptable health risk if the method is used

Table 3: Summary of UKMEC Categories for Use of Common Reversible Methods of Contraception in women with or at risk of HIV[1,39,40]

Condition	Cu-IUD		LNG-IUS		IMP	DMPA	POP	CHC
a) High risk of HIV infection	2		2		1	2	1	1
b) HIV infected								
(i) CD4 count ≥200	2		2		1	1	1	1
(ii) CD4 count <200 cells/mm3	**I**	**C**	**I**	**C**	1	1	1	1
	3	2	3	2				
c) Taking antiretroviral (ARV) drugs	Certain ARV drugs have the potential to affect the bioavailability of steroid hormones in hormonal contraception. The contraceptive effectiveness of DMPA, Cu-IUD and the LNG-IUS is not reduced by concurrent use of ARV. For up-to-date information on the potential drug interactions between hormonal contraception and ARV drugs, please refer to the online HIV drugs interaction checker (www.hiv-druginteractions.org/Interactions.aspx).							

Cu-IUD = Copper-bearing intrauterine device; LNG-IUS = Levonorgestrel-releasing intrauterine system; IMP = Progestogen-only implant; DMPA = Progestogen-only injectable: depot medroxyprogesterone acetate; POP = Progestogen-only pill; CHC = Combined hormonal contraception

Table 4: Summary of WHOMEC Categories for Use of barrier Methods and emergency oral contraception in women with or at risk of HIV[41]

Condition	Condom	Diaphragm	UPA EC	LNG EC
a) High risk of HIV infection	1	4	1	1
b) HIV infected				
(i) CD4 count ≥200 cells/mm3	1	3	1	1
(ii) CD4 count <200 cells/mm3	1	3	1	1
c) Taking antiretroviral (ARV) drugs	Certain ARV drugs have the potential to affect the bioavailability of steroid hormones in EC. For up-to-date information on the potential drug interactions between EC and ARV drugs.			

UPA = 30 mg Ulipristal acetate ; LNG = 1.5mg Levonorgestrel

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Hormonal contraception and antiretroviral drug-drug interactions

For women who take ART, contraceptive choices may be restricted by potential drug-drug interactions (DDI).

Hormonal contraceptives, both oral and systemic, are generally metabolised via the cytochrome P450 isoenzyme system and the glucuronidation pathway:

- Ethinyl estradiol (EE) is predominantly metabolised by CYP3A4 and CYP2C9 and via glucuronidation by the uridine 5-diphosphate glucuronosyltransferase (UGT) isoenzymes particularly UGT1A
- Most progestogens are metabolised by the CYP3A4 isoenzyme though there is significant inter- and intra-individual variability.

As several, particularly older, ARVs induce or inhibit these systems there are numerous potential drug-drug interactions. The exceptions to the drug-drug interactions are the POICs and the LNG-IUS which to date have had no major interactions reported with any ARVs [1]. POIC clearance is approximately equal to the hepatic blood flow hence its metabolism is not likely to be affected by DDI and the local effect of progestogen in the LNG-IUS limits the impact of DDI on its efficacy. **Therefore, the POICs and the LNG-IUS can be used with all ARVs.**

The remaining hormonal contraceptive methods, the combined oral contraceptive pill, the progestogen only pill, the contraceptive patch, the contraceptive vaginal ring, and the progestogen only subdermal implant do have the potential to be impacted by DDI with some of the ARVs and these are all discussed below under the grouping “hormonal contraceptives”.

The **NRTI class** of ARVs is the usual backbone to most treatment regimens. These are renally eliminated and are not metabolised by CYP450 nor glucuronidation pathways. **NRTI can be used with all contraceptives** [2,3].

Conversely, non-nucelose reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs) and one of the integrase inhibitors (INIs), elvitegravir boosted with cobicistat, may interact with hormonal contraceptives as several are inducers and/or inhibitors of either or both the CYP isoenzyme and glucuronidation pathways.

Of the NNRTIs, **efavirenz** has the ability to both inhibit and induce the enzyme pathways involved in metabolising ethinyl estradiol (EE) which appears to give a neutral net effect on the levels of EE but on the other hand, efavirenz significantly lowers progestogen levels, hence it would not be safe to use with hormonal contraceptives (bar LNG-IUS and POIC) and this has been demonstrated in several studies studies including recent data demonstrating that efavirenz reduces levels of etonogestrel when administered to women with a subdermal progestogen implant [4-8]. **Concurrent use of efavirenz and hormonal contraceptives (except POIC and LNG-IUS) is not recommended.**

Nevirapine is a CYP3A4 inducer so would be expected to lower levels of EE and progestogen, as demonstrated in older studies [9,10]. However, more recent studies demonstrated increased concentrations of both EE and progestogen [11] and no differences in ovulation or pregnancy rates [12]; further studies are needed to confirm these findings before changing the recommendation **not to use nevirapine with hormonal contraceptives (except DMPA and LNG-IUS).**

The newer NNRTIs **etravirine** [13] and **rilpivirine** [14] appear not to cause any significant alterations in oestrogen and progestogen concentrations despite etravirine being a weak CYP3A4 inducer and weak CYP2C9 inhibitor, and no loss of contraceptive efficacy is expected when they are co-administered. **Etravirine and rilpivirine can be used safely with all hormonal contraceptives.**

Interactions with PIs are complicated by the pharmacokinetic effects of the booster, ritonavir or cobicistat, and the PI per se on concentrations of EE and progestogen. **Darunavir, fosamprenavir** and **lopinavir** boosted with ritonavir, which results in significantly lower EE concentrations and sometimes lower progestogen concentrations so **are not recommended to be used with hormonal contraceptives (except DMPA and LNG-IUS)** [15-17]. The effects of the newer booster **cobicistat** are unknown, but would be expected to result in different interactions as it does not induce the CYP450 isoenzymes nor glucuronidation, but it acts as a potent CYP3A4 inhibitor and weak CYP2D6 inhibitor. Current studies are underway that will give answers to this question in the immediate future.

Boosted **atazanavir (with ritonavir)** behaves differently as atazanvair on its own is an inhibitor of UGT (unboosted atazanavir results in 110% increase in AUC of norethindrone and 48% increase in AUC for EE) which counters some of the booster's induction effect. This results in only slight reductions in EE levels, but the progestogen levels remain high. Studies have indicated that boosted atazanavir can be used with the oral combined contraceptive pill that contains doses of at least 30 µg of oestrogen and the progestogen, norgestimate as this was the progestogen that was used in the studies [18-20]. The effect of raised progestogen levels is unknown but would need to be taken into consideration with regard to side effects.
The older PI indinavir which is seldom used today, is safe to use with hormonal contraceptives [21].

Maraviroc, an CCR5 entry inhibitor, is metabolised by CYP3A4 and P-glycoprotein but does not appear to induce or inhibit the isoenzymes involved in EE or progestogen metabolism and studies have shown it is safe for co-administration with hormonal contraceptives [22].

The integrase inhibitors (INIs) **raltegravir** and **dolutegravir,** are well known for their lack of drug-drug interactions and do not affect the pharmacokinetics of EE or progestogen, therefore both are safe to use with all hormonal contraceptives [23,24]. The other INI **elvitegravir** has a different pharmacokinetic profile as it is boosted with cobicistat, and itself is a modest inducer of CYP2C9. Boosted elvitegravir, lowers EE levels and raises progestogen levels but this can be

compensated by increasing the EE dose so the data suggests it can be given with an oral contraceptive that has at least 30 µg of oestrogen and norgestimate as the progestogen [25].

Because no high-quality, definitive studies exist on pregnancy rates among women on different hormonal contraceptives and ARVs, the dosing recommendations in the table below are based on consensus expert opinion. Whenever possible, the recommendations are based on available data regarding pharmacokinetic (PK) interactions between ARVs and combined hormonal methods, POICs and etonogestrel implants.

Emergency contraception
There is a paucity of data on interactions between EC and ART. Current FSRH guidance recommends that women using liver enzyme inducing drugs should be advised to use a Cu-IUD as EC. If this is not acceptable or appropriate, the current recommendation is that with enzyme inducing drugs (such as nevirapine, efavirenz and etravirine), the dose of levonorgestral is doubled and these women should be advised to take two 1.5 mg LNG tablets (3 mg) as a single dose as soon as possible and within 72 hours of UPSI. This is an off label indication and the effectiveness of double dose LNG-EC with enzyme inducers is now known; these limitations should be documented in the medical record.

There are no data on potential interactions between ART and UPA, however, ulipristal acetate is predominantly metabolized by CYP3A4, so interactions should be expected with inducers (nevirapine, efavirenz, etravirine) and inhibitors (ritonavir and cobocistat). UPA should be avoided in women on enzyme inducers currently or within the last 28 days [26].

Advice regarding DDI with emergency contraception is likely to evolve so refer to the Summary of Product Characteristics and the Liverpool interaction website.

Table 1 Summary of drug interactions between hormonal contraceptives and ARVs (correct at time of publication, always check Summaries of Product Characteristics and www.HIV-druginteractions.org for current advice)

Antiretroviral Drug	Effect on POIC (DMPA & NET)	Effect on LNG-IUS	Effect on other hormonal contraceptives *
NNRTIs			
Efavirenz	No impact on efficacy expected	No impact on efficacy expected	Alternative/additional methods
Nevirapine	No impact on efficacy expected	No impact on efficacy expected	Alternative/additional methods
Etravirine	No impact on efficacy expected	No impact on efficacy	No impact on efficacy expected

		expected	
Rilpivirine	No impact on efficacy expected	No impact on efficacy expected	No impact on efficacy expected
PIs			
Atazanavir/ritonavir	No impact on efficacy expected	No impact on efficacy expected	For the COC can use when dose of EE=30ug or more with norgestimate as the progestogen. Not advised with other hormonal methods as not studied.
Darunavir/ritonavir	No impact on efficacy expected	No impact on efficacy expected	Alternative/additional methods
Lopinavir/ritonavir	No impact on efficacy expected	No impact on efficacy expected	Alternative/additional methods
Fosamprenavir/ritonavir	No impact on efficacy expected	No impact on efficacy expected	Alternative/additional methods
INIs			
Raltegravir	No impact on efficacy expected	No impact on efficacy expected	No impact on efficacy expected
Dolutegravir	No impact on efficacy expected	No impact on efficacy expected	No impact on efficacy expected
Elvitegravir/cobicistat	No impact on efficacy expected	No impact on efficacy expected	For the COC can use when dose of EE=30ug or more with norgestimate as progestogen. Not advised with other hormonal methods as not studied.
CCR5 Inhibitor			
Maraviroc	No impact on efficacy expected	No impact on efficacy expected	No impact on efficacy expected

*Hormonal contraceptives: Combined oral contraceptive pill, progestogen only pill, combined contraceptive patch, combined contraceptive ring, progestogen only subdermal implant

Table 2

Use of contraceptive methods when woman is using an enzyme-inducer and within 28 days of stopping treatment **(Reproduced from FSRH Guidance on Drug Interactions with Hormonal Contraception 2017) [27]**

See page 8 FSRH guidance – copyrighted, permission pending
https://www.fsrh.org/standards-and-guidance/documents/ceu-clinical-guidance-drug-interactions-with-hormonal/

Method	Clinical recommendation
CHC	• Not advised. • Recommend an alternative method. ▶ Women taking rifampicin and rifabutin should **always** be advised to change to an alternative method. ▶ If a woman wishes choice with other enzyme-inducing drugs, consider use of a minimum 50 µg (30 µg + 20 µg) EE monophasic pill during treatment **and** for a further 28 days with a continuous or tricycling regimen plus pill-free interval of 4 days. ▶ Breakthrough bleeding may indicate low serum EE concentrations. Exclude other causes (e.g. chlamydia) and dose of EE can exceptionally be increased up to a maximum of 70 µg EE after specialist advice. ▶ Use of two patches or two rings is not recommended.
POP	• Not advised. • Recommend an alternative method.
IMP	• Not advised. • Recommend an alternative method.
DMPA LNG-IUS	• No interaction. • No need for extra precautions.
Cu-IUD (EC)	• No interaction. • No need for extra precautions. • Most effective method of EC.
LNG-EC	• Can use **DOUBLE DOSE** i.e. 3 mg (2 x 1.5 mg tablet) as a single dose within <72 hours of unprotected sexual intercourse (UPSI) if Cu-IUD is declined or unsuitable.
UPA-EC	• Not advised. • Recommend an alternative method.

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Contraception and HIV Acquisition, Transmission and Disease Progression

Recommendation

- Women and their partners should be informed about a possible increased risk of HIV acquisition and transmission with injectable hormonal contraception, and about the importance of dual protection with condoms to reduce HIV risk.

There have been theoretical concerns that contraceptive methods could increase susceptibility to HIV infection, increase risk of transmission, or influence the course of HIV disease. Some observational studies have suggested that women using POIC, are at higher risk of HIV acquisition, although other studies have not demonstrated this. Balancing potential risks of contraception with the benefits is a particular challenge in countries where women have a high risk of acquiring HIV, where maternal mortality rates are high, and where injectable methods are in popular use. Most studies have been conducted in these high-risk populations and the relevance of the findings to the general population is unclear. Modelling studies have suggested that a reduction in DMPA use would be unlikely to result in public health benefit, with the possible exception of those countries in southern Africa with the largest HIV epidemics [1]. A major RCT is on-going aiming to clarify the degree of risk associated with different methods (expected to report 2019), and further work remains to be done on how the use of ARV modifies the effects of contraception on HIV disease. Information about contraceptive options for people at risk of HIV or living with HIV should include any potential risks related to HIV.

Acquisition in HIV-negative women

Three types of evidence have raised concerns about hormonal contraception and increased HIV acquisition. High dose progestogen has been found to greatly increase HIV acquisition in non-human primates [2]. Biological plausibility is provided by the hypo-oestrogenic state and vaginal mucosal thinning induced by progestogen contraception [3], increased cervical ectopy, alterations in expression of immune mediators [4-9], changes in immune cell populations [10-12], and alterations in the vaginal microbiome [3]. Medroxyprogesterone acetate has been shown to have greater influence on immune function than other progestogens [13]

Epidemiological evidence is mixed, with some but not all studies indicating an increased risk of HIV acquisition in users of hormonal contraception. The quality of evidence has improved over time as a result of better differentiation between contraceptive formulations, and consideration of confounders such as condom use. Over-reporting of condom use by hormonal contraceptive users has been thought to be a potential source of bias, but recent analyses have weakened this theory [14].

Most epidemiological studies have reported an association between DMPA and increased risk of HIV acquisition. In a meta-analysis of observational studies, ten of the twelve included studies indicated moderate increased risk of HIV acquisition among women using DMPA; none of the included studies indicated increased risk among women using oral contraceptive pills [15]. Another meta-analysis pooled

individual participant data from 18 studies, including 37,124 women [16]. This meta-analysis found that DMPA use was associated with HIV acquisition relative to non-hormonal method use: adjusted hazard ratio (aHR) 1.50 (95% CI 1.24-1.83). A statistically non-significant risk was found for norethisterone enantate (NET-EN) use: aHR 1.24 (95% CI 0.84-1.82). COC use was not associated with HIV acquisition: aHR 1.03 (95% CI 0.88-1.20). Similar risk estimates were reported in an updated systematic review [17].

After review of the evidence, WHO and the UKMEC guideline development group considered that DMPA should be classified UKMEC2 for women at high risk of HIV ie benefits outweigh risks. The FSRH advice is " A woman who is identified to be at high risk of HIV infection can continue to be offered all methods of contraception (assuming that there are no other contraindications). She should be made aware that some studies have found that users of progestogen-only injectables have an increased risk of HIV acquisition but that it is not known whether the progestogen-only injectable itself causes the increased risk or whether this is due to confounding factors eg non use of condoms. All women at high risk of HIV infection should be advised to use effective contraception to reduce the risk of unplanned pregnancy and to use condoms reliably to minimise the risk of acquiring HIV and other STI."

Little evidence is available on HIV acquisition risk and other contraceptive methods. There remain no data on use of contraceptive patches, rings, or hormonal IUDs and HIV acquisition. Implant use was studied in a prospective observational study of Zambian women in which no association was found between injectable methods, OCP or implant use and HIV acquisition risk relative to non-hormonal methods [18]. The Zambian study was underpowered but was rigorous in adjusting for confounders such as frequency of unprotected sex which was found to be higher in injectable and OCP users. No increased risk of HIV acquisition was reported in two other studies assessing implant use [19,20].

Contraceptive diaphragms have traditionally been used with the spermicide nonoxinol-9 which may increase the risk of HIV acquisition by increasing the rate of genital ulceration [21]. Alternative spermicidal agents are available but there is limited data on HIV acquisition. A study of the diaphragm, lubricant gel (Replens®) and condoms showed no increased risk of HIV acquisition [22], and no added protective benefit compared with use of condoms alone. There are limited data on intrauterine contraception but neither biological studies [23] nor epidemiological data [24] indicate any increased risk of HIV acquisition.

Transmission from HIV-positive women to HIV-negative men

Most of the evidence around contraception and risk of HIV transmission is based on markers of infectivity. Direct evidence of transmission rates is currently limited. An observational study suggested a two-fold increased risk of female-to-male HIV transmission with use of injectable contraceptives, but not for oral contraceptive pills [19]. A smaller retrospective study did not show significant risk of HIV transmission with DMPA or oral contraceptives but the study lacked statistical power [20].

Studies of HIV-1 shedding during the menstrual cycle have demonstrated that HIV-1 RNA reaches its highest levels in genital secretions during the luteal phase, when progesterone predominates [25,26]. However, findings of studies of genital HIV shedding in women using hormonal contraception have been inconsistent [27].

Indirect mechanisms by which hormonal contraceptive use may contribute to HIV-1 infectivity include increased risk of cervical STIs [28], which may increase cervical HIV-1 shedding [29,30]. Data concerning the effect of hormonal contraception on reactivation of genital herpes, which also increases genital HIV-1 levels [30-32], are inconsistent.

Plasma viral load has also been investigated as a marker of infectivity. While one study among Kenyan sex workers suggested an association between DMPA use at the time of HIV infection and a higher plasma viral load setpoint [33], these findings have not been corroborated by subsequently published data [34,35].

Disease progression in HIV-positive women

Early studies demonstrated that women using DMPA or oral contraceptive pills at the time of HIV-1 acquisition were more likely to acquire multiple viral genotypes [36], which in turn has been associated with higher plasma viral load set point and faster decrease in CD4 cells [37,38].

However, in a systematic review of 11 studies [39], only one RCT showed increased disease progression in women using hormonal contraception who were not receiving ART [40]. Although the study was randomised it had limitations including high levels of switching and loss to follow-up, and lack of power to detect an impact on HIV progression by method of contraception. The other 10 cohort studies did not suggest any increase in disease progression. A US study not included in the systematic review indicated that adolescent females using hormonal contraception had a slightly diminished response to ARV therapy compared to women not using hormonal contraception as measured by viral load and CD4+ T cell counts [41]

The effect of the implant, patch or vaginal ring on disease progression has not been assessed. A small study of the levonorgestrel-releasing intrauterine system in HIV-infected women did not show any effect on CD4 lymphocyte counts compared to HIV-infected non-users over 5 years [42]

Evidence of hormonal contraception adversely affecting HIV disease progression is currently very limited. Further research is required to ascertain the clinical relevance of these effects, if any. In the UK, where ART is recommended for all PLWH, there is no clinically important impact of contraceptive choice.

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Management of the menopause in women living with HIV

Recommendations

- We recommend baseline assessment of menstrual cycle and annual review thereafter.
- We recommend proactive assessment of menopausal symptoms on women aged >45 (including hot flushes, sweats, sleep disturbance, genitourinary symptoms, and changes in mood).
- We recommend use of HRT as per NICE guidelines
- We recommend WLWH in mid-life are provided information on menopause and treatment options [GPP]
- We suggest management of menopause in primary care according to NICE guidelines
- We recommend bone screening in line with BHIVA monitoring guidelines

Approximately 8700 women of potentially menopausal age (between 45 and 56) attended for HIV-related care in the UK in 2014, a six-fold increase over a ten year period [1]. Whilst there is some evidence to suggest that women living with HIV experience menopause at an earlier age and that they have more symptoms, there is no clear consensus in the literature around an impact of HIV infection on either timing or symptomatology of the menopause [2]. Given the possibility of earlier menopause, we recommend routine annual enquiry about menstrual pattern and menopausal symptoms (including hot flushes, sweats, sleep disturbance, genitourinary symptoms, and changes in mood) in women living with HIV aged 45 and over. Laboratory investigations to support the diagnosis (such as follicle-stimulating hormone) are not routinely indicated in women aged over 45 years with menstrual irregularity and/or vasomotor symptoms [3]. Menopause is diagnosed after ≥12 months of amenorrhoea in women not on hormonal contraception (or on the basis of menopausal symptoms in those without a uterus).

HIV and its treatment can predispose WLWH to a variety of metabolic complications [4,5], many of which are also associated with ageing and the menopause. The effect of the menopause transition on the risk of osteoporosis and cardiovascular disease in women living with HIV is therefore likely to be of importance. Bone loss is known to accelerate in the perimenopause and early postmenopause [6] and we recommend 3-yearly assessment of fracture risk using the FRAX tool in postmenopausal women (≥12 months amenorrhoea or following surgical menopause), and women aged >50.

In the absence of evidence on best management strategies for menopausal WLWH (including the efficacy and safety of hormone replacement therapy [HRT]), we advise management within primary care (where appropriate) in accordance with current National Institute for Health and Care Excellence (NICE) menopause guidelines [3]. HRT is not contraindicated in women living with HIV for the management of menopausal symptoms. Transdermal HRT, already recommended first-line by NICE [3], is likely to have an important role when managing menopause in HIV-positive women as it minimises the risk of nausea, and venous thromboembolism and stroke.

Finally, WLWH entering their midlife should be provided with adequate information about the menopause and possible treatment options (www.menopausematters.co.uk), including advice about lifestyle modification aimed at reducing menopausal symptoms and improving longer term health (such as exercise, reducing alcohol intake, and smoking cessation). Women in the perimenopausal and early postmenopausal phase should be advised on contraception [7]. They should also be encouraged to attend for routine screening for cervical and breast cancer as per national guidelines.

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Intimate Partner Violence

Recommendations

- We recommend routine enquiry about domestic abuse, including intimate partner violence, in sexual health & HIV clinics in accordance with NICE guidelines [grade?]
- We recommend services develop local guidelines & pathways based on BASHH guidance prior to the introduction of routine questioning (Responding to domestic abuse in sexual health settings. BASHH 2016)

Intimate partner violence (IPV) is defined as physical, sexual or psychological harm by a current or former partner, or spouse and is a form of domestic abuse. It also includes controlling behaviour such as isolating a person from family and friends, monitoring their movements and restricting access to financial resources, employment, education or medical care. It is widespread globally and viewed as a public health epidemic by the World Health Organisation due to its detrimental and extensive effects on physical and mental health [1].

There is a large evidence base globally showing links between IPV and HIV in women. Multiple forms of IPV are associated with HIV acquisition in women and are thought to be due to forced sex, difficulties negotiating condom use and a higher likelihood of male perpetrators having HIV and other sexually transmitted infections [2-4]. Women living with HIV are more likely to experience IPV than HIV-negative women and in the UK, lifetime prevalence has been reported as high as 52% [5-7]. IPV is a predictor of worse HIV outcomes and has been associated with lower use of ART, reduced self-reported ART adherence and significantly worsened viral suppression amongst women [8,9]. It may also impair a woman's ability to disclose her HIV status [10].

IPV is also common in the LGBTQ community and it has been shown that all forms of IPV occur at rates similar to or higher than those documented among women in heterosexual relationships [11, 12]. Although there is little data on IPV in the HIV-positive LGBTQ community, it can be assumed that prevalence is high. A recent meta-analysis showed that MSM who have experienced IPV are more likely to engage in unprotected anal sex and be HIV-positive [13] and that forced sex and difficulties with condom negotiation may be common in abusive LGBTQ relationships [14].
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IPV causes significant long and short-term effects on physical and mental health and as such, people experiencing IPV are more likely to be in regular contact with health care professionals than those who are not experiencing IPV, providing important opportunities to identify and offer support [15, 16]. The National Institute for Health and Care Excellence recommends that all sexual health clinics should routinely enquire about domestic abuse including IPV [17]. It is crucial that enquiry and management of a disclosure of IPV is carried out safely with local guidelines, appropriately trained staff and clear referral pathways to relevant services and safeguarding. Detailed guidance on adequately preparing a service to respond to

domestic abuse has been published by BASHH and we would endorse its use before introducing routine enquiry in HIV services [18].

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Female genital mutilation

Recommendations

- In line with the rest of the NHS, in the UK it is mandatory for HIV services to report female genital mutilation and collect data
    - HM Government. Multi-agency statutory guidance on female genital mutilation (2016)
    - HM Government. Mandatory reporting procedural information (2015)

Female genital mutilation (FGM) is a cultural practice widely carried out in many African countries such as Nigeria, Somalia and Egypt and some areas of the Middle East. The World Health Organisation (WHO) estimates that there are 100 million women and girls living with the consequences of FGM globally with 2 million procedures occurring a year. FGM is defined as procedures that include the partial or total removal of the external female genital organs for cultural or other non-therapeutic reasons. It can range from genital piercing to total infibulation, where the clitoris and labia minora are excised and the labia majora are stitched together to leave a very small orifice for the passage of urine and menstrual blood. This type is the most common and results in the most severe sequelae. Short-term risks of FGM include pain, excessive bleeding and wound infections. Long-term sequelae include chronic pain, menstrual problems, urinary tract and pelvic infections, keloid scar formation, dyspareunia and sexual dysfunction, obstetric complications, post-traumatic stress disorder and depression [1,2].

We could not find any data demonstrating direct causal links between FGM and HIV transmission in our literature review, but several studies have suggested mechanisms by which it could occur. The procedure is often performed on many girls at the same time and a study in Dar es Salaam showed that 97% of the time, the same cutting equipment was used for 15-20 girls increasing the likelihood of possible HIV spread through shared tools [3]. FGM can also often make vaginal intercourse more difficult due to scarring and a reduction in the size of the orifice. This increases trauma to the genital tissues and mucosal tearing, increasing the risk of viral transmission [2, 4, 5]. Difficulty with vaginal intercourse may also make couples more likely to engage in anal intercourse, which has a higher risk for HIV transmission than vaginal sex [2]. Women who have experienced FGM are also more likely to develop recurrent genitourinary infections such as vaginal candidiasis, which cause mucosal inflammation and increase the risk of tears and thus HIV acquisition [2].

FGM is a form of child abuse and is illegal in the United Kingdom (FGM Act 2003). It is also illegal to arrange for a child to be taken abroad for FGM. If caught, offenders face a large fine and a prison sentence of up to 14 years [6]. It is mandatory for health and social care professionals who identify FGM in girls aged <18 years to report cases to the police by the end of the next working day. Local safeguarding procedures should also be followed to see if any other actions are required. For women aged 18 years or over who have had FGM, parents/guardians who disclose their child has had FGM, girls thought to be at risk of FGM or have had FGM, but

have not disclosed or there are no signs, symptoms, local safeguarding procedures must be followed [7]. NHS acute trusts, mental health hospitals and general practice surgeries must submit data about patients who have had FGM to the Health and Social Care Information Centre (HSCIC) using the FGM Enhanced Dataset Information Standard [8]. This information is used nationally and locally to improve the NHS response to FGM and to help commission the services to support women who have experienced FGM and safeguard women and girls at risk of FGM.

In line with the rest of the NHS, it is mandatory for health and social care professionals working in HIV services to report FGM and collect data. More guidance on this with information on pathways and training can be found on the government website [7,8].

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Sexual dysfunction and HIV

Recommendations

- We recommend that annual enquiry about sexual function, and broader sexual wellbeing, should be standard of care for all PLWH.
- Access to sexual dysfunction services should be available, and pathways in place for referral from HIV services to services skilled in treating sexual problems.
- We recommend that all men with sexual problems have a full sexual history and a focused physical examination, including evaluation of cardiovascular risk.
- We recommend investigation of male sexual problems should include evaluation of bioavailable fasted morning testosterone level, prolactin and thyroid function as a minimum, along with fasting lipids and screening for diabetes if not recently tested.
- All women presenting with sexual pain should be offered a physical examination by a clinician with expertise in sexual problems or sexual health
- It is good practice to offer examination to all women where physical factors associated with their sexual problem cannot otherwise be excluded
- We recommend services record data collected during annual reviews to develop an evidence-base regarding sexual function in transgender people living with HIV

It is well recognised that a healthy and satisfying sex life is associated with living longer, staying healthy and improved mental-health and wellbeing [1]. The presence of sexual problems has been associated with reduced adherence to medications [2,3] and the additive effects of sexual difficulties and mood disturbance may further negatively affect adherence to medication. Sexual dysfunction has also been associated with poor condom use and risky sexual behaviour [2,4].

Sexual problems, concerns, difficulties and dysfunctions amongst PLWH are common [2,4] and studies have shown a higher prevalence of problems amongst individuals living with HIV than in the general population [5,6], with many reporting continued high rates despite the widespread use of ART [2,7]. The reasons for this are multifactorial and commonly include both psychological and biological influences. In the UK, an ageing HIV cohort, with a burden of co-morbidities and polypharmacy, is likely to experience continued high levels of sexual problems into the future [8].

High rates of mental health problems, including anxiety and depression, amongst PLWH frequently co-exist with sexual dysfunction [9]; the relationship between mental health and sexual function is likely to be bi-directional. Depression and anxiety may predict subsequent sexual dysfunction [10], and this may be due to both a direct effect of mood disturbance as well as the effect of medications used to treat mood problems [10]. The BASHH MSM guidelines note that ‘sexual difficulties have been associated with low self-confidence and poor self-image and there are complex interactions between sexual dysfunction, recreational drug and alcohol use, mood

disturbance, sexual risk taking and HIV infection especially amongst HIV positive MSM' [11].

Supporting PLWH to achieve a healthy and satisfying sex life should be part of routine clinical care. Annual enquiry about erectile dysfunction (ED) is a NICE recommended standard for management of other chronic conditions, such as diabetes [12]. We recommend that annual enquiry about sexual function, and broader sexual wellbeing, should be standard of care for all PLWH. Access to services should be available, and pathways in place for referral from HIV services to services skilled in treating sexual dysfunction.

Sexual difficulties are under-reported and patients may not raise the subject themselves so it is important to ask about sex directly. For clinicians that are less confident or knowledgeable about asking sexual well-being questions, training to ask open-ended questions, which are respectful of different sexual preferences and sexualities, is encouraged. Given the multi-faceted nature of sexual problems we recommend a bio-psycho-social approach to assessment and treatment.

For sexual problems that may indicate underlying medical conditions, such as erection difficulties and pain on sex, local pathways for timely access to relevant medical investigations and treatment are crucial. Where there is a predominantly organic basis to sexual problems psychological support, alongside medical treatments, to support adjustment to changes in sexual function may be helpful and facilitate a sex-life that still has value. For those people in whom lifestyle factors significantly contribute to their sexual problem, for instance substance use and alcohol misuse, conversations around behaviour change are encouraged. Brief psychological interventions can be effective at supporting individuals to make behavioural changes, including motivational interviewing combined with cognitive-behavioural-therapy (CBT).

Specialist sexual dysfunction and psychosexual services should be accessible and appropriately tailored to the population they serve. A step-care model can be a cost-effective way to improve access to psychosexual interventions at the level that individuals need them.

In line with the 'Standards for Psychological Support for Adults living with HIV' [13] and NICE mental health guidelines, we recommend the provision of accessible and tailored self-help material for PLWH. This should include access to accurate information about sexual arousal, and evidence-based self-help material about common sexual problems. However, accurate information is sparse and inaccurate information is easily accessible (e.g. via pornography). Psycho-education can be a useful and cost-effective first-line intervention for sexual concerns and problems, especially given inaccurate beliefs about 'normal' sexual arousal and response, and the distress can result from comparisons to unrealistic myths and norms. Guided self-help, including tailored material, is particularly effective when there is a psychological aspect to the presenting problem. In addition to self-help, timely integrated medical and psychological assessment and treatment is important.

Detailed guidance on the management of specific sexual difficulties is beyond the scope of this guideline and what follows is a summary of some key issues to be considered when managing PLWH; where available signposting to relevant national/international published guidance is included.

MEN

Erectile Dysfunction (ED)
ED is a highly prevalent problem and prevalence increases with age [14]. Early studies reported an association with ED and treatment with protease inhibitors [15], but more recent studies find no association [16]. Peripheral neuropathy (PN) secondary to older ARV agents, particularly NRTIs, may contribute to ED, but ED has not been consistently linked with any particular antiretroviral class [17].

Importantly, the association between ED and coronary artery disease (CAD) is increasingly recognised, and ED may be an early marker for more generalized arteriopathy including undiagnosed coronary artery disease [18]. The link between ED and CAD is not fully explained, but may involve an interplay between androgen dysregulation, chronic inflammation, and cardiovascular risk factors that determines endothelial dysfunction and atherosclerosis, resulting in disorders of penile and coronary circulation [18]. In HIV infection, risk of cardiovascular disease and endothelial dysfunction has been documented [19], it is recommended that all men living with HIV with ED should have a thorough cardiovascular risk assessment undertaken and any risk factors for CHD addressed vigorously.

ED has been associated less safe sexual practices [20], particularly amongst MSM and this is discussed further in “Sexual Problems and Dysfunctions in MSM, Dr Stuart Gibson”[12].
Sexual history should include enquiry about concomitant drug therapy (such as anti-depressants and antihypertensives) and recreational drugs (including anabolic steroids, alcohol and psychoactive substances) as these may be implicated in the development of ED [21]. We suggest services develop pathways for psychological support for patients to explore their sexual choices and/or develop confidence about methods to reduce sexual risks. Sex therapy techniques, for instance, can improve men’s confidence about using condoms.

ED in the context of HIV disease may also be commonly related to psychological factors such as fear of onward transmission of HIV, disclosure concerns, changes in body image, stigma and issues around condom usage [22], all of which should be explored in the sexual history and may require psychological input. Where there is a significant contribution of psychogenic causes for ED, access to psychosexual therapy should be available. The potential merits of sex therapy, in conjunction with medical therapy when appropriate, should be discussed and even when ED is primarily organic, psychological therapy can support the individual, or couple, to adjust to changes in their sexual function.

Assessment and response to treatment may be aided by the use of validated scales such as International Index of Erectile Function (IIEF) [23] which was adapted for use in HIV positive MSM [24], however this cannot replace a detailed sexual history. Scales intended to measure broader aspects of sexual well-being, including sexual confidence and enjoyment, are in the process of being validated for clinical populations.

Useful up to date guidance on management of erectile dysfunction can be found via the European Association of Urology [25] and British Society of Sexual medicine [26].

Phosphodiesterase inhibitors type 5 (PDE5Is) namely sildenafil (Viagra®), tadalafil (Cialis®), Avanafil (Spedra®)and vardenafil (Levitra®) are usually the first-line medical treatment for ED; all undergo predominantly hepatic metabolism via the cytochrome P450 3A4 isoenzyme [27]. Any drug affecting this P450 isoenzyme system has the potential to affect PED5i levels. Consequently, care and dose adjustment is required with reduced and less frequent dosage recommended when PDE5Is are co-administered with protease inhibitors, or other boosting agents such as cobicistat, along with vigilance to associated adverse events such as hypotension, syncope, visual disturbances and priapism. The PDE5i may also require dose adjustment when co-administered with some NNRTIs that induce the cytochrome P450 3A4 isoenzyme, due to reduced bioavailability of PDE5I. In contrast there is no dosage adjustment required for any of the ARVs when used concomitantly with the PDE5Is.We recommend that drug interactions should be checked on the Liverpool HIV drug interactions website prior to prescribing PDE5i to patients on ART [28].

Patients who use amyl nitrate or other recreational nitrate agents should be cautioned not to use these agents in conjunction with PDE5Is due to risk of fatal hypotension.

Use of intracorporeal alprostadil is an effective second line treatment for ED, but patients must be cautioned that the injection site may expose patient/partners to blood-borne infection; patients should be counselled to ensure that a condom is rolled back to cover the injection site and to ensure safe needle disposal. Alprostadil is also available as a trans-urethral preparation (MUSE©) which can cause local side effects including urethritis which may theoretically increase the risk of onward HIV transmission, or acquisition of another STI by the patient. Vitaros is an alprostadil containing cream licensed for treatment of ED and is administered to the urethral meatus. Penile and vaginal irritation has been reported using this product and condoms should be used with it, especially if the female partner is at risk of getting pregnant.

Ejaculatory disorders

There are few data describing prevalence of ejaculatory disorders; factors potentially contributing to delayed ejaculation in men with HIV may include medications (especially antidepressants), penile sensation loss due to neuropathy (including drug-induced) [21], endocrinopathies, and psychological aetiologies [29].

An increasing proportion of men report using substances to prolong ejaculation; given substance use is associated with higher risk sexual practices this is an important area for further research. Routinely recording ejaculatory disorders will facilitate better understanding of the prevalence. Along with medical treatments for men reaching the criteria for early ejaculation, psychological interventions are an effective for men to increase their control over how they ejaculate, as well as more broadly in relation to anxiety around sex.

Treatment recommendations for delayed ejaculation [30] are published by BASHH Sexual dysfunction special interest group and guidance on management of rapid ejaculation [31] are published by ISSM and are freely available.

Desire

Problems related to loss of sexual desire have been described at high prevalence rates in HIV-infected men, with studies reporting prevalence rates of up to 48% of seropositive MSM [30,32]. There are a host of possible psychosocial contributing factors and the individual often cites psychological reasons as the putative cause [20,30]; an integrated psychological and medical assessment is optimal. Hormonal abnormalities can affect desire and lack of desire associated with androgen deficiency (see below) has been described in HIV positive patients on ARVs [20,34-36]. There have been reports of men on ART with increases in serum oestradiol, which may rarely be a cause of loss of sexual desire [20,32]. As with all sexual problems a sexual history including review of medications that may cause hormonal disturbance plus a focused physical examination paying attention for signs of hypogonadism is warranted, along with hormonal assays (testosterone, prolactin and thyroid hormones as minimum), to determine if there is a physical cause contributing to low desire.

Androgen Deficiency

Prevalence estimates of androgen deficiency amongst men living with HIV have declined since the widespread introduction of cART [36], but prevalence is still higher than would be expected in the general population [37]. Androgen deficiency in this group is frequently associated with low luteinizing hormone and follicle-stimulating hormone; individuals may have a normal total testosterone but low free or bioavailable testosterone level due to increased levels of SHBG. Calculation of free and bioavailable testosterone is informative and can be made using Vermeulen equation using an online calculator tool [38].

The pathogenesis of testosterone deficiency in HIV is likely to be multifactorial and several mechanisms have been proposed including chronic illness, HIV replication, medications including ART, lipodystrophy, metabolic syndrome, other co-morbidities and co-infections [37,39]. Studies have suggested a loss of diurnal variation in free testosterone levels among HIV-infected men compared to HIV negative controls [40].

'Guidelines on the management of sexual problems in men: the role of androgens' [41] is a multi-specialty guideline produced in 2010 and is freely available on line.

Sexual function and circumcision
There are data from several large studies suggesting that circumcision of adult males as a strategy to reduce HIV acquisition is not associated with reduced sexual functioning at a population level [42-44].

WOMEN
There is a paucity of literature regarding sexual function of women living with HIV. Available data strongly supports high levels of sexual difficulties amongst women living with HIV [45-50]. Furthermore, WLWH are rarely asked by their healthcare provider about sexual function (FSD) [51,52] despite the fact that it is likely that questioning about sexual function is of benefit [52]. It is therefore likely that sexual problems are under-diagnosed and under-treated in WLWH and opportunities to improve quality of life are missed.

Female sexual dysfunction commonly relates to psychosocial issues and HIV status itself [47]. Fear of onward transmission (horizontal or vertical) may be a major cause of anxiety and dysfunction, particularly where there may be disclosure issues, and a need to negotiate condom use [51]. Poorer sexual functioning in WLWH has been associated with menopause, low CD4 count, low mood and poor body image [45,46]. Complications of HIV infection and HIV treatment, such as neuropathy (HIV or drug-induced), endocrine disturbances or atherosclerosis may cause or contribute to sexual difficulties. Menopause is associated with changes in sexual function; WLWH may experience earlier menopause [53] and more menopause-related sexual problems [54]. For women experiencing painful sex as a result of menopause-related urogenital atrophy, NICE menopause guidelines recommend that topical vaginal oestrogens may offer great symptomatic benefit with minimal systemic absorption.

Assessment of women's sexual dysfunction should be primarily via thorough sexual history taking, paying particular attention to the bio-psycho-social context in which any problem is occurring. All women presenting with sexual pain should be offered a physical examination by a clinician with expertise in sexual problems or sexual health, and it is good practice to offer examination for all women where physical factors associated with their complaint cannot otherwise be excluded with confidence. Scales used to measure female sexual dysfunction include Female Sexual Function Index (FSFI), Female Sexual Distress Scale (FSDS), Sexual Interest and Desire Inventory (SIDI); these may have limited usefulness in assessment and monitoring of sexual problems, and have not been specifically validated amongst WLWH

TRANSGENDER INDIVIDUALS
There are no data describing HIV-positive transgender men and women's sexual functioning. We recommend services record data collected during annual reviews to develop an evidence-base regarding sexual function in this population. We suggest signposting to specialised transgender services, where available, and seeking advice from colleagues with expertise where required.

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