British HIV Association, BASHH and FSRH guidelines for the management of the sexual and reproductive health of people living with HIV infection 2008

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1.0 Summary of key points and recommendations

Levels of evidence:

I = high-quality meta-analyses, systematic reviews of randomized control trials (RCTs);

II = other good-quality trials such as case-control or cohort studies;

III = non-analytic studies such as observational studies, case reports or case series;

IV = consensus or expert.

1.1 Sexual and reproductive health of women and men living with HIV

1.1.1 Sexual health support

All HIV-positive individuals under regular follow-up should have:

- a sexual health assessment, including a sexual history documented at first presentation and at 6-monthly intervals thereafter (II);
- access to staff trained in taking a sexual history and who can make an appropriate sexual health assessment (III);
- access to ongoing high-quality counselling and support to ensure good sexual health and to maintain protective behaviours (IV);
- an annual offer of a full sexual health screen (regardless of reported history) and the outcome documented in the HIV case notes, including whether declined (II);
- documented local care pathways for diagnosis, treatment and partner work for sexually transmitted infections (STIs) in people with HIV, which can be actively communicated to all clinic staff and to HIV-positive patients (II).

1.1.2 Management of sexually transmitted infections in HIV-positive men and women

- The majority of STIs in people with HIV, including gonorrhoea and chlamydial infection, can be managed as in people without HIV (II).
- STIs should be considered in the differential diagnosis of presentations such as skin rash or proctitis in HIV-positive patients (I).

- Syphilis serology should be documented at baseline and at 3-monthly intervals and taken as part of the routine HIV blood set (unless indicated otherwise) to detect asymptomatic syphilis (II).
- There are British Association for Sexual Health and HIV (BASHH) guidelines for the management of syphilis, genital herpes and warts in people with HIV. These should be referenced if managing individuals with these conditions (I).

1.1.3 Management of hepatitis and blood-borne viruses

All HIV-positive individuals under regular follow-up should have:

- hepatitis A, B and C screening at baseline; if not already immune to hepatitis B (HBV), they should be vaccinated against it regardless of sexual orientation (III);
- screening for hepatitis B and C, which should be offered annually in those who have exposure risks (IV).

1.1.4 Post-exposure prophylaxis

- All units should have explicit policies and procedures on post-exposure prophylaxis (PEP) following sexual exposure (IV).
- All HIV-positive individuals should be made aware of the units’ procedures to access PEP (IV).

1.1.5 Pre-conceptual counselling, natural conception and assisted reproduction

- HIV-positive men and women and their partners planning to have children should receive pre-conceptual counselling on all their conception options, including HIV transmission risks associated with each case, so that they can make an informed choice (IV).
- Detailed comprehensive pre-conceptual counselling should be available for couples considering conceiving. This should review the available options and the possible risks of each method. All discussions should be documented clearly in clinical notes (IV).
- Clinics advising serodiscordant couples on risk-reduction strategies for natural conception should obtain signed consent that both parties understand and accept the small risks of HIV transmission (IV).

1.2 Cervical and anal pre-cancers and cancers

1.2.1 Cervical cancer

- All newly diagnosed HIV-positive women should have a sexual and gynaecological history as part of their initial medical assessment, including cervical cytology and a sexual health screen if appropriate (III).
• Advanced HIV disease is the strongest independent risk factor for developing cervical abnormalities. All abnormal smears (mild dyskaryosis) should be referred to specialist colposcopy services (II).
• Annual cervical smears are currently recommended (IV).
• The management of cervical intraepithelial neoplasia (CIN) in HIV-positive women should not differ from that in the general population (III).
• There is limited and controversial data on the effect of highly active antiretroviral therapy (HAART) on the natural history of disease; therefore, management of women should be the same whether they are receiving therapy or not (II).

1.2.2 Anal cancer
• All major HIV units should develop clinical guidelines for the management of suspected anal cancer and pre-cancer (IV).
• All major HIV units should develop either local clinical expertise or referral pathways for suspected anal cancer and pre-cancer (IV).

1.3 Psychosocial issues
• Psychological considerations are of key importance in several issues including conception and HIV in pregnancy, sexual behaviours to reduce HIV transmission and sexual functioning (II).
• All units involved in HIV service delivery should consider the funding and provision for mental health and behavioural aspects of sexual and reproductive health (SRH) (IV).
• An updated understanding of HIV prevention, risk behaviour, reproduction and mother/father perspectives should feed into policy and service provision (IV).

1.4 HIV sexual transmission and HAART
• HAART reduces the risk of HIV sexual transmission; for individuals with chronically suppressed viral loads, the transmission risk may be negligible in the absence of STIs (II).
• In most circumstances, counselling and advice should continue to promote the use of condoms to reduce the transmission risk of HIV and other STIs (III).
• Detailed individual counselling, including the use of harm reduction, should be available for individuals in sero-different and sero-same long-term relationships who wish to consider unprotected sexual intercourse (IV).
• The risk of HIV superinfection may diminish with the time from initial infection. Although it appears more likely in the first 3 years following seroconversion, a risk persists after this (II).
• HIV-positive individuals should be counselled regarding the low but possible risk of superinfection, particularly those who choose to serosort (i.e. have unprotected intercourse with partners who are also HIV-positive) (II).

1.5 HIV and criminalization
• Healthcare staff should be aware of the important legal issues regarding HIV transmission and their responsibilities to the duty of care of patients, confidentiality and public health concern (IV).
• All units should develop local policies and guidelines on partner notification and disclosure (IV).

1.6 Contraception for women with HIV infection
• Consistent condom use should be encouraged in conjunction with the additional contraceptive methods (II).
• For HIV-positive women not on HAART, all available contraception methods are suitable (II).
• A full choice of options for contraception should be discussed, with appropriate counselling about potential drug interactions and reduced contraceptive efficacy (III).
• Because of potential interactions between antiretroviral therapy (ART) and the combined oral contraceptive pill (COC), ORTHO EVRA™, the progestogen-only pill (POP) and implants, these methods may be best avoided for women on HAART or other liver enzyme-inducing drugs (III).
• There are no known adverse interactions between HAART and depot medroxyprogesterone acetate (DMPA), the levonorgestrel intrauterine system (LNG-IUS) and intrauterine devices (IUDs) (II).
• For emergency contraception, an emergency IUD is the preferred option for women on ART. If Levonelle® 1500 is used, an additional dose (total 3 mg) is required for women on ART (III).

1.7 Reproductive and sexual health in men
• Use of barrier contraceptives should be encouraged to prevent the spread of HIV, superinfection and co-infection with other STIs (I).
• Education on proper use appears to be more important than the thickness of the latex condom (II).
• There may be legal implication in having unprotected sex, particularly when an individual has not disclosed their HIV status and transmission occurs. This should be raised in the context of safer sex discussions. Further guidance should be sought from relevant sources (IV).
• The use of mineral oil-based lubricants with latex condoms, and the use of nonoxinol-9 (N-9), should be discouraged. There is no published evidence that specific antiretroviral (ARV) agents affect male fertility (III).

1.8 Investigation and management of sub-fertility in men
• There is some evidence that men with advanced disease may have abnormal sperm production; optimizing HIV treatment should be part of the management of such men (III).
• Investigation should be in line with National Institute of Health and Clinical Excellence (NICE) guidelines; it is recommended that both partners undergo assessment (IV).

1.9 Erectile dysfunction
• There is some evidence that men with HIV infection are more likely to experience erectile dysfunction (ED). This may adversely affect effective condom usage, and should be treated (III).
• There are some important drug interactions between PDE5 inhibitors and protease inhibitors (PIs), which may necessitate dose modification of the PDE5 inhibitor (II).
• Recreational drug use may affect condom use and erectile function, and needs to be assessed. Inhaled nitrates are contra-indicated when using PDE5 inhibitors (III).

2.0 Introduction and general issues

2.1 Addressing the sexual and reproductive health needs of people living with HIV/AIDS in the era of successful HIV therapy

The incidence and prevalence of HIV infections continue to rise in the UK [1,2]. Because of the effectiveness of HIV treatment regimens there is now an increasing number of HIV-positive individuals living well on suppressive ART [3]. More attention is thus being given to the wider health needs of people living with HIV/AIDS (PLHA), including a renewed focus on SRH needs.

Men who have sex with men (MSM) (this term is used throughout to refer to homosexual men and other men who have sex with men – see Section 2.4) and culturally diverse heterosexual populations from sub-Saharan Africa account for large proportions of people living with HIV and accessing treatment and care services in the UK. It is recognized that any guidance on SRH must consider the diversity of needs of those living with HIV despite there sometimes being limited access to the specialized services required.

PLHA have the right to protect their own health and to enjoy meaningful sexual relationships and reproductive health. These rights come with responsibilities, however: in particular, to avoid passing infections on to others.

A number of key SRH issues for PLHA have been documented in the literature.

There have been several outbreaks of infectious syphilis and gonorrhoea in HIV-positive MSM [4,5] as well as a more recent outbreak of lymphogranuloma venereum [6]. It is well documented that HIV progression and transmission are increased and facilitated by STIs. Some groups have questioned whether the availability of HAART has resulted in an increase in unsafe sexual behaviour in some MSM [7].

More HIV-positive women are choosing to have children [8], and an increasing number of couples are requesting fertility investigations and assisted conception. Couples that are either seroconcordant (both HIV-positive) or serodiscordant clearly require different clinical management strategies.

In recent years there has been a fall in the prevalence of transmitted drug resistance in the UK: from 16% in 2002 to 9% in 2004 [9]. Nevertheless, this suggests that transmission occurs from individuals taking HIV drug therapy who would therefore know of their infection. There is a need to develop health prevention messages and sexual health services for HIV-positive people. However, it should be remembered that most HIV transmission occurs in circumstances when individuals do not know their own status.

2.2 Objectives and development of these guidelines

The aim of these guidelines is to complement the existing guidance contained in the British HIV Association (BHIVA) guidelines on the management of HIV in pregnancy [10] and the BASHH guidelines on the management of STIs in people living with HIV [11], syphilis with HIV [12] and PEP [13]. It also draws upon reproductive health guidance from the Clinical Effectiveness Unit of the Faculty of Family Planning (www.ffprhc.org.uk).

This is the first time that expert guidance from the three key UK specialist organizations has been brought together in one place. Central to the development of these guidelines was the involvement of PLHA and community organizations able to both address the specific needs of different PLHA populations and contribute to the knowledge and
evidence for planning. These guidelines have been developed with the collaboration of PLHA groups and the voluntary sector, with representation on the writing committee.

2.3 Who are these guidelines for?

These guidelines have been developed for use by healthcare staff in various disciplines including gynaecologists, staff in primary care, fertility experts and all those involved in the care of HIV-positive individuals. They will also be of use to a wider audience including commissioners, public health specialists and communities or individuals living with or affected by HIV.

2.4 The use of terminology

These guidelines cover many of the medical aspects of sexual health and reproduction in the presence of HIV infection. It is important that throughout the document and in practice, practitioners are sensitized to the emotional overlay between sexuality, sexual health and reproduction. At times, clear descriptive medical terminology may not capture the complexity of the emotional or relationship experience. In the HIV field, particular care has been taken to explore the meaning of terminology and avoid judgemental and potentially discriminatory language, even if unintentionally utilized. In this regard the HIV community has been invaluable in providing feedback and guidance on terminology. Clinicians should be aware and sensitive to this. Within the context of these guidelines, three such areas have been pointed out, and this document should be read and applied taking these into account. Adherence refers more accurately to medication taking, whereas compliance reflects a judgemental and unidirectional approach. The former term is preferable. Concordant and discordant couples describe HIV status accurately, but ‘discordant’ (although often utilized in the literature) may have a negative connotation. Sero-same and sero-different are often easier to describe. Similarly, ‘men who have sex with men’ may be descriptively accurate but may not acknowledge the divergence and complexity of relationships. In the context of sexual health, these very relationship variations are relevant. Clinicians should be aware of such terms.

2.5 Issues not addressed within the 2008 guidelines

There are a number of evolving issues for which guidance will not be provided at this time but that are important enough to be mentioned:

- the role of circumcision in HIV prevention;
- the management of the menopause and hypogonadism in chronic HIV infection.

It was felt that there was insufficient evidence to provide definitive guidance at this time, although it is hoped that this will be available in future guidelines.

3.0 Sexual and reproductive health issues affecting both men and women living with HIV

3.1 Management of sexually transmitted infections in HIV-positive men and women

3.1.1 STIs in HIV-positive women

Of the 7450 HIV infections acquired through heterosexual contact that were diagnosed in the UK in 2005, 63% were in women [2]. Heterosexual women living with HIV infection are on average younger than heterosexual men, which may partly reflect an earlier age of infection and an earlier age at diagnosis. The increase of HIV infections in women has been greater than that in heterosexual men. Sixty-four per cent of diagnosed women were aged 25–39. Many of these women living with HIV remain sexually active and have SRH needs. HIV care providers are now being urged to include regular STI risk assessments and investigations in the ongoing care of their patients [11]. Women living with HIV should be supported and have access to services that enable them to benefit from optimal sexual health and prevent onward transmission of HIV or other sexual infections.

3.1.2 STIs in HIV-positive men

Homosexual and heterosexual men accounted for over 60% of the 53,000 people living with HIV in 2004 [1]. Although the best way to provide access to STI services for HIV-positive individuals is still not entirely clear, there are clear reasons why attention to service provision is important. Sexual transmission is the main route of transmission of HIV in the UK and globally; it is well documented that both ulcerative [14–16] and non-ulcerative STIs [17] increase the risk of HIV transmission and acquisition. There is also an increased possibility of complications from hepatitis B and C, syphilis and herpes simplex virus (HSV) in those who have HIV infection. Ensuring that HIV-positive individuals have access to effective sexual health services should improve their sexual health and reduce the risks of onward transmission and superinfection. Recent outbreaks of STIs in HIV-positive MSM groups have highlighted the need to ensure that the ongoing sexual health issues of PLHA are addressed.
3.1.3 STI service provision and delivery
Recommendations from the BASHH on the development and arrangement of STI services for PLHA [11] suggest that services should develop either facilities for STI treatment or pathways of referral to sexual health/genito-urinary (GU) services. Having HIV services provided within GU settings is not a guarantee that STI screens will occur, so it is important that all clinics providing HIV care make provision for addressing the service requirements of patients to ensure prompt diagnosis and treatment of STIs and other sexual health-related issues.

Service delivery for women and men should include [18]:

- sexual health assessment, including a sexual history, documented at first presentation and thereafter at 6-monthly intervals;
- provision of key prevention activities including screening for hepatitis A, B and C and immunization for the former two;
- access to investigation, diagnosis and treatment of STIs (including hepatitisites) and partner notification;
- syphilis serology included in the routine HIV blood tests at first diagnosis and at 3-monthly intervals thereafter;
- annual cervical cytology performed in all HIV-positive women with access to colposcopy services if required;
- counselling to serodiscordant couples with availability of post-sexual exposure prophylaxis;
- information and advice regarding re-infection and superinfection;
- access to contraceptive services including provision of condoms;
- support around disclosure;
- clear pathways for advice and services for conception, pregnancy and fertility issues.

The management of the following infections does not differ significantly in patients who are HIV-positive: gonorrhoea, non-specific urethritis, uncomplicated chlamydia and lymphogranuloma venereum. The presentation and management of syphilis differ compared to HIV infection. Guidance on the specific management of STIs in HIV-positive adults, including hepatitis B and C, is available [11,12,19,20]. One important aspect of the overall management of STIs in HIV-positive individuals is ensuring regular routine screening for asymptomatic infections, which can be performed in GU and non-GU settings.

3.1.4 HIV and the sexual transmission risks of hepatitis C
It is important to highlight the sexual transmission risk of hepatitis C (HCV) [21] and to ensure that this is not forgotten by clinicians. Although the transmission risk has been identified as being relatively low, with 1–3% of partners of HCV-infected patients found to be infected in cross-sectional studies [22], literature reports highlight that the transmission risk may be increased in MSM [23]. Co-infection with HIV, the duration of the relationship or chronic liver disease may be independent co-factors increasing the risk of transmission. Ensuring that people living with HIV are aware of the risk of HCV transmission and undergo appropriate screening is an important part of a sexual health strategy for all HIV clinical services.

3.2 Key points and recommendations

3.2.1 Sexual health support
All HIV-positive individuals under regular follow-up should have:

- a sexual health assessment including a sexual history documented at first presentation and at 6-monthly intervals thereafter (II);
- access to staff trained in taking a sexual history and who can make an appropriate sexual health assessment (III);
- access to ongoing high-quality counselling and support to ensure good sexual health and to maintain protective behaviours (IV);
- an annual offer of a full sexual health screen (regardless of reported history) with the outcome documented in the HIV case notes (II);
- documented local care pathways for diagnosis, treatment and partner work for STIs in people with HIV that can be actively communicated to all members of clinic staff and to HIV-positive people (II).

3.2.2 Management of STIs in HIV-positive men and women

- The majority of STIs in people with HIV, including gonorrhoea and chlamydial infection, can be managed the same as in people without HIV (II).
- STIs should be considered in the differential diagnosis of presentations such as skin rash or proctitis in HIV-positive people (I).
- Syphilis serology documented at baseline and at 3-monthly intervals should be taken as part of the routine HIV blood set (unless indicated otherwise) to detect asymptomatic syphilis (II).
- There are BASHH UK guidelines for the management of syphilis, genital herpes and warts in people with HIV. These should be referred to if managing individuals with these conditions (I).

3.2.3 Management of hepatitis and blood-borne viruses
All HIV-positive individuals under regular follow-up should have:
• hepatitis A, B and C screening at baseline and, if not already immune to HBV, should be vaccinated against it regardless of sexual orientation (III);
• screening for hepatitis B and C offered annually in those who have exposure risks (IV).

3.3 Post-exposure prophylaxis following sexual exposure

Detailed guidelines concerning the use of ARV drugs as PEP following sexual exposure (PEPSE) to HIV have recently been published by BASHH. The present writing committee endorses these guidelines, which should be read in detail [13]. Some general comments about PEP in this situation follow.

(1) Randomized controlled studies are difficult to organize and have not been performed. However, animal experiments indicate that infection of monkeys with simian immunodeficiency virus (SIV) virus can be prevented by ART up to 24 h after the exposure of rectal or cervical mucosa to SIV. Two cohort studies where some sexually active patients, but not others, have been given ART have indicated a reduced rate of transmission of HIV. It is widely accepted (in the absence of randomized controlled studies) that PEP following parenteral exposure to HIV in healthcare workers is associated with a reduced risk of transmission of HIV. There is no a priori reason to suppose that responses to PEPSE would be different. Thus the present state of evidence indicates but does not prove that PEPSE is likely to have a favourable risk–benefit ratio.

(2) The time following sexual intercourse at which PEP might be effective is unknown. Data obtained in monkeys indicate that following SIV exposure of the cervix, there is a latent period of 24 h when no HIV can be detected and is presumably present and replicating in the antigen presenting cells. Rapidly thereafter, HIV infection can be found in surrounding activated CD4 cells and local lymph nodes. Because ART given during this initial latent period has the greatest likelihood of preventing infection, most guidelines continue to suggest that PEPSE should be offered for up to 72 h after exposure but recognize that such prophylaxis is likely to be more effective the more quickly it is given. The guideline stops short of recommending PEPSE only up to 48 h but there is little basis to provide it after this time.

(3) One of the major problems with PEP is the ability of the patients to adhere to the regimen. Such individuals are often psychologically vulnerable and relatively intolerant of side effects. Therefore, the choice of drugs is crucial to prevent both short-term toxicity and the risk of serious toxicity in individuals who have little chance of developing HIV infection. Most guidelines recommend a PI-containing regimen. Non-nucleoside reverse transcriptase inhibitors (NNRTIs) are not usually recommended. Nevirapine is contraindicated in people with a normal immunological system and the side effects of efavirenz are likely to be a barrier to short-term adherence. Lopinavir in the new tablet formulation, tenofovir and emtricitabine (Truvada) are recommended as drugs for PEPSE.

The optimum length of PEP remains a matter of conjecture but again most guidelines recommend a month’s course of treatment.

(4) It is recognized that the risks of HIV transmission following sexual exposure are low, with passive anal intercourse having a higher risk than active anal intercourse in MSM. Insertive vaginal intercourse is of lesser risk, and less so for the male partner compared to the female partner; passive oral sex has a very small but definite risk of HIV acquisition. The precise risk remains unknown because of the difficulties of establishing a denominator in individuals practising exclusively oral genital sex only. Following sexual intercourse with a partner of unknown HIV serostatus, the risk will depend upon the prevalence of HIV in that particular population, but overall the risks are likely to be much lower than those following sexual intercourse with a person who is known to be HIV-seropositive.

(5) If PEP following sexual intercourse is going to become a public health priority [24], this will require either the setting up of specialized clinics or the education of accident and emergency departments and general practitioners in the treatment and care of accident and emergency departments and general practitioners in the treatment and care of such individuals. A number of models have been used to look at the likely cost-effectiveness of such an approach. These models may not be directly applicable to the situation in the UK, having mainly been derived from American data. Nevertheless, it is likely that offering prophylaxis is cost-saving despite the cost of administration of drugs for a month to a relatively large number of individuals who would not develop HIV infection. In general, offering PEP to men having unprotected sex with other men is likely to be more cost-effective than offering PEP to heterosexuals, particularly when the serostatus of the partner is unknown. The risk of sexual transmission of an individual who is known to be HIV-positive but whose viral load is less than 50 HIV-1 RNA copies/mL using a sensitive polymerase chain reaction (PCR) assay is unknown for certain; however, data suggest that the risks in such individuals are extremely low.
In summary, with the incomplete data available to us, any recommendations have to be tentative but it is likely that the risk–benefit analysis is favourable for prescribing PEPSE for up to 72 h following an episode of sexual intercourse where there has been a risk of HIV transmission. This is highly likely to be cost-effective when the partner is known to be HIV-positive and is not on ART. Cost-effectiveness is also likely in homosexual relationships with a partner of unknown serostatus and in heterosexual relationships where the partner is known to be HIV-positive. We believe that these data are clearly strong enough to offer PEPSE on an adventitious basis and to encourage non-government organizations to explore innovative ways in which such prophylaxis can be offered within a short time of sexual intercourse, but recognizing the need for informed consent and an explanation of the possible risks of taking such prescription drugs. While there are theoretical worries that this more proactive approach might increase risk-taking behaviour, there is no evidence that this is the case.

The issue of providing widespread pre-exposure prophylaxis, i.e. taking ART (potentially just one drug) prior to risk-taking sexual activity, is controversial. Animal data suggest that such an approach may reduce but not obviate the risks of transmission of retroviruses. Trials mounted primarily in resource-limited settings to test pre-exposure prophylaxis have run into ethical difficulties surrounding the need for HIV testing prior to randomization in the trial, the provision of ART to those who develop HIV during the course of the study and the provision of adequate counselling advice to reduce high-risk behaviour. Nevertheless, there is anecdotal evidence that such an approach is already quite widespread and there is an urgent need to explore whether such treatment encourages risk-taking behaviour and is associated with protection or with the development of ARV resistance if monotherapy approaches are used.

3.4 Key points and recommendations

- All units should have explicit policies and procedures on PEPSE.
- All HIV-positive individuals should be made aware of the units’ procedures to access PEP.

3.5 Conception issues

3.5.1 Pre-conceptual counselling, natural conception and assisted reproduction

The change in the natural history of HIV infection and reduction in mother-to-child transmission as a result of ART has led to a re-evaluation of the ethical and moral arguments previously used to deny assisted reproduction to HIV-infected patients [25–28]. Increasingly, parenting is regarded as a realistic option for couples where one or both partners is infected and the demand for reproductive care is rising [29]. Although few centres in the UK are equipped to offer assisted reproduction to HIV-positive patients, the needs of these patients are now recognized and increasingly supported by state funding.

The main objectives in offering reproductive care are to ensure that couples fully understand their reproductive options and the risks and benefits associated with each method so that they can make an informed choice. They should be advised on the risks of natural conception methods pertinent to their circumstances and on assisted conception techniques that can enhance protection of the uninfected partner and future child from viral infection and increase the chances of successful pregnancy when fertility factors are identified. Centres offering assisted conception to infected patients should address the safety of healthcare workers and other patients attending the fertility centre through formal risk assessment and consequent adaptations of all procedures and laboratory and clinical facilities used.

3.5.2 Natural conception – unprotected intercourse

Conceiving through timed unprotected intercourse and abandoning condom use has previously been contraindicated in couples where one or both partners is infected with HIV. Current evidence supports a more open discussion of this option with the couple to quantify, as far as is reasonably possible, the risks in individual cases to enable them to make an informed decision on whether the level of risk is one that is acceptable to them as a couple and in particular to the HIV-negative partner in serodiscordant cases.

Viral transmission during vaginal intercourse in serodiscordant couples depends on numerous factors but those that are most relevant to couples in stable monogamous relationships who are attempting to conceive are plasma viral load of the infected partner, presence of STIs and frequency of intercourse. If an infected man is in a stable relationship but not taking ART, the risk of HIV transmission to his uninfected female partner is quoted as 0.1–0.3% per act of intercourse, provided the couple are not participating in any other form of high-risk activity [30–32]. The risk for female-to-male transmission is reported to be lower at 0.03–0.09% [33]. Because viral load in plasma is generally correlated well to that in genital secretions [34,35], the risk is considerably lower in a man or woman with long-term undetectable viral load through use of ART. A review of 19 empirical studies (n = 1226) of
the association between serum viral load and semen viral load found a mean correlation of 0.45 [36]. Although semen viral load was in general lower than in blood plasma, the review concluded that the factors that had a major influence on the relationship between plasma viral load and semen viral load were co-existing STIs, use of and adherence to ART that had optimal penetration of the genital tract, and the absence of drug resistance.

When the infected man or woman is fully suppressed through long-term ART, biological data support the view that an undetectable viral load can also be achieved in genital secretions [35,37,38].

The presence of STIs (e.g. syphilis, urethritis) increases viral load substantially in genital secretions but not in plasma, even when the patient is asymptomatic [39,40]; this effect is reduced by prompt treatment of the STI [41]. On the basis of this evidence, it is not unreasonable for serodiscordant couples where the infected partner has an undetectable serum viral load for more than 6 months through use of ART to consider the option of conceiving through carefully timed unprotected intercourse, provided they have also been counselled on the alternative options [42,43].

One of the difficulties in counselling serodiscordant couples on natural conception methods involving unprotected intercourse is that the risk to the uninfected partner is difficult to quantify but can certainly not be quoted as zero. Mathematical models cite a risk of 1 in 100,000 per act of intercourse. In practice, viral shedding in semen has been reported to occur even in men fully suppressed on ART because of different compartmentalization of HIV in plasma and semen [44–46]. A recent retrospective study of 551 semen samples analysed in HIV-1 infected men undergoing sperm washing identified 15 cases of detectable HIV-1 in ejaculated semen in men with long-term undetectable plasma viral load through use of ART, highlighting a need for caution when couples consider a natural conception approach [47]. In the case of serodiscordant couples where the woman is HIV-positive, the evidence is equally concerning: detectable HIV has been identified in follicular fluid and endometrial samples from a series of HIV-positive women undergoing in vitro fertilization (IVF), even when plasma viral load was suppressed fully through the use of ART [48].

A review of the retrospective and prospective epidemiological literature on sexual transmission risk in serodiscordant couples attempting to conceive through unprotected intercourse indicates that data are limited and sample sizes small. A prospective cohort study of 453 HIV serodiscordant couples in Rakai, Uganda, reported a dose effect for infected patients with no transmission in cases where the infected partner had plasma viral loads of <1000 copies/mL [49]. A prospective study of 393 heterosexual couples having unprotected intercourse over a 14-year period reported no HIV transmission when the infected partner was on ART compared to an 8.6% risk when not on ART [50]. A prospective study of 92 serodiscordant couples having unprotected intercourse reported no seroconversions in the partners of the 41 patients on ART compared to six seroconversions where the partner was not on treatment [51]. Three studies have analysed infection risk in serodiscordant couples attempting to conceive naturally. The first was a prospective study conducted prior to the widespread use of ART and examined the risk of unprotected intercourse timed to the fertile window in 96 discordant couples where the male was infected. Four seroconversions were noted in the female partners, two during pregnancy and two post-partum [27]. The seroconversions were identified in couples in whom condom use post-conception and outside the fertile window was inconsistent. A more recent, retrospective study attempted to quantify the risks of unprotected intercourse in discordant couples where the man had an undetectable viral load through use of ART for at least 6 months. There were no seroconversions in 62 discordant couples who conceived [52]. Apart from the small sample size, the study is further weakened by the fact that seroconversions were not analysed in couples who failed to conceive, where the risk might be enhanced by repeated exposures. The only study to prospectively assess viral transmission risk in serodiscordant couples attempting to conceive naturally where the man was fully suppressed on ART and additional pre-exposure prophylaxis (PrEP) was used in the female partner involved only 22 couples [53] (see section 4.6).

The number of reported cases is still far too small to provide couples with a precise risk index if they wish to conceive naturally, but does reflect an increasing tendency by serodiscordant couples to pursue natural conception methods if they cannot access, fund or do not wish to go down the sperm washing/assisted conception route. This review of the literature also emphasizes the need for much larger multi-centre prospective monitoring of both pregnancy outcome and viral transmission risk in these couples if we are to improve the advice we can give to them. The physician does need to ensure that the uninfected partner has a full understanding of the small possibility of becoming infected through unprotected intercourse. More importantly, the need for ART adherence and regular attendance for STI screening in the couple and viral load checks in the infected partner should be stressed. In order to reduce the risk of unnecessary exposure in couples experiencing fertility issues, the couple should be advised of the benefits of having a fertility screen prior to
attempting to conceive naturally. This should include a semen analysis for the male partner and an endocrine profile and baseline pelvic scan in the early follicular phase of the cycle (day 2–5) for the female partner together with a mid-luteal progesterone to confirm whether ovulation is occurring and non-invasive test of tubal patency (e.g. hysterosalpingogram), unless there is a history of pelvic pain or infection (in which case, laparoscopy and dye should be used to assess tubal patency) [54].

Clinics should consider asking couples to sign a form confirming that they have received comprehensive pre-conceptual counselling covering all their options for conceiving, including natural conception, and that they fully understand the risks associated with each method.

For seroconcordant couples attempting to conceive through unprotected intercourse, there are no conclusive data on the overall risk of superinfection (see section 4.6.4). The only scenario where concordant couples should be discouraged from attempting to conceive naturally is when drug resistance has been identified in one or other partner.

3.5.3 Reproductive options for HIV-positive men and HIV-negative women involving assisted conception techniques

HIV discordant couples where the male is infected who desire to eliminate or significantly reduce HIV transmission risk to their uninfected partner are limited to the following options:

1. Insemination using donor sperm: this effectively removes the risk of viral transmission because sperm donors are screened for HIV and other blood-borne viruses. However, it also removes the option of genetic parenting from the infected male. In the UK, there is a current shortage of donor sperm because all donors are to be identifiable by the future child.

2. Sperm washing: the female partner is inseminated with the infected partner’s sperm, centrifuged first to separate spermatozoa from seminal fluid and associated non-sperm cells.

3. Adoption: this is a more difficult option for couples because current adoption practice regards HIV in one or both partners as a significant undesirable factor when assessing the suitability of parents requesting to adopt. Nevertheless, this is an approach that has been successful for some serodiscordant couples.

3.5.4 Sperm washing

Sperm washing is a well-established, effective and safe risk-reduction fertility option for both discordant couples where the man is HIV-positive and the woman HIV-negative and concordant couples where viral resistance has been identified. Sperm is centrifuged to separate live sperm (which does not carry HIV) from seminal plasma and non-germinal cells (which may carry HIV) and then inseminated into the female partner at the time of ovulation. If a couple have additional fertility issues, sperm washing can be combined with ovulation induction, IVF or intracytoplasmic sperm injection (ICSI). The technique is based on the observation that HIV is present in seminal fluid and as cell-associated virus in leucocytes and non-spermatozoa cells (NSC) but is not capable of attaching to, or infecting, spermatozoa. This is well supported by the literature on the subject, which is extensive [55–59].

In technical terms, sperm-washing involves centrifuging ejaculated semen in a 40–80% colloidal, silica density gradient to separate progressively motile HIV-free sperm from NSC and seminal plasma, which remain in the supernatant. The sperm pellet at the bottom is resuspended in fresh medium and centrifuged twice before the preparation of a final swim-up. As a quality control for the procedure, and to protect the service from medico-legal action, an aliquot of washed sperm (approximately 100 µL) should be tested for detectable HIV RNA prior to the sample being used for treatment [54,60]. A nucleic acid-based sequence amplification (NASBA; Biomerieux, Basingstoke, UK) or similar commercial assay can be used. The risk of the sample having detectable HIV is 3–6% [61–63]. This is because centrifugation fails to remove all the seminal plasma and leucocytes in a small proportion of cases. The number of washes is limited because repeated centrifuging leads to loss of sperm quality and quantity. A double tube technique has been proposed to increase yield and reduce the need for post-wash HIV testing but has not been adopted by the majority of centres offering this treatment because it is not currently available commercially [64]. There have been no reported cases of infection of the female partner when sperm washing is carried out following published protocols in over 3000 cycles of sperm washing combined with intrauterine insemination (IUI), IVF or ICSI published to date [65]. A multi-centre retrospective analysis of 1036 serodiscordant couples from eight centres in Europe offering sperm washing reported the results of 2840 IUI cycles, 107 IVF cycles, 394 ICSI cycles and 49 frozen embryo transfers with careful HIV follow-up of the negative female at least 6 months post-treatment. All tests recorded on the female were negative (7.1% lost to follow-up), giving a calculated probability of contamination equal to zero [95% confidence interval (CI) 0–0.09%]. Clinical pregnancy rates recorded with all forms of treatment were comparable to those found in cycles carried out in HIV-negative couples [66].
3.5.5 Clinical management of couples undergoing sperm-washing treatment

Clinical work-up prior to sperm washing should include a sexual health screen and fertility screen in both partners. The sexual health screen is performed to ensure that the viral status of both partners is known at the time of treatment and that any genital lesions or infections can be treated – these increase the risk of viral transmission [67] and reduce pregnancy rates. The purpose of the fertility screen is to define the optimum mode of treatment. The screen includes a semen analysis in the male partner and endocrine profile and baseline pelvic scan in the early follicular phase of the cycle (day 2–5) for the female partner together with a mid-luteal progesterone and non-invasive test of tubal patency (e.g. hysterosalpingogram), unless there is a history of pelvic pain or infection (in which case laparoscopy and dye should be used to assess tubal patency).

The couple should be advised to continue with protected intercourse prior to and during treatment. A case of female seroconversion has been reported following condom breakage in a couple awaiting IVF treatment with washed sperm. Failure to take adequate precautions could lead to the incorrect reporting of treatment failure because of poor sperm preparation technique [68].

Most couples electing to have sperm washing are voluntarily infertile and do not have significant fertility issues. For these couples, IUI is the preferred first-line treatment and should be carried out in a natural cycle, unless the woman is anovulatory (in which case clomifene or injectable gonadotrophins are recommended). Ultrasound follicular tracking is used to time insemination accurately and, where possible, human chorionic gonadotrophin is administered to ensure that the timing of ovulation is known precisely. Between three and six cycles of IUI are recommended before a couple are offered assisted conception with either superovulation and IUI or IVF. If there is evidence of tubal blockage, the couple are advised to have IVF with washed sperm. If the semen analysis is poor then ICSI is advised. IVF and ICSI outcome are not affected by the use of washed sperm compared to the use of ejaculated sperm. The protocol described is similar to that used in the majority of European centres offering sperm washing and aims to minimize the high costs and risks of multiple pregnancy and ovarian hyperstimulation associated with IVF and ICSI treatment.

3.5.6 Effect of HIV on semen parameters and the outcome of sperm washing and intrauterine insemination

The majority of HIV-positive men have semen parameters within the defined World Health Organization (WHO) normal range. In the largest analysis of semen parameters in HIV-positive men to date [69], Nicopoulos and colleagues found all parameters to be significantly impaired compared to HIV-negative controls and a positive correlation between total count and total and progressive motility and CD4 cell count. There was no correlation between viral load, years since diagnosis, use of or duration of ART with any semen parameter. These findings are consistent with previous reports in the literature. Analysis of 140 cycles of IUI with sperm washing found that semen parameters did not have a significant impact on IUI outcome following sperm washing. However, markers of HIV infection affected IUI outcome significantly. Clinical pregnancy rate was significantly higher in cycles where the man had a low viral load (<1000 copies/mL) and where the man was on ART. CD4 cell count had no impact on IUI outcome. There are insufficient data at present to recommend starting ART purely to improve IUI success rates, and the decision to start medication should be based primarily on the health of the individual.

3.5.7 Management of HIV-positive women

HIV-positive women planning to have children should receive pre-conceptual counselling on mother-to-child transmission risks, their long-term health and the possible effects of ARV medication on the foetus. Women not taking ART should be advised to avoid unprotected intercourse and be instructed on how to carry out self-insemination of her partner’s sperm at the time of ovulation in order to minimize viral transmission risk through unprotected intercourse. Women with effective viral suppression through long term use of ART should also be instructed on self-insemination but also be counselled on the current evidence regarding the low, but possible, risk of viral transmission to their uninfected partner if they attempt to conceive naturally. Should they elect to attempt natural conception, the couple should have regular screening for STIs and be advised to limit intercourse to the time of ovulation; the woman should also be advised on the importance of adherence to medication and regular checking of plasma viral load.

There is increasing evidence to suggest that HIV-positive women have reduced fertility as a result of reduced ovarian reserve and tubal damage [70]. HIV-positive women undergoing IVF have been noted to have lower IVF success rates than HIV-negative controls because of a reduced response to superovulation [71]. In this study, there was no difference in IVF outcome in HIV-positive women undergoing ovum donation compared to HIV-negative controls – pointing towards an effect of HIV on ovarian response and ovarian reserve rather than implantation. Retrospective data from sub-Saharan Africa [72,73] and prospective data from the UK indicate an increased incidence of tubal

infertility in HIV-positive women [69]. For these reasons, there is a good argument for carrying out a fertility screen from the outset on HIV-positive women electing to conceive naturally to avoid unnecessary exposure if they have a fertility issue that can only be overcome with assisted conception methods such as insemination or IVF. Women trying to conceive through timed self-insenmination should be referred for fertility evaluation if they have not conceived within 6–12 months of self-insenmination. Referral should be earlier if there is a history of pelvic inflammatory disease or they are over 35 years of age.

3.5.8 Reducing risks associated with pregnancy

Minimizing risk in HIV-positive women lies primarily in reducing mother-to-child transmission. There are no specific measures that can be taken during fertility treatment to further reduce this risk. There is concern that invasive procedures such as IVF could increase the chances of the embryo becoming infected. The number of women treated so far is small and prospective data limited. A study of 10 women undergoing IVF or ICSI demonstrated that HIV was detectable in follicular fluid removed during vaginal egg collection in all patients with a detectable serum viral load and 60% of those with an undetectable serum viral load [48]. This raises the theoretical possibility of the embryo becoming infected at the laboratory stage, even before the embryo is transferred back to the woman. Centres electing to treat HIV-positive women need to monitor all IVF or ICSI cycles in positive women and audit short- and long-term outcome.

Management of HIV-positive women should involve a multidisciplinary team comprising HIV physician, fertility specialist and obstetrician with a special interest in HIV. The couple should have a sexual health screen for the same reasons as couples undergoing sperm washing. Likewise, they should have a fertility screen in a similar way to HIV-negative couples (early follicular phase endocrine profile and pelvic scan, mid-luteal progesterone and test of tubal function) and the male partner should have a semen analysis.

3.5.9 Pre-conceptual counselling

The most important aspect in the management of serodiscordant and concordant couples wishing to conceive is reproductive counselling prior to starting treatment to enable them to make an informed choice about their reproductive options, the inherent risks and costs of each treatment and the likely chances of success. Pre-conceptual counselling of HIV discordant couples must include a summary of the available data on safety for each method together with advice on additional methods of reducing risk such as limiting intercourse to the fertile window, regular screening for STIs, the need to identify at an early stage the presence of reduced fertility or sterility in either or both partners and the use of PrEP. The discussion should balance the risk of natural conception with that of more established risk-reduction methods such as sperm washing or risk-free options such as donor insemination. Although it is well recognized that timed unprotected intercourse may be a preferable option for discordant couples unable to access (or finance) options such as sperm washing or donor insemination, the limited number of cases reported in the literature assessing the risk and safety of this approach should be emphasized. Consideration should be given to the duration of counselling and the specialist inputs required. Although there is currently little literature to inform units, establishing a multidisciplinary approach with fertility specialist and HIV counsellor could be considered (C. Gilling-Smith, personal communication).

Pre-conceptual counselling should also address the possibility of treatment failure and how the couple would cope if they successfully had a child but the infected parent became more seriously ill or died. Those electing to have assisted conception with sperm washing have to understand that this is a risk-reduction method and not a risk-free method; technically, virus could still be present in the washed sample at a titre below the detection limit of the HIV assay. When the female partner is HIV-positive they need to understand the risks of mother-to-child transmission and the methods used that will reduce this risk to < 2%. They should plan and agree to attend a specialist obstetric unit once pregnant to ensure that they receive the best possible advice to minimize mother-to-child transmission risk. Fertility clinics treating HIV-positive patients have a moral, ethical and medico-legal responsibility to ensure that specialist counselling is available at all stages of treatment and that the welfare of the future child has been taken into account [74]. Reproductive counselling is particularly pertinent in concordant couples where prognosis and life expectancy in each should be discussed carefully with the HIV physician [75].

3.5.10 Safety of healthcare workers and non-infected patients

The Human Fertilization and Embryology Authority (HFEA), which regulates all UK assisted conception clinics, currently requires all patients undergoing assisted conception to be screened for HIV, hepatitis B and C before undergoing treatment. Under the HFEA regulations, gametes and embryos from patients with known viral infections must be cryopreserved in separate tanks for each infection and infection combination. Unfortunately, this requires large areas of the clinic to be dedicated to cryostorage and numerous storage tanks to be purchased,
which in practice has led to only a few laboratories in the UK offering treatment to infected patients. Both the HFEA and European Tissue Cells Directive require assisted conception units to have quality management systems that ensure detailed risk assessments are performed regularly and audits carried out on all aspects of care. Handling and freezing gametes and embryos from patients who are HIV-positive carries a small risk of cross-contamination to samples from HIV-negative patients and health workers involved in assisted reproduction; viral cross-infection has been reported in other areas of laboratory practice [76]. Unfortunately, conventional methods of cleaning and sterilization cannot be applied in areas handling human gametes and embryos. For this reason, in addition to the deployment of universal precautions, it is recommended that samples from patients with known or suspected blood-borne viruses are handled in a separate laboratory or laboratory area with equipment (e.g. incubators, flow hoods, cryostorage tanks) dedicated to handling infected samples [76]. An alternative to this, if space and cost are issues, is to schedule viral-positive cases to be treated at a different time to viral-negative ones.

### 3.5.11 Demand for fertility care

It is difficult to estimate the demand for reproductive care among HIV-positive patients. A UK audit of demand for assisted reproduction techniques in HIV-infected patients found that 16% of men and 4% of women attending HIV specialist clinics had enquired about fertility treatment. Following the HFEA recommendation of compulsory HIV, HBV and HCV screening prior to offering assisted reproduction techniques, 30% of fertility centres stated that they planned to start treating HIV-positive males and 26% planned to treat positive females. In practice, very few centres in the UK have elected to treat HIV-positive patients and equipped themselves with the necessary laboratory facilities. Many patients arrange to have their reproductive counselling, investigation and monitoring in their local centres and have only the IVF or sperm-washing treatment in the specialist centre to minimize cost and travelling.

### 3.5.12 Key points and recommendations

- HIV-positive men and women and their partners planning to have children should receive pre-conceptual counselling on all their conception options including HIV transmission risks associated with each option so that they can make an informed choice (IV).
- Detailed comprehensive pre-conceptual counselling should be available for couples considering conceiving. This should document the available options and the possible risks of each method. All discussions should be documented clearly in clinical notes (IV).
- Clinics advising serodiscordant couples on risk-reduction strategies for natural conception should obtain signed consent that both parties understand and accept the small risks of HIV transmission (IV).

#### 3.5.12.1 Management of couples where the male is HIV-positive

- If the man is not taking ART, protected intercourse should be encouraged at all times and pre-conceptual counselling should explore the options of sperm washing, donor insemination and adoption.
- If the man has long-term undetectable viral load (>6 months) through the use of ART, pre-conceptual counselling should also cover the risks of natural conception with intercourse timed to the fertile window, with and without the use of PrEP in the female, and the need for ART compliance, regular screening for STIs in the couple and regular checks on plasma viral load in the man.
- If either natural conception or sperm washing is contemplated, both partners should undergo a sexual health screen and fertility screen.
- Couples electing to have timed unprotected intercourse should be advised of any fertility factors identified and assisted conception options discussed if these are deemed to improve their chances of successful outcome. Any STIs should be treated and advice on the correct timing of intercourse to the fertile window given.
- Couples electing to have sperm washing should initially be offered natural cycle insemination with washed sperm unless the fertility screen identifies abnormalities in the female or seminology.
- Superovulation with insemination, IVF or ICSI using washed sperm should be considered if conception has not occurred after between three and six cycles of treatment or fertility factors are identified.
- Sperm should be centrifuged in a density gradient according to published protocols and samples tested for the presence of HIV RNA before being used for insemination to protect the clinic from litigation.
- To avoid cycle cancellation because of the sample testing positive post-washing, a previous sample of washed and tested sperm can be frozen as a back-up.
- Couples should sign a consent form before sperm-washing treatment confirming they understand sperm washing to be a risk-reduction procedure.
- An audit system should be in place to monitor the HIV status of the female partner post-treatment (HIV test 3 months after last treatment) and paediatric outcome.


3.5.12.2 Management of couples where the female is HIV-positive. In women not on ART, protected intercourse should be encouraged at all times and couples advised on the method of timed insemination into the vagina of sperm ejaculated into a condom free of spermicidals.

In women on ART with long-term HIV suppression (>6 months), pre-conceptual counselling should also discuss the risks of unprotected intercourse timed to ovulation in the female cycle and the need for regular viral load and STI monitoring along with adherence to therapy stressed if the couple elect to conceive in this way. Fertility screening of both partners should be offered from the outset to minimize unnecessary exposure of the uninfected male if fertility factors are identified.

Fertility investigations should be arranged when pregnancy is not achieved within 6–12 months of self-insemination or natural conception. In women with a history suggestive of tubal disease or anovulation, fertility investigations should be offered from the outset.

Assisted reproductive techniques (IUI, IVF or ICSI) should only be offered within centres equipped to carry out procedures on patients with HIV and trained to audit outcome: little is known of the impact of invasive procedures such as IUI, oocyte retrieval and embryo transfer on vertical transmission risk.

Treatment should be planned to minimize any risk of multiple pregnancy (i.e. controlled superovulation, maximum of two embryos transferred).

When the male partner is also infected with HIV and viral resistance has been identified, the sperm should be washed to reduce the risk of transmitting mutated resistant HIV strains to the female partner and offspring.

- ARV medication should be discussed with the treating HIV physician and adjusted pre-conceptually according to BHIVA recommendations [16]. If the patient is not on ART, a plan should be made to initiate this by the third trimester, at the latest.
- Known teratogenic agents such as efavirenz should be stopped pre-conceptually.
- Once pregnancy is confirmed, referral should be made to a specialist obstetric centre if expertise in the antenatal management of HIV-positive females is not available locally.
- The decision to provide licensed treatment in HIV-infected individuals, particularly when both are infected, should be based on a ‘welfare of the child’ assessment, as in any other couple [74]. The treating HIV physician should be asked to provide the assisted conception centre with a summary of the patient’s care and prognosis; he/she is likely to be best informed of ongoing high risk activity and medical issues that might affect long-term health.
- The couple should be advised to continue with protected intercourse during treatment and pregnancy, and not expose themselves to high-risk activity such as intravenous drug use.
- Units electing to treat female patients infected with HIV on ART should monitor short- and long-term paediatric outcome to identify any potential adverse effects of ART at the time of conception on the child.

4.0 Sexual dysfunction in HIV-positive men and women

Men and women commonly report sexual difficulties in the presence of HIV. These range from the loss of desire to difficulties in establishing and maintaining partnerships, to specific EDs.

4.1 Erectile dysfunction: investigation and management

ED is a common problem and the prevalence increases with age [77]. There is a small amount of evidence that HIV-negative MSM are more likely to present with an erectile problem [78,79]. However, there have been many reports of an increased prevalence of erectile difficulties in HIV-infected MSM [79–85], which may contribute to unsafe sex practices [81]. The precise reasons for the increased rates appear complex, and may be physical or psychological in origin. And whether the ED predates infection has not been studied. Although one study [86] identified only PIs as an associated factor, other studies have confirmed a higher prevalence in patients not on HAART or on non-PI-containing combination therapy regimens [79,83,84].

The European Association of Urology has recently updated guidelines on the investigation and management of ED [87] and other recommendations have been published in the British Medical Journal [88]. An overview of the management of HIV-infected men with erectile problems was also published in 2002 [86,89]. In the management of any sexual dysfunction, it is important to make an assessment of the sexual relationship(s) and the need for psychological interventions for either one or both partners.

Although the management of ED is not significantly altered by HIV infection per se, it is important to be aware of other major contributing factors. Psychological problems, concomitant drug therapy (such as anti-depressants, anti-psychotics, anabolic steroids, megestrol, lipid-lowering agents) and recreational drugs (including anabolic steroids, alcohol and psychoactive substances) have all
been implicated [90]. Neuropathy and atherosclerotic disease from any cause, but especially diabetes mellitus, may manifest as erectile failure.

The first-line agents recommended to manage ED, unless contraindicated by concomitant nitrate therapy, are the orally active phosphodiesterase inhibitors type 5 (PDE5Is): namely sildenafil (Viagra), tadalafil (Cialis) and vardenafil (Levitra). All these agents appear efficacious, although patients may have a preference for one drug, and all are predominantly metabolized by the liver by cytochrome P450 3A4 [91]. Interactions with erythromycin, ritonavir and ketoconazole have all been reported and shown to increase significantly the drug levels of sildenafil or other PDE5Is [92]. Therefore, other drugs that inhibit this system may be predicted to have a similar effect and should be used cautiously (including all PIs, other macrolides but not azithromycin [92] and some other anti-fungal agents). The lowest starting dose is recommended and titrated according to response and side effects. Most recently, a study confirms that if sildenafil is taken with darunavir (boosted with ritonavir), dosing should be at 25 mg over a 48-h period. Based on these findings, it is suggested that the vardenafil dose should not exceed 2.5 mg in a 72-h period and that the tadalafl dose should not exceed 10 mg in 72 h [93] (www.hiv-druginteractions.org).

No studies on the effects of the currently licensed NNRTIs (efavirenz, nevirapine) on PDE5Is have been published, but inducers of cytochrome P450 might be predicted to reduce levels and higher doses of PDE5 inhibitors may be required to achieve a clinical effect. The currently unlicensed investigational NNRTI, TMC278, does appear to significantly decrease plasma sildenafil concentrations, and a higher PDE5I dose may be required if used concurrently [94].

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

A study by Sherr et al. [95] has shown that there is no increase in risk behaviour in the presence of sildenafil itself, but that those who use sildenafil also tend to be higher users of other risk-related substances (drugs and alcohol) - suggesting that some people have added PDE5Is to a risk-taking profile rather than the PDE5I per se triggering HIV-related risk behaviour. The relationship between high-risk behaviours, possible HIV transmission and PDE5I use has been highlighted recently in the USA [96]. Access to PDE5Is by non-conventional methods (Internet prescribing) does not normally allow for a proper discussion on safer sex, or discussion around safe use of these drugs with recreational agents.

No significant drug interactions with ARV agents have been described with other currently available classes of drugs used to treat ED.

Use of intracorporeal alprostadil is very effective, but needs careful explanation for correct use and to prevent priapism, and may not be acceptable to the patient. Furthermore, because the injection site may expose partners to blood-borne microbes (such as HIV, HBV, HCV and syphilis), patients should be counselled to ensure that a condom is rolled back to cover the injection site. Safe needle disposal also needs to be addressed. Alprostadil is also available as a trans-urethral preparation. It may cause local side effects including urethral pain and have a less reliable clinical effect, but may be more acceptable than administration by injection.

4.1.1 Key points and recommendations

- There is some evidence that men living with HIV infection are more likely to experience erectile difficulties, which may adversely affect effective condom usage and should be treated.
- There are important drug interactions between PDE5 inhibitors and PIs, which may necessitate dose modification of the PDE5 inhibitor.
- Recreational drug use may affect condom use and erectile function, and needs to be assessed. Inhaled nitrates are contraindicated when using PDE5 inhibitors.
- A full recreational drug history is an important part of the assessment of ED. Patients should be counselled on safer sex, possible drug interactions and contraindications to PDE5 inhibitor use.

4.2 Other male sexual dysfunctions

Although ED is the most common sexual dysfunction in men, other problems including ejaculatory problems (premature/rapid ejaculation and retarded ejaculation), loss of libido and arousal problems can occur.

4.2.1 Ejaculatory disorders

There is little evidence that rapid ejaculation is more common, although there is evidence that drug-induced peripheral neuropathy may result in retarded ejaculation [90]. Guidelines on the management and investigation of rapid (premature) ejaculation and retarded (delayed) ejaculation have been published by BASHH [97,98]. Retarded ejaculation in the context of neuropathy may be extremely difficult to treat, and may be exacerbated by concomitant use of anti-depressants to treat the neuropathic pain, but it may have a psychological cause [81].

4.2.2 Loss of desire

Problems of loss of sexual desire have been described at high prevalence rates in HIV-infected men, affecting
41–48% of seropositive MSM [79,98]. Although hormonal abnormalities can affect desire and have also been described in patients on ARVs [81,83,99,100], no causal link has been established firmly; the individual often cites psychological reasons as the putative cause [81,98]. However, a review of medications that may cause hormonal disturbance (sex steroids, prolactin and thyroid hormones) and signs of hypogonadism, together with hormonal assays, is warranted to determine if a physical cause can explain the symptom.

There is some data to suggest that men on HAART have increases in serum oestradiol, which may be a cause of loss of sexual desire [79,81] and may respond to testosterone therapy (unpublished).

With HAART, and with the reduction in the prevalence of late-stage HIV disease, it is likely that the prevalence of hypogonadism has decreased [100]. However, the prevalence of hypogonadism increases with age and it is likely that this entity will still be clinically relevant.

Furthermore, in a recent study in 296 HIV-positive men in the USA, researchers found that 17% of the men had low testosterone levels and another 16% had borderline levels – an increased prevalence relative to the general population [101]. Low plasma testosterone was related to increased age, advanced HIV, higher body mass index and lipodystrophy. All hypogonadal individuals in this study had evidence of a central origin with decreased follicle-stimulating hormone and luteinizing hormone. Sixty-three per cent of those patients who received androgens reported satisfaction with this therapy.

However, analysis of a cohort of men with sexual problems published in 2006 [96] did not show hypogonadism to be a common finding (although raised oestradiol was), despite low sexual desire being a common presenting complaint. A questionnaire survey of HIV-positive MSM in another central London clinic [102] showed that 41% of sampled men (14/34) use anabolic steroids ‘recreationally’, and this exogenous source might lead to an underestimate of the problem of hypogonadism, or even be a cause of it acutely on cessation (because of suppressed testicular production).

Secondary hypogonadism warrants estimation of other hormones [cortisol, thyroid stimulating hormone (TSH), prolactin (PRL)] and magnetic resonance imaging of the pituitary fossa (particularly if there is hyperprolactinaemia), and referral to an endocrinologist should be considered.

Although androgens have been used for the treatment of HIV-related wasting and for chronic hypogonadism, many questions remain unanswered, including those regarding the long-term effects (if any) and hence safety. Known side effects include hepatic dysfunction, polycythaemia, acne, testicular atrophy, male pattern baldness and gynaecomastia. Transdermal patches, gels, muco-adhesive sustained-release buccal tablets and long-acting intra-muscular testosterone esters are designed to provide testosterone levels that are approximate to normal physiological levels, in order to improve patient acceptability, reduce adverse events and to further increase the number of treatment options available. In patients with chronic hypogonadism, forms of testosterone replacement that provide stable physiological levels of testosterone may be preferable to those that result in supra-physiological levels. However, some of the topical preparations can cause local irritation and the patient may prefer injections.

There is the potential for inducers of cytochrome P450 3A4, such as ritonavir, to increase the levels of some androgen preparations (www.hiv-druginteractions.org).

Men with androgen-dependent cancers such as prostatic carcinoma should not receive testosterone supplementation.

4.2.3 Key points and recommendations

- Guidelines for the management of rapid and delayed ejaculation have been issued by BASHH and other organizations [90,98]; these should be consulted for guidance (IV).
- Peripheral neuropathy (of any cause) may manifest as retarded ejaculation, and therefore may occur in patients with HIV or on certain ARV agents (III).
- Lowered sexual desire may have a psychological basis (in both men and women) but warrants hormone measurements to exclude an organic cause (III).

4.3 Women and sexual dysfunction

Very little has been published on sexual dysfunction in women, and even less in the context of HIV infection. Therefore, the body of evidence in terms of specific management guidance in this context is sketchy. Furthermore, a recent study suggests that women with HIV are rarely asked by their treating physician(s) about female sexual dysfunction (FSD) [103] and therefore problems are presumably under-diagnosed and under-treated.

There are reports of high prevalence rates in women with HIV [104–107] and this may be greater, at least in the pre-HAART era, than the rate in the general population.

There may be a psychological, physical or mixed basis to the presenting difficulty, but in general FSD usually relates to psychosocial issues and the HIV diagnosis itself. Morphological changes associated with ART may cause body image problems as well as stigma. 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 [103].

It is important that women are asked about any problems and an appropriate history and examination is performed before they are referred to a healthcare provider with expertise in FSD.

Organic causes of FSD are comparable to organic male dysfunctions and may be caused, for example, by neuropathy (HIV- or drug-induced), endocrine disturbances or atherosclerosis [104].

4.3.1 Key points and recommendations

- FSD is often under-reported and under-treated. Healthcare providers should be mindful of this when caring for women with HIV (III).
- Where a problem is identified, an assessment should be made and the patient should be referred if necessary (IV).
- Psychological issues are often a key component to such problems (III).

4.4 HIV, cervical and anal pre-cancers and cancers

4.4.1 Cervical intraepithelial neoplasia (CIN) and cervical screening

4.4.1.1 Introduction. Both cervical cancer and the pre-invasive lesion of the cervix (CIN) are significantly more common in HIV-positive women compared to HIV-negative women [108,109]. The risk of having CIN in the setting of HIV appears to be related to the degree of immunosuppression [107,110]. The development of cancer of the cervix from pre-invasive lesions can take up to 10 years in immunocompetent women; this factor forms the basis of cytological screening programmes, which target the detection of such pre-invasive lesions. It is clear that cytological screening is as effective in HIV-positive women as it is in HIV-negative women [107].

Since 1993, invasive cervical cancer in HIV-positive women has been classified as an AIDS-defining illness [111]. World-wide, cervical cancer is the second most common cancer in women [112], although rates vary from country to country and depend on endemic rates, life expectancy following HIV diagnosis and access to routine screening, with the highest rates in developing countries. HIV-infected women have more aggressive and advanced disease and a poorer prognosis [113].

4.4.1.2 Role of human papilloma virus. The role of HPV in the pathogenesis of cervical cancer and CIN is now well established [114]. Studies have led to the classification of HPV types according to oncogenic risk [115]. It is known that HIV-positive women have a higher prevalence of cervical HPV infection than HIV-negative women and this is further increased in women with lower CD4 cell counts [116]. HPV infection is also more persistent in HIV-positive women [117,118], particularly with the more oncogenic types [118].

Because HPV is known to be an aetiological agent of cervical cancer and present in nearly all women with high-grade CIN, testing for high-risk HPV has been proposed as a method of improving cervical screening. Molecular techniques for the identification of HPV DNA are highly sensitive and specific. Patients and providers may be reassured with negative HPV testing but long-term management of positive HPV testing (especially in conjunction with negative cytology) is unclear. HPV testing in routine clinical practice is therefore not recommended until more data are available.

A quadrivalent prophylactic HPV vaccine (HPV 6/11/16/18; Gardasil®, Merck, Whitehouse Station, NJ, USA) has recently been licensed in the USA for use in women. There are no current data around safety or efficacy for such vaccines in HIV-positive patients, and studies are awaited.

4.4.1.3 Impact of HAART on cervical disease. There have been dramatic reductions in morbidity and mortality related to HIV following the introduction of HAART [119]. Because women live longer in the post-HAART era, there is potentially a longer time for the progression of disease associated with CIN. HAART has the potential to improve immune function and possibly facilitate clearance of HPV, thereby inducing regression of CIN or prevention of CIN development. However, the evidence for this has been inconsistent to date. Other factors such as cellular genetic changes (which are not influenced by HAART) may well play a key role in the development of disease. Data available on the natural history of HPV-related cervical disease in HIV-positive women prior to the introduction of HAART indicate that spontaneous regression occurs rarely [120,121]. Heard et al. [122] found that despite regression of CIN with HAART there was persistence of HPV. A further Italian study noted no effect on HPV following initiation of HAART [123], although follow-up in both of these studies was limited. The data on the effect of HAART on CIN are variable, with some studies showing a benefit in terms of CIN regression [124] and others showing no positive impact [125]. The paucity of definitive data means that current screening guidelines for CIN in HIV-positive women should not be modified if women are receiving HAART.

4.4.1.4 Cervical screening in HIV infection. Because of the high prevalence of CIN and cervical HPV infection in HIV-positive women, CIN should be aggressively screened for and treated. Guidelines for the NHS Cervical Screening Programme [126] currently recommend that all women newly diagnosed with HIV should have cervical surveillance performed by, or in conjunction with, the medical
team managing the HIV infection. Annual cytology should be performed with an initial colposcopy if resources permit. Subsequent colposcopy for cytological abnormality should follow national guidelines, although immediate referral to specialist colposcopy services following an initial abnormal smear (mild dyskaryosis) is advised based on the frequent persistence of CIN in HIV-positive women. The guidelines also suggest that the age range screened should be the same as for HIV-negative women, i.e. first invitation at 25 years and ending at 65 years. There are few data regarding the prevalence of cervical lesions in sexually active HIV-positive adolescents who may have been immunosuppressed for many years. Therefore, there may be a need for more intense surveillance on a case-by-case basis.

4.4.1.5 The use of newer techniques for cervical screening. Liquid-based cytology (LBC) is now the preferred technique for cervical screening and is recommended by the NHS Cervical Screening Programme (NHSCSP) [126] and NICE. This technique is currently being rolled out nationally across the NHSCSP. These newer Pap smear screening techniques using liquid-based media appear to increase sensitivity and decrease inadequate smears; they also offer the ability to perform direct HPV testing on collected specimens. They are more expensive and there are no current data examining the utility of these tests in HIV-positive women.

Some data suggest that in high-risk populations, the sensitivity of LBC may be no greater than the sensitivity of conventional cytology.

Guidelines for cervical cancer and CIN screening will continue to evolve as knowledge of the pathogenesis of the disease as well as the role of HPV expands.

4.4.1.6 Key points and recommendations

- All newly diagnosed HIV-positive women should have a sexual and gynaecological history as part of their initial medical assessment including cervical cytology and a sexual health screen if appropriate (III).
- Advanced HIV disease is the strongest independent risk factor for developing cervical abnormalities. All abnormal smears (mild dyskaryosis) should be referred to specialist colposcopy services (II).
- Annual cytology is recommended for all women living with HIV to detect cervical pre-cancer. The result of each smear should be documented in the HIV case notes regardless of where the test is carried out (including those performed in community settings) (II).
- The management of CIN in HIV-positive women should not differ from that in the general population (III).
- There are limited data on the effect of HAART on the natural history of disease and so management of women should be the same whether they are receiving therapy or not (II).

4.4.2 Anal cancer

4.4.2.1 Epidemiology. Cancer of the anus and anal canal was recorded in England and Wales in 2003 at incidence rates per 100 000 population of 1.2 in men and 1.7 in women [127]. In the general population, anal cancer mortality rates are about 30% of these [126]. However, men and women with HIV infection have a much higher risk of anal cancer than the general population. For example, US national data showed relative risks (RRs) of invasive anal cancer for men and women with HIV infection of 37.9 and 6.8, respectively [128]. However, receptive anal intercourse is a very strong risk factor for anal cancer in both HIV-negative and HIV-positive men, and the degree of excess risk associated with HIV infection in MSM at the present time remains unclear [129,130]. Although anal cancer shows a strong association with a history of receptive anal sex in men (RR 33.1, 95% CI 4.0–272.1), in women the association is weak or non-significant (RR 1.8, 95% CI 0.7–4.2) [131]. Data from the entire Chelsea and Westminster Hospital (London) HIV-positive cohort showed rates of anal cancer of 60/100 000 [132] between 1984 and 2003, which was 120 times higher than an age-, sex- and regionally matched control population [132]. Higher rates of 92/100 000 were recorded in the post-HAART era (1996–2003) compared to the pre-HAART era, but this difference did not reach statistical significance. Patients were treated with combined modality chemoradiotherapy [133,134]. The 5-year overall survival was 47%, and the 5-year disease-free survival was 66%. There was no difference in overall survival between pre- and post-HAART eras.

4.4.2.2 Natural history. Anal cancer shows many similarities to cervical cancer in that HPV infection is the causative factor in most or all cases. Somewhat less is known about anal cancer to date, but for cervical cancer it is now accepted that HPV is a necessary cause. Two recent series that conducted HPV typing of anal cancer specimens reported HPV positivity rates of 83% and 81% (all men), 95% and 88% (women) and 98% (MSM) [135,136]. Most of these HPV infections were with 'high oncogenic risk' (HR) HPV types such as HPV 16, 18, 31, 33, 35, etc. However, 'low oncogenic risk' HPV types such as HPV 6 and 11 can be detected alone in a small minority (~ 2.5%) of anal cancers [137,138]. It should be noted that current cigarette smoking is also a significant risk factor for anal cancer, both in men [odds ratio (OR) 3.9, 95% CI 1.9–8.0] and in women [OR 3.8, 95% CI 2.4–6.2] [135].

HPV is a very frequent STI that is usually asymptomatic. Prevalence rates of anal HPV infection in HIV-negative MSM are 50–60% across all age groups [139]. Most anogenital HPV infections are transitory, resolving spontaneously within ~ 9 months, although longitudinal data on anal HPV infections in HIV-negative MSM are sparse to
date. In general, persistent HPV infections are more frequent in persons over 30 years of age and the immunosuppressed. A quadrivalent prophylactic HPV vaccine (HPV 6/11/16/18; Gardasil™, Merck) has just been licensed in the USA for use in women, but whether it will be effective in men and whether HIV infection may abrogate vaccine-induced protection are not known at the present time.

The anal canal has a transformation zone (TZ) at the junction of the anal squamous and rectal columnar epithelia [140], similar to the cervix, and thus anal cancer probably arises because of HR HPV infection of metaplastic reserve cells in the anal TZ, which have a higher propensity to oncogenic transformation. However, receptive anal sex is not a pre-condition for such HR HPV infection and neoplasia of the anal canal, as shown by the occurrence of anal neoplasia in men and women with no history of receptive anal sex [141].

Anal neoplasia shows many parallels with cervical cancer, and a spectrum of anal pre-cancerous changes referred to as anal intra-epithelial neoplasia (AIN) is seen [139,142]. AIN can be classified as in the original Richart CIN classification, i.e. AIN 1, AIN 2, AIN 3, where AIN 3 is full-thickness anal mucosal pre-cancerous change, or using the more recent Bethesda system where the terms low-grade or high-grade squamous intra-epithelial lesion (LSIL = HPV/AIN 1, HSIL = AIN 2/3) are used and where cytological and histological diagnoses are likely to be more reproducible. Unlike cervical cancer, where we know that women with CIN 3 have a ~30% progression to invasive cancer over 10 years, there are no formal natural history studies of AIN 3 demonstrating progression rates to anal cancer. However, there is no doubt that such progression occurs, as evidenced by individual case observations, by the usual finding of invasive cancer within surrounding AIN3 and the overwhelming HR HPV ‘smoking gun’ evidence. However, the frequency of progression is not accurately known, although a figure of ~5% overall is sometimes quoted on the basis of progression rates of perianal Bowen’s disease [137,138].

Natural history studies of anal pre-cancer in HIV-positive MSM have been conducted in the pre-HAART era [143,144]. Persistent HPV was associated strongly with progression from normal to HSIL ($P = 0.0001$): 24% of men normal at baseline progressed to HSIL over 4 years, and such progression was more frequent with lower CD4 cell counts [145].

4.4.2.3 Are there tests that can detect anal pre-cancer? Anal warts are encountered frequently in clinical practice, and can be problematic to treat. Ano-genital warts are caused by HPV 6 and HPV 11. Recent studies using sensitive PCR methodology have detected either HPV 6 or HPV 11 in ~100% of genital wart lesions, but have also shown that genital wart lesions are frequently co-infected with HR HPV types – especially in HIV-infected individuals, where co-infection rates of up to 100% are seen [143]. Thus when anal warts are present AIN can be frequently detected concomitantly. In a study of 47 men with anal condylomata, where 79% of men were HIV-positive and where random biopsies from each anal canal quadrant were taken, these biopsies showed 16/47 (34%) to have AIN 2/3 and 3/47 (6.4%) to have invasive cancer [146].

AIN affecting the peri-anal skin, perineum or natal cleft can produce symptoms of itching and soreness. It also often produces recognizable clinical signs of pigmentation, white lesions, fissuring, etc. If there is ulceration, tests for herpes should be carried out. Diagnostic punch biopsies should be carried out if there are physical signs suggestive of AIN, or persistent ulceration.

However, when AIN alone affects the anal canal there are usually no symptoms and often no overt clinical signs. Occasionally AIN can be suspected on naked-eye inspection, manifesting as white plaques or red lesions. When invasive cancer is present there may be symptoms of soreness and bleeding, and there are signs of ulceration or induration.

‘Sub-clinical’ AIN can be diagnosed through cytology, anal colposcopy (also referred to as high-resolution anoscopy; we will arbitrarily use the term colposcopy) or histological examination of biopsy specimens. Nowadays, cytology is usually performed using liquid-based technology; many series attest to its utility [140,145,147]. Colposcopy uses techniques that are similar, but distinct, to those used for the examination of the cervix [126]. After visualization of any aceto-white areas, local anaesthetic can be infiltrated using a dental syringe and forceps (e.g. Tischler’s) used to take small biopsies. One issue that is similar for the cervix is the accuracy and reproducibility of these various diagnostic techniques. All have downsides: cytology tends to under-call diagnoses compared to biopsy [139,144–146], colposcopic-directed biopsies may miss the worst histological lesion [146] and histopathological reporting may be inaccurate [148].

Various ancillary tests could be proposed for the diagnosis of AIN; these need further research and evaluation. HPV tests, in particular the detection of high-risk HPV types, seem a logical proposition; in reality, these are too sensitive and have a very low positive predictive value [146]. Tests with good operational characteristics for the detection of AIN 3 would be ideal. There are a number of new candidates for such an approach, including tests for cell cycle proteins such as p16INK4a, which can be performed on LBC samples [149].

4.4.2.4 Are there treatments for anal pre-cancer, and are they effective? The current definitive treatment for CIN 3 is excision of the cervical TZ. Unfortunately, the anatomy and complex physiology of the anal canal precludes any similar approach. The anal mucosa also surmounts only a narrow bandwidth of sub-mucosa before deeper fundamental structures are encountered, and thus excision or ablative surgical therapies performed on minority areas of the mucosa have to be restricted to the superficial layers, and excision of too extensive an area can result in the serious consequence of anal stenosis. Perhaps because of these difficulties, a variety of treatments for AIN have been described [141,150,151]. These include treatments that are evidence-based for genital warts, including podophyllotoxin, trichloracetic acid, imiquimod and electrosurgery, although the evidence base for using these treatments for genital warts in HIV-infected individuals is much smaller. However, at present the number of published trials that have actually examined treatments for AIN systematically is tiny [152,153]. There is a particular dearth of data on the outcomes of the medical therapies referred to earlier.

Chang et al. [152] described the outcomes of a single out-patient electrosurgical treatment of AIN 2/3 during the period 1995–1999 performed with sedation and often a field block. In HIV-positive men over a mean follow-up of 29 months, 23/29 (79%) developed a recurrence of their disease. Goldstone et al. [153] described the outcomes of out-patient infrared coagulation therapy of localized AIN 2/3 in HIV-positive men performed under local anaesthesia during the period 1999–2003. Recurrent disease developed in 44/68 (65%) at a median time of 7 months. Second and third re-treatments were administered for recurrent disease, after which the overall prevalence of persistent disease was 40% at 14 months. It has been suggested that even when surgical therapy for AIN has been conducted and disease has relapsed/recurred, the incidence of subsequent invasive cancer may be 75% lower than in an untreated individual [154]. Although this could be possible, there are no data to justify the assertion.

There has been debate over whether the use of ART affects the prevalence of AIN. A recent study of 92 HIV-positive men used multivariate regression analyses to evaluate risk factors for histological AIN (all grades), and concluded that nadir CD4 cell count was a significant risk factor (OR 2.0, 95% CI 1.1–3.3) and that current use of ART was protective (OR 0.09, 95% CI 0.01–0.75) [155]. Larger studies would allow similar analyses restricted to AIN 2/3.

4.4.2.5 Current uncertainties on systematic testing for anal pre-cancer in HIV-positive men and women. There are many issues in this area, even with respect to terminology. The term ‘screening’ should be properly used to describe the application of a preventive technology to an entire population, or a defined sub-set of that population. For example, it could be proposed that all homosexual men in the UK population were offered screening for anal cancer. However, we believe this would not be practicable, deliverable or desirable, and is also outside the remit of these guidelines. However, when it is proposed that a particular preventive technology is applied to a defined group of patients, it is more accurate to describe such an application as systematic testing. Thus we will discuss whether systematic testing for anal cancer and its precursors is warranted in HIV-infected individuals, and specifically in the sub-groups HIV-positive MSM, heterosexual men and women.

There are already wide differences of opinion in this area. Whereas one group concluded that testing HIV-positive MSM with anal cytology every 2 years ‘offers quality-adjusted life expectancy benefits at a cost comparative with other accepted clinical preventive interventions’ [154], another group concluded that ‘more information is needed on the recurrence rates of high-grade AIN and the relative morbidities for the various techniques before widespread screening programmes can be implemented’ [155].

There are a number of fundamental uncertainties and issues to be resolved in this area:

1. The rate of progression from AIN 2/3 to anal cancer in the three HIV-positive sub-groups (MSM, women and heterosexual men) is not known.
2. Existing data concerning treatments for AIN 2/3 are very limited with large uncertainty factors. Much more research is needed, including prospective studies of existing therapies, new approaches to therapy – including combination treatments and novel therapies (e.g. therapeutic vaccines) – and determining whether such therapies actually decrease subsequent cancer risk.
3. Given the current lack of knowledge concerning progression rates and the outcomes of treatment, is there justification for triage based on any anal cytological abnormality triggering anal colposcopy and biopsy? If current practice really only delivers early detection of invasive lesions, would anal cytology and prospective follow-up alone deliver similar benefits?
4. If patients with HIV are delivered accurate information about existing knowledge and lack of knowledge in this area, including risk/benefit of the various possible screening/triage/conservative or therapeutic management strategies, what is the acceptability of the various
potential strategies in the three HIV-positive sub-groups (MSM, women and heterosexual men)?

4.4.2.6 Key points and recommendations

- All major HIV units should develop clinical guidelines for the management of suspected anal cancer and pre-cancer (IV).
- All major HIV units should develop either local clinical expertise or referral pathways for suspected anal cancer and pre-cancer (IV).
- The role of annual anal cytology and anoscopy is not yet proven; however, patients should be encouraged to check and report any lumps noticed in the anal canal (IV).

4.5 Psychological aspects of HIV and reproduction

The desire to conceive and parent is universal. There is good evidence that this is affected but not altered by the presence of HIV infection, for both women and men. The availability of HAART has changed the views on reproduction of both men and women.

4.5.1 Psychological issues of HIV and reproduction

These can be summarized by understanding behavioural factors and emotional responses linked with:

- safer sexual behaviour to prevent transmission of HIV to others, risk behaviours and behavioural patterns;
- pregnancy and HIV;
- fatherhood issues;
- emotional health.

4.5.2 Safer sexual behaviour to prevent transmission of HIV to others: risk behaviours and behavioural patterns

There is a considerable literature on risk behaviours and HIV prevention. Earlier studies have focused on HIV prevention among HIV-negative persons or those of unknown HIV status. More recently, the importance of positive prevention has been highlighted and provides a particular need for those treating HIV-positive people. A number of reviews have examined the trends in risk behaviour and adoption of safe behaviour and interventions to promote safety and reduce risk. General findings show that HIV risk continues [156] and counselling interventions (with follow-up booster sessions) can effectively reduce risk behaviours (and subsequent STI infections) [157,158]. Community-based interventions have some effects [159], while there is evidence for and against the efficacy of peer programmes [160].

4.5.3 Pregnancy and HIV

Psychological considerations are relevant in relation to:

- HIV issues for all pregnant women;
- reproductive issues for all HIV-positive people, such as:
  - reproductive choices in the presence of HIV;
  - counselling to prevent unwanted pregnancy and STIs;
  - pregnancy and parenting in the presence of HIV.

4.5.4 Ante-natal HIV testing

The availability of interventions to dramatically reduce infant infection has prompted the wide-scale introduction of ante-natal HIV testing for all pregnant women. There are clear guidelines on integrating HIV discussions into routine ante-natal care [161]. The standards of counselling, informed consent and support should not be compromised in pregnancy. For many women, HIV testing in pregnancy may be the moment they discover their positive status. Thus all such programmes should have clear links into routine HIV provision prior to initiating any generalized ante-natal screening. In the UK the majority of women will test HIV-negative, and the occasion of the HIV test can be used to promote HIV prevention in future. The UK Department of Health advises a routine offer of HIV testing in pregnancy. Different centres have trained all midwifery staff on HIV issues, appointed an HIV-specific midwife or counsellor, integrated HIV testing into the routine battery of tests on offer in ante-natal care or made specific efforts to address HIV (especially in areas of higher prevalence such as London). Uptake rates of HIV testing in such environments are high (in excess of 80% in many London clinics), and the corresponding drop in HIV-positive infants has been notable. Most women who find out their HIV status during pregnancy take up the basket of interventions on offer (ART to prevent mother-to-child transmission, Caesarean section and avoidance of breast feeding). Treatment choice and decision-making is a complex process. This is enhanced by the presence of continuity of care, providing a dedicated carer knowledgeable in HIV and an opportunity to explore options and revisit decisions.

Couple testing and couple counselling are seen as cost effective [162], yet women-only counselling is more common in the UK. The literature clearly shows some neglect in responding to and catering for the needs of fathers who are equally affected at such times. HIV-positive men (both homosexual and heterosexual) have reproductive concerns and find it difficult to raise these in clinics [163]. These concerns should be discussed with HIV-positive men and women.
4.5.5 Family planning and termination of pregnancy

HIV provision in family planning and termination clinics lags behind ante-natal provision, with little rationale. Ideally, services should make such testing routinely available for all family planning and termination clinic attendees [164].

4.5.6 Counselling around HIV testing

The widespread increase of HIV testing, specifically with routine offers of testing in ante-natal clinics, has raised the profile of HIV and acted as a cornerstone in the HIV response. The role of HIV testing in prevention is also well established. All those attending for voluntary counselling and testing (VCT) should be counselled on contraception and safer sex as well as prepared for HIV testing. Quality counselling has been shown to be effective [165]. In many settings brief, perfunctory counselling is all that is possible. This is good for gaining informed consent and notifying people of service provision but may not be the most effective in achieving behaviour change or emotional preparation. Services should have in-house provision or have systems of referral available as part of the planning process when setting up ante-natal HIV testing provision.

In reproductive health, men are rarely included in HIV testing and counselling provision while the service for women varies. Evidence suggests that male services are not provided, although the literature suggests that it should be made available and integrated into services.

4.5.7 Ethics on fertility treatments

People with HIV may experience fertility problems and may have difficulty accessing fertility treatments. There are well-documented emotional sequelae (for both men and women) of infertility. Furthermore, the process of fertility treatment may bring anxiety and emotional upheaval.

4.5.8 Parenting in the presence of HIV

People with HIV have general parenting concerns as well as those particularly added by the presence of HIV in one or both partners. The level of burden and the nature of concern are often altered by the HIV status of the child. Goldstein et al. [166] noted that approximately 20% of HIV-positive parents in the USA had parenting concerns (no similar figures exist for the UK). Psychological distress, anxiety and depression are common (over 30% screen positive). Supportive cohabiting partners act as a buffer to such stresses. Issues to be mindful of include:

- Depression around HIV testing, during pregnancy and post partum [167].
- Adherence: parents (particularly mothers) prioritize their child’s HIV care over their own in terms of clinic attendance and other variables.
- Decision making: many decisions have to be made by HIV-positive parents, including the decision to conceive, treatment options and parenting decisions. The availability of ART has had an impact on such decisions and the risk of vertical transmission plays a key role in these decisions [168,169].
- Custody plans: planning for the future is challenging for parents with HIV and is noted for being a slow and unstable process. Rotheram-Borus [223] found that 44% of parents died without custody plans, and that parents frequently changed their plans – the majority of which involved family members.

4.5.9 Developmental issues

It is well established that mental health factors in parents affect child development. There is no reason to believe that these findings do not relate to HIV. Furthermore, there are direct and indirect effects of HIV on child development. These are often mild but noticeable. Mechanisms are unclear, with contributions from the virus itself (on HIV-positive children), illness, school absence, hospitalization, medication side effects, parental illness/absence/death and educational/learning opportunities that are affected by stigma and trauma. Clear ongoing family programmes are needed to support and provide for the needs of families in the presence of single or multiple HIV.

4.5.10 Fatherhood issues

It is trite to assume that reproduction should be focused totally on women. Men – homosexual and heterosexual – have needs and roles in relation to reproduction and fathering. Many men who have been exposed to HIV through a same-sex relationship may still have fatherhood issues, may indeed have sought fatherhood, or may have emotional needs in relation to procreation. Heterosexual men are also involved in fathering [162]. Fatherhood desires are high, although some studies show that in couples with HIV there may be differences in desires [170]. Studies of HIV-positive men desiring children show that men anticipate disapproval, believe they would experience discrimination, are rarely provided with full and adequate information and would like referral to fertility services [171]. Decision-making, help-seeking and resource provision should be made available to men as well as women.

4.5.11 Emotional health

SRH, fertility and infertility issues and relationships are all emotionally laden experiences. The mental health literature notes that progressing through care may often result in raised anxiety, mood fluctuation, depression and emotional pain. Furthermore, there is some evidence that hetero-
sexual men with HIV are less likely to be referred to mental health provision [152]. There may be additional anxiety linked to the medical process and procedures; this may be exacerbated by the clinical approach, which is often viewed as cold and mechanical in what is emotionally and physically a very different experience for individuals and couples. Good communication, adequate time and acknowledgement of emotions should be seen as an adjunct to care provision. For a proportion of people with reproductive or sexual health issues, referral to counselling, clinical psychology or psychiatry may be appropriate. Good service provision should establish links, liaison and referral pathways as an integrated part of care.

4.5.12 Key points and recommendations

- Psychological considerations are of key importance in several issues including conception and HIV in pregnancy, sexual behaviours to reduce HIV transmission and sexual functioning.
- All units involved in HIV service delivery should consider the funding and provision for mental health and the behavioural aspects of SRH.
- An updated understanding of HIV prevention, risk behaviour, reproduction and mother/father perspectives should feed into policy and service provision.

4.6 HIV sexual transmission and HAART

4.6.1 Introduction

There have been several advances in the field of HIV transmission science that have implications for the counselling and clinical management of PLHA. Patients need evidence-based information and advice in order to make important decisions in developing and maintaining long-term meaningful relationships.

In general, and in short-term casual relationships, advice and support on safer sex and the use of condoms to reduce the transmission or acquisition of HIV or other STIs is still recommended [172]. However, couples in long-term monogamous relationships may wish for information in order to make decisions about whether or not to cease using barrier protection. This may be for couples who are either sero-different or sero-same.

There is currently no UK guidance on counselling on HIV transmission in the era of HAART; it is envisaged that because this is an increasingly important and controversial area, detailed guidance will be developed in the near future. In the interim, we present the currently available evidence, which may be useful in guiding consultations and discussions.

4.6.2 Risks of HIV transmission on HAART

Studies have shown that the risk of HIV transmission correlates with the level of plasma HIV RNA for sexual [49,173] and mother-to-child [174,175] transmission. It is now well established that treatment with HAART reduces HIV infectiousness [35,176]. Extrapolations from epidemiological and biological data have led Swiss experts to the opinion that individuals with chronically suppressed viral loads taking HAART and with no STIs are not sexually infectious if certain key criteria are met [177]. The Swiss experts state that viral load suppression must be for at least 6 months and that the person must be on effective suppressive therapy under regular clinical follow-up.

Although the precise transmission risk on suppressive ART is not known, prospective studies have shown no transmissions between sero-different couples if viral loads were undetectable [50,178]. Similarly, during therapy the concentration of HIV diminishes in both semen [37] and cervico-vaginal fluid [35,38]. Mathematical modelling of transmission data by Chakraborty et al. [179] shows that as the viral load in semen reduces, the transmission rate per sexual act reduces exponentially to approach zero. Although there is compelling evidence to reach similar conclusions to the Swiss where oral and vaginal intercourse are concerned, gaps exist in currently available evidence regarding the transmission risk of anal intercourse – which is practised not only by MSM but also by a significant minority of heterosexuals, who may be unwilling to disclose this to healthcare workers. There would also be concern about the interpretation of this statement by individuals who might make decisions about their infectiousness based on incorrect assumptions, e.g. about the presence of STIs if they were asymptomatic, or who have multiple casual partners.

Nevertheless, providing information on HIV transmission to HIV-positive individuals is vital, and clear information based on the evidence must be provided in ways where the possibility of ambiguity does not arise. Time should be made available for detailed counselling and information provision, which can support PLHA to develop and maintain healthy and fulfilling sexual relationships, including the choice of procreation. Key areas of discussion are included as follows with a summation of the evidence to date in each case.

4.6.3 HIV transmission between two HIV-positive individuals

In a situation where both partners in a sexual relationship are HIV-positive, the potential risks of unprotected sexual intercourse include the transmission or acquisition of other STIs and the possible transmission or acquisition of a second strain of HIV – superinfection. The extent to which
4.6.4 HIV superinfection

Multiple infections can occur at three distinct phases of HIV disease. They can occur during primary infection (known as simultaneous infection) if two different strains of HIV infect the same cell. They can also occur after primary infection but before the immune system has produced antibodies to HIV (in the ‘window period’). This has been termed sequential infection. Infection with two or more different viruses at this stage is termed dual infection. However, if re-infection occurs once HIV has become a chronic infection, this is known as superinfection.

4.6.4.1 Timing of superinfection. Research in both primates [184,185] and humans suggests a ‘window of susceptibility’ to superinfection with most infections occurring shortly after primary infection. Up to 24 cases of apparent superinfection in HIV-infected individuals have been reported [186–188]. In most of these cases, the second virus appeared within the first three and a half years of HIV infection. However, in two cases, the second virus may have appeared up to 12 years after initial infection [162,164,165,189].

4.6.4.2 Risk of superinfection in recent HIV infection. The risk of superinfection may be relatively high during the first few years of infection; in fact, the majority of case reports of apparent superinfection have been within the first year of infection. Smith et al. [182] found a 5% incidence rate of HIV-1 clade B superinfection within 6–12 months of initial infection among recently infected homosexual men with frequent partner change. Similarly, Grant et al. [190] estimated a first-year apparent superinfection incidence rate amongst recently infected homosexual men of between 2.1% and 8%. The lower estimate reflects the overall cohort, about 50% of whom did not report HIV exposure after initial infection. The higher estimate reflects those men for whom an exact timing of first infection was known and who reported continued HIV exposure after initial infection.

Taken together, these data suggest that the rate of superinfection during the first year of HIV infection may be comparable to the overall incidence of new HIV infections seen among high-risk populations.

4.6.4.3 Risk of superinfection in chronic HIV infection. No apparent superinfection cases have been reported among chronically infected individuals – either untreated or on ART – in cohort studies. Gonzales et al. [180] looked for superinfection in 718 people (representing 1072 person-years of follow-up), the majority of whom were on ART, in a clinic cohort and found no evidence of it. However, no data on continued HIV exposure were reported. Tsui et al. [181] documented high-risk behaviour among injecting drug users over 215 person-years of observation and also found no evidence of superinfection. There was no evidence of superinfection among HIV-positive couples with genetically distinguishable virus at baseline after 233 person-years of follow-up, representing an estimated 20859 exposures during unprotected anal or vaginal intercourse. Based on self-reported risk behaviour, they calculated that they would have expected to see 89 new infections during this time if one of the partners had been HIV-negative [181].

Although two recent case reports suggest that superinfection may still occur in chronically infected individuals, either on or off ART [187,188], the overall conclusion from the literature is that it is extremely rare. Notably, even when superinfection has been found to have occurred, it is only very rarely clinically relevant. Healthcare workers should provide counselling on the possible risks of superinfection and, perhaps more importantly, other STIs for individuals of the same serostatus. The mainly hypothetical risk of superinfection needs to be discussed, taking into account individual circumstances including whether both partners are on suppressive treatment or not. PLHA have to balance the possible risks with other life choices and it is important that discussions occur in an open and supportive environment.

4.6.5 HIV transmission in HIV discordant couples

As mentioned earlier, there is increasing evidence that HAART reduces the risk of sexual transmission and this will play an increasing role in HIV prevention in the future. The fact that almost two thirds of PLHA on HAART in the UK have an undetectable viral load means that information on the risks of HIV transmission on HAART is relevant to many. However, given that the average time for remaining undetectable on ART is limited [222], there are important considerations that need to be taken into account regarding the public health implications of any recommendations or advice given to patients. Similarly to other national and international positions, the current guideline cannot fully
endorse the Swiss consensus statement. However, it is acknowledged that in many instances long-term sero-discordant partners may seek advice about risk reduction in certain instances such as natural conception. Information on risk reduction should be provided because it has been shown that many couples who cannot access fertility services eventually conceive.

4.6.6 Pre-conceptual, pre-exposure prophylaxis in sero-different couples
The number of centres that provide conception services is limited and in many instances the procedure is costly. Although the exact number of couples who practice unprotected sex in order to conceive is not known, it is likely to be underestimated. It has been reported that up to one-third of couples who have been on waiting lists for fertility clinics do not attend and a significant number of these conceive naturally [191].

Data on the use of pre-exposure prophylaxis with tenofovir and risk reduction counselling have been presented recently by Vernazza and colleagues [53]. Within counselling discussions on minimizing the transmission risks whilst trying to conceive, 22 couples where the male partner had fully suppressed viral load (<50 copies/mL) were offered the option of timed intercourse with tenofovir pre-exposure prophylaxis. With 50% of women conceiving after three cycles, the conception rate was higher than with artificial conception techniques and all of the women tested negative 3 months after last exposure. These preliminary data and results from pre-exposure animal studies suggest that harm reduction strategies such as this will be important for the future but currently no recommendation on the use of pre-conception prophylaxis for sero-discordant couples can be made.

4.6.7 Key points and recommendations
- HAART reduces the risk of HIV sexual transmission and for individuals with chronically suppressed viral loads the transmission risk may be negligible in the absence of STIs (II).
- In most circumstances, counselling and advice should continue to promote the use of condoms to reduce the transmission risk of HIV and other STIs (III).
- Detailed individual counselling including the use of harm reduction should be available for individuals in sero-different and sero-same long-term relationships who wish to consider unprotected sexual intercourse (IV).
- The risk of HIV superinfection may diminish with the time from initial infection. Although it appears more likely in the first 3 years following seroconversion, a risk persists after this (II).
- HIV-positive individuals should be counselled regarding the low but possible risk of superinfection, particularly those who choose to serosort (i.e. have unprotected intercourse with partners who are also HIV-positive) (II).

4.7 HIV, disclosure and criminalization
There have been several UK convictions for transmission of HIV from individuals who were aware of their status to other individuals and it is important that healthcare professionals and all those involved in the care of HIV-positive people are aware of the issues regarding this important topic. The situation is complex with several important factors that have relevance, including duty of care, client confidentiality, public health concerns, the doctor–patient relationship and the need for a trusted protective environment in which issues of disclosure can be raised and explored.

No simple guidance can be issued but healthcare workers and services should be aware of the issues and should develop local policies and guidance on partner notification and disclosure. A recent briefing paper is available for review [224], and further guidance will be made available as it is published. The briefing paper focuses on the responsibilities and duties of healthcare staff, and provides guidance on the duties of healthcare workers regarding confidentiality and disclosure. It is important to stress that although this is not accepted guidance there are some key areas for which there are accepted professional standards.

- A healthcare worker must properly advise a patient on ways of protecting their sexual partners from infection. A failure to do this may give rise to legal liability if the patient’s sexual partner becomes infected as a result. Liability may also arise where a healthcare worker negligently fails to diagnose the patient as having the infection.
- A healthcare worker has a legal responsibility to maintain confidentiality of patient information unless the patient has consented to disclosure or disclosure is necessary in the public interest. A failure to maintain confidentiality may give rise to legal liability.
- A healthcare worker may disclose information on a patient (either living or dead) in order to protect another person from serious harm or death. However, there is no statutory obligation to do this.
- It is also important to remember that disclosure is a process rather than an event and that maintaining trust and therapeutic relationships with patients in order to allow them safe space to examine disclosure issues will
ultimately lead to far more beneficial outcomes than threats of litigation.

- Further useful information on HIV and criminalization is available on the Terence Higgins Trust website (www.tht.org).

### 4.7.1 Key points and recommendations

- Healthcare staff should be aware of the important legal issues regarding HIV transmission and their responsibilities to the duty of care of patients, confidentiality and public health concern.
- All units should develop local policies and guidelines on partner notification and disclosure.

## 5.0 Sexual and reproductive health issues for women

### 5.1 BHIVA guidelines for the management of HIV infection in pregnant women and the prevention of mother-to-child transmission of HIV

Throughout these guidelines, extensive reference has been made to the management of HIV in pregnancy for which guidelines exist. These are available on the BHIVA website (www.bhiva.org), are updated regularly and should be consulted as appropriate [10].

### 5.1.1 Contraception for women with HIV

#### 5.1.1.1 Introduction

As the health of women and men living with HIV continues to improve with the use of ART, changes in decision-making around sexuality and reproduction may result. Women with HIV infection, like other women, may wish to plan pregnancies, to limit their families, or to avoid pregnancy altogether and therefore require advice on and access to a range of contraceptive methods.

Evidence-based guidelines on contraception management in HIV-positive women do not yet exist and therefore decisions regarding contraception choice must be practical, pragmatic and acceptable to each woman. These contraception guidelines aim to be used as an adjunct to existing FSRH documents, which provide evidence-based guidance on a variety of contraceptive methods (www.ffprhc.org.uk). In addition, the Clinical Effectiveness Unit of the FSRH has produced the UK Medical Eligibility Criteria (UKMEC) for contraceptive use (www.ffprhc.org.uk/admin/uploads/UKMEC200506.pdf). These criteria represent an adaptation, for UK practice, of previous WHO Medical Eligibility Criteria, and classify a range of medical conditions into eligibility categories by contraceptive type.

#### Table 1 UK medical eligibility criteria (UKMEC) for contraceptive use

<table>
<thead>
<tr>
<th>UKMEC category</th>
<th>Definition of category</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>A condition where there is no restriction for use of the method</td>
</tr>
<tr>
<td>2</td>
<td>A condition where the advantages of using the method generally outweigh the theoretical or proven risks</td>
</tr>
<tr>
<td>3</td>
<td>A condition where the theoretical or proven risks generally outweigh the advantages of using the method</td>
</tr>
<tr>
<td>4</td>
<td>A condition that represents an unacceptable health risk if the method is used</td>
</tr>
</tbody>
</table>

The eligibility criteria range from 1 (no restriction for use of the contraceptive method with that condition) to 4 (where use of the contraceptive method represents an unacceptable health risk) (see Table 1).

The UKMEC categories for each of the contraceptive methods for women with HIV/AIDS are summarized in tabular form at the end of this section (Table 3).

#### 5.1.1.2 General contraception management

Development of managed care networks or integrated SRH services will ensure that patients have access to both HIV services and reproductive health services, including contraception. HIV-positive women requiring contraception should be given information about all methods of contraception and be supported in making an informed choice. Women should be provided with the most effective method of contraception that is acceptable to them. All women should receive detailed information – both verbal and written, if possible – to enable them to choose a method and use it effectively. Counselling should be sensitive to cultural differences and religious beliefs. Women should be informed when contraceptives are used outside the product licence and there should be clear written documentation in the notes as to why this is necessary. Women may be taking multiple pills in terms of their HIV disease, and factors around adherence should be taken into account when choice of contraceptive method is made.

Most available methods of contraception may be considered in HIV-positive women and are safe and effective; however, special considerations need to be made in women currently taking or about to commence ART.

All women being considered for contraception should have an appropriate medical and sexual history taken as part of routine assessment. Transmission of HIV and other STIs must also be discussed and screening for STIs should be offered where appropriate. Safe sex should always be promoted when prescribing contraception. Women who have HIV-negative partners (i.e. discordant couples) should also be advised of the availability of PEPSE.

Contraceptive efficacy is variable between methods (Table 2), and a method that is effective in preventing HIV transmission (i.e. condoms) may offer less contraceptive
and HIV transmission, she may need to use dual methods. For an individual woman to achieve optimal protection against pregnancy and HIV transmission, she may need to use dual methods.

5.1.1.3 Barrier methods
5.1.1.3.1 Condoms. The effectiveness of both male and female condoms in preventing pregnancy is dependent on correct and consistent use, with unplanned pregnancy rates in the first year of use of around 2% and 5%, when used perfectly. Condoms are, of course, user-dependent and can only be used at time of coitus. In practice with typical use, failure rates of around 15% and 21% can be anticipated [192]. Latex and non-latex male condoms have been shown to offer similar efficacy in pregnancy prevention [193]. Male condom use offers a high degree of protection against HIV sexual transmission [194] and STIs [195] if used correctly. The consistent use of a condom for each episode of vaginal intercourse in serodiscordant couples reduces the risk of HIV transmission by 80% [196]. There may be issues around negotiation of male barrier methods and patients should be counselled and supported appropriately.

The female condom consists of a polyurethane sheath, with a flexible ring at either end. The upper ring is placed in the upper vagina, and the lower ring covers the introitus [197]. Laboratory evidence suggests that female condoms also provide protection against STIs [198,199], although widespread use of female condoms has been limited.

N-9 is the only spermicide available in the UK. It is a mucosal irritant and has been shown to increase the risk of HIV transmission. It offers no protection against other STIs such as gonorrhoea or chlamydia [198,199] and does not reduce pregnancy rates when compared to non-spermicidally lubricated condoms [198]. Condoms lubricated with N-9 are therefore not recommended [200].

Dual protection or ‘doubling up’ – using both barrier and either hormonal or intrauterine contraception – is the most effective way to both prevent pregnancy and reduce horizontal transmission of HIV. In addition, use of effective contraception will inevitably reduce cases of vertical transmission to the neonate, by preventing unplanned pregnancies. Nonetheless, some women with HIV will decide to use condoms alone, for prevention of both transmission and pregnancy. In such circumstances, women should be aware of emergency contraception, and know how to access a supply in a timely manner. Emergency contraception is more effective the earlier it is used, and providers should consider advanced provision of emergency contraception for women to keep at home and use as required.

UKMEC categorizes HIV infection, whether using HAART or not, and AIDS as category 1 for both male and female condom use, i.e. there is no restriction on use of the method.

5.1.1.3.2 Diaphragms and caps. Diaphragms cover the cervix and part of the vaginal wall, and caps cover only the cervix. With both methods relatively large areas of the vaginal mucosa remain exposed, thus permitting potential viral transmission. In addition, caps and diaphragms are recommended to be used with N-9; as outlined earlier, this would not be appropriate in a woman who is HIV-positive or when there is a significant risk of HIV. UKMEC therefore recommends that the risks of a diaphragm or cap generally outweigh the benefits (UKMEC category 3).

5.1.1.4 Hormonal contraception
Hormonal contraceptive methods are among the most widely used family planning methods worldwide. They include the COC, the combined contraceptive patch, POP, injectable progestogens and the progestogen implant.

5.1.1.4.1 Combined oral contraceptive pill. The COC is the most commonly used contraceptive method by women in the general UK population aged 16–49 years [201]. In current practice, low-dose COCs containing 20–35 μg ethinylestradiol (EE) in combination with a progestogen have replaced older COCs containing 50 μg EE or more. Progestogens include norethisterone, levonorgestrel, desogestrel, gestodene, norgestimate and the newest progestogen, drospirenone. COCs act on the hypothalamic-pituitary-ovarian axis to inhibit ovulation and also have some effects on cervical mucus and the endometrium. The method offers high contraceptive efficacy, with a perfect use failure rate of 0.1% in the first year, although typical-use failure rate may be up to 5%.

This method is safe and effective for women with HIV who are not taking ART and is categorized as UKMEC 1. There is limited evidence suggesting no association between COC use and changes in HIV viral load or CD4 cell counts in HIV-positive women. Overall evidence is inconsistent regarding whether there is increased risk of...
HIV-1 acquisition with hormonal contraception use. One meta-analysis of 28 studies showed a positive association between COC use and HIV-1 risk [202], although many other studies have shown no association. A recent study with over 6000 participants showed no association between either combined oral or injectable progestogen contraception and HIV [203]. Hormonal contraceptives cannot replace the ability of barrier methods to prevent transmission of HIV and other STIs; condoms should therefore be recommended in conjunction with any hormonal method.

For women taking HAART, some ARV drugs may reduce the efficacy of hormonal contraception (Table 4). A few agents increase contraceptive steroid levels, but more commonly levels are reduced. ARV drugs such as PIs (e.g. lopinavir, ritonavir) and NNRTIs (e.g. nevirapine) are metabolized by the CYP3A4 liver enzyme system and can affect liver enzymes (see Table 3). Women with HIV may use combination therapy where one or more drugs may affect the liver enzymes. The contraceptive efficacy of COC may be reduced by such drugs. Unfortunately, few studies have been published that investigate the pharmacokinetics of oestrogen and progestogen with ARV drugs and none on the effect on contraceptive efficacy. Serum concentrations of EE were reduced when women taking a 50-μg EE COC were also using ritonavir, but no pregnancies have been documented [204]. In HIV-positive women on non-enzyme-inducing ART, UKMEC category 2 applies – i.e. the advantages of the method generally outweigh the risks.

When enzyme-inducing ART is used the condition remains UKMEC category 2, but additional contraceptive precautions should be advised. Guidance from the Faculty of Family Planning and Reproductive Health Care advises that a COC with at least 50 μg EE (e.g. Norinyl-1®, or a combination of a 20 μg and 30 μg pill such as Mercilon plus Marvelon) is used in those women who are using liver-enzyme-inducing drugs and wish to start or continue the COC. Additional contraceptive protection, such as condoms, is also strongly advised [205]. Some women may opt to use an alternative method of contraception that is not affected by enzyme-inducing drugs, such as an intrauterine method, but this will not be acceptable to everyone. It is

<table>
<thead>
<tr>
<th>Drug</th>
<th>Effect on hormonal contraception</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>NNRTIs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Efavirenz</td>
<td>Not studied fully – likely reduction in EE and progestogen concentrations</td>
<td>FDA category D; additional or alternative contraceptive methods advised</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>Decrease in EE and progestogen concentrations</td>
<td>Additional or alternative contraceptive methods advised</td>
</tr>
<tr>
<td>PIs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nelfinavir</td>
<td>Decrease in EE and progestogen concentrations</td>
<td>Additional or alternative contraceptive methods advised</td>
</tr>
<tr>
<td>Saquinavir</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fosamprenavir</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lopinavir</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atazanavir</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ritonavir</td>
<td>Decrease in EE concentration</td>
<td>Avoid oestrogen-based contraceptives (COC)</td>
</tr>
<tr>
<td>Indinavir</td>
<td>No clinically significant interaction</td>
<td></td>
</tr>
<tr>
<td>NRTIs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abacavir</td>
<td>No evidence for PK interactions with EE and progestogens</td>
<td></td>
</tr>
<tr>
<td>Didanosine</td>
<td></td>
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<tr>
<td>Lamivudine</td>
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<tr>
<td>Emtricitabine</td>
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<td>Zidovudine</td>
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<td>Stavudine</td>
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</table>

Table 3  Summary of UK medical eligibility criteria (UKMEC) categories for use of common reversible methods of contraception in women with or at risk of HIV

<table>
<thead>
<tr>
<th></th>
<th>COC</th>
<th>POP</th>
<th>DMPA</th>
<th>Implant</th>
<th>Cu-IUD</th>
<th>LNG-IUS</th>
<th>Condom</th>
<th>Diaphragm</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-risk of HIV</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>HIV- positive, not using ART</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>HIV- positive, using ART</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>

ART, antiretroviral therapy; COC, combined oral contraceptive pill; Cu-IUD, copper-bearing intrauterine device; DMPA, depot medroxyprogesterone acetate; LNG-IUS, levonorgestrel intrauterine system; POP, progestogen-only pill.

Table 4  Effects of antiretroviral drugs on hormonal contraception [225]

important to consider that use of a COC, even with an enzyme inducer, is likely to confer better contraception than no method at all.

The COC is metabolized by the liver and its use in women with cirrhosis is considered UKMEC 3/4. Caution should also be exercised in women with abnormal liver function because of co-infection with hepatitis B and/or C, or history of alcohol misuse.

There will also be potential drug interactions between other drugs that induce liver enzymes and hormonal contraception. Some HIV-positive women who may not be receiving ART may be on medication to treat tuberculosis, for example. Use of rifampicin decreases the contraceptive effectiveness of the COC [206,207] and an alternative or additional contraceptive method should be considered for such women.

5.1.1.4.2 Combined contraceptive patch. The transdermal patch delivers EE (20 µg) and norelgestromin (150 µg) daily, and is applied weekly for 3 weeks followed by a 7-day patch-free interval. A Cochrane systematic review concluded that self-reported compliance was better with the patch compared to the COC, although overall efficacy is similar for both methods. There are no currently available data on the use of the patch in women using liver enzyme-inducing drugs such as ART. Although first-pass metabolism in the liver is avoided with transdermal administration of hormones, the effectiveness of the patch is likely to be reduced by drugs that induce hepatic enzyme activity. The patch is classified by UKMEC as category 1 for HIV-positive women not using ART, and category 2 for women on ART (i.e. as for COC). If a woman on enzyme-inducing ART opts to use transdermal contraception, then additional contraception, usually in the form of condoms, should be strongly encouraged.

5.1.1.4.3 Progestogen-only pill. Traditional POPs contain levonorgestrel, norethisterone or ethynodiol diacetate and mainly work by thickening cervical mucus, and by a lesser effect on the endometrium. The newer desogestrel POP works by inhibiting ovulation in the majority of women. POP is classified as UKMEC category 1 for women with HIV and not on HAART. ARV drugs have the potential to either increase or (more commonly) decrease the bioavailability of progestogen steroid hormones in the POP, thereby reducing contraceptive efficacy. Thus use of POP by women on HAART is classified as category 2, and use of an additional method of contraception, such as condoms, should be advised.

5.1.1.4.4 Long-acting injectable progestogens. These are DMPA, which is given every 12 weeks, and norethisterone enantate (NET-EN), which is given every 8 weeks. DMPA is the more commonly used injectable in the UK and is a safe and effective method of contraception for women with HIV. The use of condoms will, of course, continue to be encouraged to reduce transmission of virus.

The metabolism of DMPA is unaffected by liver enzyme-inducing drugs and thus DMPA can be used in women taking ART without loss of contraceptive efficacy. DMPA and NET-EN should continue to be given at the usual intervals of 12 and 8 weeks, respectively. Women on long-term DMPA have been shown to have an increased risk of low bone density, and FSRH guidance suggests discouraging women at high risk of low bone density from using DMPA [208]. HIV infection itself has been found to be associated with reduced bone density, and some ARTs can further reduce bone density. Women may continue to opt for DMPA after discussion, but it may be prudent in such circumstances to offer a baseline bone density scan prior to initiation of DMPA.

5.1.1.4.5 Progestogen-only sub-dermal implants. The etonogestrel implant is an extremely effective contraceptive and acts by suppressing ovulation. It lasts for 3 years and is a safe and effective method of contraception for women with HIV not on ART (UKMEC 1). Use of enzyme-inducing medication is likely to increase the metabolism of etonogestrel, leading to a potential reduction in efficacy. Thus concomitant use of HAART reclassifies etonogestrel to category 2 in HIV-positive women, and an additional contraceptive method may be recommended.

5.1.1.5 Intrauterine contraception
5.1.1.5.1 Levonorgestrel intrauterine system. The LNG-IUS is used by 1% of women aged 16–49 years using contraception in the UK, and lasts for 5 years. LNG is released into the uterine cavity at a constant dose of 20 µg per day and the main mode of action is a direct local effect on the endometrium, preventing implantation. Women in the UK who are HIV-positive may be offered an IUS after risk assessment and STI testing, if appropriate.

There is no evidence that the effectiveness of the IUS is reduced when taking liver enzyme-inducing drugs, and use of the LNG-IUS is classified as UKMEC 2 for women with HIV both on and off HAART. Initiation of a LNG-IUS in women with AIDS is classified as category 3 (risks outweigh the advantages), but women with AIDS and a LNG-IUS already in situ may continue to use the method under category 2. Condom use will again be encouraged concurrently, to reduce virus transmission. The majority of women with an LNG-IUS will have a significant reduction in menstrual bleeding within a few months of insertion. This reduction in blood loss may be relevant in reducing the risk of horizontal transmission by reduction in viral shedding.

5.1.1.5.2 Copper-bearing intrauterine devices. Copper-bearing IUDs (Cu-IUDs) act by preventing fertilization
and inhibiting implantation, and are used for between 5 and 10 years, depending on the device. IUD use is a safe and effective method of contraception for women living with HIV, with no evidence of increased complications when compared to HIV-negative women. In addition, there is no evidence of increased transmission of HIV to partners when a Cu-IUD is in situ. Women in the UK who are HIV-positive may be offered an IUD after risk assessment and testing as indicated. Condom use should also be advised, as for all methods.

5.1.1.6 Emergency contraception

Women will require emergency contraception to reduce the risk of unplanned pregnancy when unprotected intercourse has occurred or when their usual method of contraception has failed. Women with HIV infection not on ART may be offered progestogen-only emergency contraception (POEC) if within 72 h of sexual intercourse, or insertion of a copper IUD as an alternative if within 5 days (UKMEC 1).

Levonorgestrel 1.5 mg recently became available in the UK [209] and replaces previous regimens with two doses of 0.75 mg. POEC is available as an over-the-counter preparation, as well as on prescription from general practices, some accident and emergency departments, and sexual and reproductive clinics.

The latest guidance from the FFPRHC [209] states that women using liver enzyme-inducing drugs should be advised that an emergency IUD is the preferred option for emergency contraception because this method is unaffected by concomitant drug use. If this is not acceptable or appropriate, the guidance also states that the dose of levonorgestrel should be increased by 100% for women who are using liver enzyme-inducing drugs – that is, women should be advised to take two tablets of levonorgestrel (1.5 mg), total dose 3 mg, as soon as possible and within 72 h of unprotected sexual intercourse. No studies are available to confirm that this dose increase is required and the recommendation is based on clinical judgement. Use in these circumstances is outside the product licence. Women should be advised of this and it should be documented in the notes.

5.1.1.7 Key points and recommendations

- Consistent condom use should be encouraged in conjunction with an additional contraception method.
- For HIV-positive women not on ART, all available contraceptive methods are suitable, although N-9 spermicide should be avoided.
- Because of induction of liver enzymes, COC, POP and etonogestrel, implant may be less effective in those on HAART. Nonetheless, there is a role for these methods in conjunction with an additional method.
- The efficacy of DMPA, LNG-IUS and Cu-IUD are not known to be affected by liver enzyme inducers, and offer very effective contraception for those on HAART.
- A Cu-IUD is the recommended method of emergency contraception for women on HAART. If POEC is used, a doubling of the standard dose to 3 mg stat (immediately) is recommended.

6.0 Sexual and reproductive health issues for men

6.1 Male condoms and other contraceptive methods

Prevention is still the mainstay of the response to the HIV/AIDS pandemic. The male condom is the single most effective intervention to prevent HIV transmission and the transmission of other STIs from men to women, from women to men and between men [209–211]. The use of mineral oil-based lubricants with latex condoms should be discouraged – because of condom damage and increased breakage rates [212] – in favour of water-based lubricants that do not contain N-9. Although latex and polyurethane condoms such as Avanti™ appear equally efficacious at preventing pregnancy [190,213], no comparative studies looking at HIV transmission have been published. There has been one randomized study that concluded that ‘thicker’ latex condoms marketed for anal sex were no more effective than condoms of normal thickness [214].

The use of microbicides such as N-9 can cause a significant increase in genital symptoms, and epithelial disruption [192] may cause rapid rectal epithelial exfoliation [193]; a major study in high-risk women [194] and a meta-analysis [195] do not show any protection against STIs. Given the effects on the genital epithelium the use of N-9 cannot be recommended except in groups at low risk of acquiring STIs and HIV.

6.1.1 Key points and recommendations

- Use of barrier contraceptives should be encouraged to prevent spread of HIV, superinfection and co-infection with other STIs.
- Education on proper use appears to be more important than the thickness of the latex condom.
- There may be legal implications in having unprotected sex, particularly when an individual has not disclosed their HIV status and transmission occurs. This should be raised in the context of safer sex discussions. Further guidance should be sought from relevant sources. These include medical defence organizations, the Terence Higgins Trust (UK-wide), the National AIDS Trust...
6.2 Investigation and management of sub-fertility in men

There are few published data on the direct effect that HIV/AIDS has on the fertility and semen quality of infected men. However, two studies have shown little effect of HIV (or HCV) on sperm production [215,216] compared to WHO criteria. One study in the pre-HAART era showed that men with advanced disease, and not on zidovudine monotherapy, had reduced sperm counts and an increased percentage of abnormal sperm forms, but no significant impairment at CD4 cell counts of over 200 [217]. However, there is a single case report of reduced semen parameters in an individual whose semen was analysed prior to and after HIV-1 seroconversion [218].

The effect of specific ARV agents on human sperm production has not been published. One study [219] showed no adverse effect of HAART on sperm production but confirmed that those with CD4 cell counts <200 cells/μL were more likely to have lower sperm counts. Another study looked at men on HAART requesting assisted reproductive technology, and showed some impairment of sperm motility, total sperm counts and ejaculate volume compared to matched seronegative controls. This study also showed a correlation with lower CD4 cell count and increased abnormalities, but the differences observed were probably not marked enough to alter fecundity.

In the absence of good evidence that treated or early HIV disease affects male fertility, it is prudent to follow the NICE guidelines [220] in the investigation and management of male sub-fertility in these men. Patients with low CD4 cell counts or advanced disease with abnormal semen should be advised that optimizing ART, with a rise in CD4 cell count, may improve semen quality [221], but direct evidence of this is lacking and such men should be assessed and investigated to exclude other causes of sub-fertility according to national guidelines.

6.2.1 Key points and recommendations

- There is no published evidence that specific ARV agents affect male fertility.
- There is some evidence that men with advanced disease may have abnormal sperm production; therefore, optimizing HIV treatment should be part of the management of such men.
- Investigation and management should be in line with NICE guidelines and it is recommended that both partners undergo assessment.

7.0 References


23 Bernard EJ. Sexual transmission of hepatitis C. Available at: www.aidsmap.com/files/file000701.pdf

24 Donaldson L. Letter from Sir Liam Donaldson to all chief executives of primary care trusts and strategic health authorities in England: PEP access in the UK. Available at: www.i-base.info/htb/v7/htb7-5/PEP.html


35 Vettore MV, Schechter M, Melo MF, Boechat LJ, Barroso PF. Genital HIV-1 viral load is correlated with blood plasma HIV-1 viral load in Brazilian women and is reduced by antiretroviral therapy. J Infect 2006; 52: 290–293.


43 Vernazza P, Hirschel B, Bernassconi E, Flepp M. HIV-positive individuals without additional sexually transmitted diseases (STD) and on effective antiretroviral therapy are sexually non-infectious. Bull Med Suisses 2008; 89: 5.


51 Melo M, Varella I, Nielsen K, Turella L, Santos B. Demographic characteristics, sexual transmission and CD4 progression among heterosexual HIV-serodiscordant couples followed in Porto Alegre, Brazil. 16th International AIDS Conference. Toronto, ON, Canada, August 2006 [Abstract TUPE0430].


93 Sekar V, Lefebvre E, DeMarez T. Pharmacokinetic interaction between TMC114, a new protease inhibitor, and sildenafil. 8th International Congress on Drug Therapy in HIV. Glasgow, UK, November 2006 [Abstract A-0369].


209 Faculty of Family Planning and Reproductive Health Care Clinical Effectiveness Unit. Faculty Statement from the Clinical Effectiveness Unit on Levonelle® 1500 and the Use of Liver Enzyme Inducing Drugs. London: FFPHC, 2006.


