

2007 UK guidelines for the management of sexual and reproductive health (SRH) of people living with HIV infection

Produced jointly by the British HIV Association (BHIVA), the British Association for Sexual Health & HIV (BASHH) and the Faculty of Family Planning & Reproductive Health Care

May 2007

Authors: A. Fakoya, H Lamba, N. Mackie, R Nandwani¹ A. Brown,² EJ Bernard, C Gilling-Smith, C Lacey, L. Sherr, P Claydon, S Wallage, B Gazzard.

¹ on behalf of BASSH, ² on behalf of the FFPRHC

SUMMARY OF KEY POINTS AND RECOMMENDATIONS	4
INTRODUCTION AND GENERAL ISSUES.....	8
Addressing the sexual and reproductive health needs of people living with HIV/AIDS in the era of successful HIV therapy	8
SEXUAL AND REPRODUCTIVE HEALTH ISSUES AFFECTING BOTH MEN AND WOMEN LIVING WITH HIV	10
Management of sexually transmitted infections in HIV Positive men and Women	10
Sexually transmitted infections in HIV positive women.....	10
Sexually transmitted infections in HIV positive men.....	10
HIV and the sexual transmission risks of Hepatitis C	11
Key points and recommendations	11
Post exposure prophylaxis following sexual exposure (PEPSE).....	12
Key points and recommendations	14
Conception issues	15
Preconception counselling and assisted reproduction	15
The risks of timed unprotected intercourse	15
Reproductive options for HIV-positive men and HIV-negative women.....	16
Sperm washing.....	16
Clinical management of couples undergoing sperm washing treatment.....	17
Effect of HIV on semen parameters and the outcome of sperm washing IUI	17
Management of HIV-positive women	18
Safety of healthcare workers and non-infected patients	19
Demand for fertility care.....	19
Key points and recommendations	19
Management of couples where the male is HIV-positive.....	19
Management of couples where the female is HIV-positive.....	20
SEXUAL DYSFUNCTION IN HIV POSITIVE MEN AND WOMEN	21
Erectile Dysfunction: Investigation and Management	21
Key points and recommendations	22
Other male sexual dysfunctions.....	22
Key points and recommendations	24

Women and Sexual Dysfunction	24
Key points and recommendations	25
HIV, cervical and anal pre- cancers and cancers.....	26
Cervical intraepithelial neoplasia (CIN) and cervical screening.....	26
Cervical screening in HIV infection.....	27
Key points and recommendations	27
Anal cancer.....	28
Epidemiology	28
Natural history	28
Are there tests that can detect anal pre-cancer?.....	29
Key points and recommendations	31
Psychological aspects of HIV and Reproduction	32
Safer sexual behaviour to prevent transmission of HIV to others and risk behaviours and behavioural patterns	32
Pregnancy and HIV	32
Ante-natal HIV testing.....	33
Family Planning and Termination of Pregnancy	33
Counselling around HIV testing	33
Ethics on fertility treatments.	34
Parenting in the presence of HIV.....	34
Fatherhood issues	34
Key points and recommendations	35
HIV superinfection	35
Key points and recommendations	38
HIV, Disclosure and Criminalisation	39
Key Points and recommendations.....	39
SEXUAL AND REPRODUCTIVE HEALTH ISSUES FOR WOMEN	40
BHIVA guidelines for the management of HIV infection in pregnant women and the prevention of mother-to-child transmission of HIV	40
Contraception for Women with HIV.....	40
Introduction.....	40
Barrier methods	42
Hormonal Contraception.....	42
Levonorgestrel intrauterine system (LNG-IUS).....	45
Copper Bearing Intrauterine Devices (Cu-IUD)	45
Emergency Contraception	45
Key points and recommendations	47
SEXUAL AND REPRODUCTIVE HEALTH ISSUES FOR MEN	48
Male Condoms and Other Contraceptive Methods.....	48
Key points and recommendations	48
Investigation and Management of Sub-fertility in Men.....	48
Key points and recommendations	49

Summary of Key Points and Recommendations

Levels of evidence:

- I = High quality meta-analyses, systematic reviews of randomised control trials (RCTs) or 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

Sexual and reproductive health of women and men living with HIV

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 if declined - **II**.
- Documented local care pathways for diagnosis, treatment and partner work for sexually transmitted infections in people with HIV which can be actively communicated to all members of clinic staff and to HIV-positive people – **II**.

Management of sexually transmitted infections in HIV positive men and women

- The majority of sexually transmitted infections 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+ people – **I**.

- Syphilis serology documented at baseline and at 3 monthly intervals 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**.

Management of hepatitis and blood borne viruses

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

- Hepatitis A, B, C screening at baseline and if not already immune to hepatitis B, should be vaccinated against regardless of sexual orientation – **III**.
- Screening for hepatitis B and C should be offered annually in those who have exposure risks – **IV**.

Post exposure Prophylaxis

All units should have explicit policies and procedures on PEP following sexual exposure- **IV**

- All HIV positive individuals should be made aware of the units' procedure to access PEP- **IV**

Preconception counselling and assisted contraception

HIV-positive women and their partners planning to have children should receive pre-conceptual counselling on HIV transmission risks, their long term health and the possible effects of antiretroviral medication on the foetus. -**IV**

HIV positive women whose partners are HIV negative should receive instructions on how to carry out self-insemination in order to minimise viral transmission risk through unprotected intercourse. -**IV**

Cervical and anal Pre cancers and Cancers

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 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 HAART on the natural history of disease and so management of women should be the same whether receiving therapy or not. -II

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

Psychosocial Issues

Psychological considerations are key 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- IV

An updated understanding of HIV prevention, risk behaviour, reproduction and mother/father perspectives should feed into policy and service provision. IV

HIV superinfection

- The risk of HIV superinfection may diminish with the time from initial infection. Although it appears more likely in the first three years following seroconversion, a risk persists after this. II
- All HIV-positive individuals should be counselled regarding the risk of superinfection, particularly those who choose to sero-sort (i.e. have unprotected intercourse with partners who are also HIV-positive). II
- Where there is limited access to specialised conception services sero-concordant couples who wish to conceive should be counselled regarding the risk of superinfection in attempting to conceive. III

HIV and criminalisation

Health care staff should be aware about 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

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**

Due to potential interactions between ART and COC, EVRA®, 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 DMPA, LNG-IUS and 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 3mg) is required for women on ART- **III**

Reproductive and sexual health in men

Use of barrier contraceptives should be encouraged to prevent spread of HIV, super-infection 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**

Thus use of mineral oil based lubricants with latex condoms, and use of nonoxynol-9 should be discouraged There is no published evidence that specific antiretroviral agents affect male fertility. **III**

Investigation and management of sub- fertility in Men

There is some evidence that men with advanced disease may have abnormal sperm production and therefore optimising HIV treatment should be part of the management of such men. **III**

Investigation should be in line with NICE guidelines and it is recommended that both partners undergo assessment **IV**

Erectile Dysfunction (ED)

There is some evidence that men with HIV infection are more likely to experience erectile difficulties. This may adversely affect effective condom usage, and should be treated. **III**

There are some important drug interactions between PDE5 inhibitors and protease inhibitors, 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**

Introduction and general issues

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 UK¹². Due to the effectiveness of HIV treatment regimens there are now an increasing number of HIV positive individuals, living well, on suppressive antiretroviral treatment³. More attention is thus being given to the wider health needs of People living with HIV/AIDS (PLHA) including a renewed focus on sexual and reproductive health (SRH) needs.

Men, who have sex with men (MSM)* and culturally diverse heterosexual populations from sub-Saharan African, account for large proportions of people living with HIV and accessing treatment and care services in the UK. It is recognised that any guidance on SRH must consider the diversity of needs of those living with HIV despite sometimes there being limited access to the specialised 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 an outbreak of Lymphogranuloma venereum more recently.⁶ It is well documented that HIV progression and transmission is increased and facilitated by STIs.^{7 8} Some groups have questioned whether the availability of HAART has resulted in an increase in unsafe sexual behaviour in some men who have sex with men⁹.

More positive women are choosing to have children¹⁰ and an increasing number of couples who request fertility investigations and assisted conception. Couples that are either sero-concordant (both HIV positive) or sero-discordant 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 2004¹¹. This still suggests that there is transmission that 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 positive people. It should be remembered however that most HIV transmission occurs in circumstances when individuals do not know their own status.

Objective and development of these guidelines

The aim of these guidelines is to complement the existing guidance on contained in the British HIV Association (BHIVA) guidelines on the management of HIV in pregnancy¹², the British Association for Sexual Health & HIV (BASHH) guidelines on the management of sexually transmitted infections in people living with HIV¹³, syphilis and HIV¹⁴ and on post-exposure prophylaxis¹⁵. It also draws upon reproductive health guidance from the Clinical

* The term MSM is used throughout to refer to gay men and other men who have sex with men, see page 8 for discussion about terminology

Effectiveness Unit of the Faculty of Family Planning and Reproductive Health Care [www.ffprhc.org.uk].

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

Who are these guidelines are for?

The guidelines have been developed for use by healthcare staff in various disciplines including, gynaecologists, and 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 and affected by HIV.

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 sensitised 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 potential discriminatory language, even if unintentionally utilised. In this regard the HIV community has been invaluable in providing feedback and guidance on terminology. Clinicians should be aware and sensitive to these. Within the context of these guidelines, 3 such areas have been pointed out, and this document should be read and applied taking these into account. Adherence more accurately refers to medication taking, whereas compliance reflects a judgemental and unidirectional approach. The former term is preferable. Concordant and Discordant couples accurately describe HIV status, but "discordant" (although often utilised 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.

Issues not addressed within the 2007 guidelines

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

- HPV vaccination
- 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 currently to provide definitive guidance at this time although it is hoped that this will be available in future versions.

Sexual and reproductive health Issues affecting both men and women living with HIV

Management of sexually transmitted infections in HIV Positive men and Women

Introduction

Sexually transmitted infections in HIV positive women

Of the 7450 HIV infections acquired through heterosexual contact that were diagnosed in the UK in 2005, 63% were women² 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 heterosexual men. 64% of diagnosed women were aged 25-39. Many of these women living with HIV remain sexually active and have sexual and reproductive health needs. HIV care providers are now being urged to include regular STI risk assessments and investigations in the ongoing care of their patients¹³. 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.

Sexually transmitted infections in HIV positive men

Homosexual and heterosexual men account for over 60% of the 53,000 people living with HIV in 2004¹. Although it is still not entirely clear what is the best way to provide access to STI services for HIV positive individuals 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 and it is well documented that both ulcerative² and non-ulcerative STIs³ increase the risk of HIV transmission and acquisition. There is also an increased possibility of complications from Hepatitis B, and C, Syphilis and HSV in those who have HIV infection. Ensuring HIV positive individuals have access to effective sexual health services should improve their sexual health and reduce the risks of onward transmission and super infection. Recent outbreaks of sexual transmitted infections in HIV positive MSM groups have highlighted the need to ensure that the ongoing sexual health issues of PLHA are addressed.

STI service provision and delivery

Recommendations from the British association for sexual health and HIV on the development and arrangement of STI services for PLHA¹³ suggest that services should either develop facilities for STI treatment or pathways of referral to sexual health / genitor-urinary 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 services requirements of patients to ensure prompt diagnosis and treatment of STIs and other sexual health related issues.

Service delivery for women and men should include¹:

- Sexual health assessment including a sexual history should be documented at first presentation and thereafter at six monthly intervals.
- Provision of key prevention activities including screening for Hepatitis A, B and C and immunisation for the former two
- Access to investigation, diagnosis and treatment of STIs (including Hepatitides) and partner notification
- Syphilis serology should be included in the routine HIV blood tests at first diagnosis and at three monthly intervals thereafter
- Annual cervical cytology should be performed in all HIV positive women with access to colposcopy services if required
- Counselling to sero-discordant 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 available for advice and services for conception, pregnancy and fertility issues for

The management of the following infections do not differ significantly in patients who are HIV positive; Gonorrhoea, non-specific urethritis, uncomplicated Chlamydia, lymphogranuloma venereum. Both the presentation and management of syphilis differs with HIV infection. Guidance on the specific management of sexually transmitted infections in HIV positive adults including Hepatitis B and C is available.^{13 14 16 17} One important aspect of the overall management of STIs in HIV positive individuals is ensuring regular routine screening for asymptomatic infections which can be done in GU and non- GU settings.

HIV and the sexual transmission risks of Hepatitis C

It is important to highlight the sexual transmission risk of Hepatitis C¹⁸, 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 studies¹⁹ literature reports highlighting that the transmission risk may be increased in Men who have sex with Men.²⁰ Co-infection with HIV, the duration of the relationships, or chronic liver disease may be independent cofactors 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.

Key points and recommendations

Women and men living with HIV

Sexual health support

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

¹ Adapted from Recommended standards for NHS HIV services , MedFASH 2003

- 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. - **II**.
- Documented local care pathways for diagnosis, treatment and partner work for sexually transmitted infections in people with HIV which can be actively communicated to all members of clinic staff and to HIV-positive people – **II**.

Management of sexually transmitted infections in HIV positive men and women

- The majority of sexually transmitted infections 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+ people – **I**.
- Syphilis serology documented at baseline and at 3 monthly intervals 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**.

Management of hepatitis and blood borne viruses

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

- Hepatitis A, B, C screening at baseline and if not already immune to hepatitis B, should be vaccinated against regardless of sexual orientation – **III**.
- Screening for hepatitis B and C should be offered annually in those who have exposure risks – **IV**.

Post exposure prophylaxis following sexual exposure (PEPSE).

Detailed guidelines concerning the use of antiretroviral drugs as post exposure prophylaxis following sexual exposure to HIV have recently been published by BASHH and the present

Writing Committee endorses these guidelines which should be read in detail¹⁵. Some general comments about post exposure prophylaxis in this situation follow.

1. Randomised controlled studies are difficult to organise and have not been performed. However, animal experiments indicate that infection of monkeys with SIV virus can be prevented by antiretroviral treatment up to 24 hours after exposure of rectal or cervical mucosa to SIV. Two cohort studies where some sexually active patients but not others have been given antiretroviral therapy have indicated a reduced rate of transmission of HIV. It is widely accepted (in the absence of randomised controlled studies) that post-exposure prophylaxis following parenterally exposure to HIV in health care 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 post exposure prophylaxis following sexual exposure is likely to have a favourable risk benefit ratio.

2. The time following sexual intercourse at which post exposure prophylaxis might be effective is unknown. Data obtained in monkeys indicates that following SIV exposure of the cervix, there is a latent period of 24 hours 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. As it is likely that antiretroviral treatment 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 hours after exposure but recognize that such prophylaxis is likely to be more effective the more quickly it is given.
3. One of the major problems with post exposure prophylaxis 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 both to prevent short-term toxicity and the risk of serious toxicity in individuals who have little chance of developing HIV infection. Most guidelines recommend a proteinase inhibitor containing regimen. Non nucleoside reverse transcriptase inhibitors are not usually recommended. Nevirapine is contra indicated in people with a normal immunological system and the side effects of Efavirenz are likely to be a bar to short term adherence. (Lopinavir in the new tablet formulation, Tenofovir and Emtricitabine – Truvada) are recommended as drugs for PEPSE.

The optimum length of post exposure prophylaxis 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 men having sex with men. Insertive vaginal intercourse is of lesser risk, and less so for the male partner compared to the female partner, and passive oral sex having 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 sero status, the risk will depend upon the prevalence of HIV in that particular population but overall the risks are likely to be much lower than that following sexual intercourse with a person who is known to be HIV seropositive.
5. If post exposure prophylaxis following sexual intercourse is going to become a public health priority²¹, this will require either the setting up of specialised clinics or

education of Accident & Emergency Departments and General Practitioners in the treatment and care of such individuals. A number of models have looked at the likely cost effectiveness of such an approach. These models may not be directly applicable to the situation in the United Kingdom 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 post exposure prophylaxis to man having unprotected sex with other men is likely to be more cost effective than offering post exposure prophylaxis to heterosexuals, particularly when the sero status of the partner is unknown. The risks of sexual transmission of an individual who is known to be HIV positive but whose viral load is less than 50 copies using a sensitive PCR assay is unknown for certain but data suggests 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 hours 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 antiretroviral therapy. Cost effectiveness is also likely in homosexual relationships with a partner of unknown sero status and in heterosexual relationships where the partner is known to be HIV positive and the model cost effectiveness in heterosexual relationships where the partner is known to be HIV positive. We believe that this data is clearly strong enough to offer PEPSE on an adventitious basis and to encourage government organizations to explore innovative ways in which such prophylaxis can be offered within short time of sexual intercourse but recognising 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 pre-exposure prophylaxis i.e. taking antiretroviral therapy (potentially just one drug) prior to risk taking sexual activity is controversial. Animal data suggests 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 randomisation in the trial, the provision of antiretroviral therapy 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 data that such an approach is already quite widespread and there is an urgent need to explore whether such treatment encourages risk taking behaviour, is associated with protection or with the development of antiretroviral resistance if monotherapy approaches are used.

Key points and recommendations

- All units should have explicit policies and procedures on PEP following sexual exposure
- All HIV positive individuals should be made aware of the units' procedure to access PEP

Conception issues

Preconception counselling 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.^{22 23 24 25} Increasingly, parenting is regarded as a realistic option for couples where one of both partners is infected and the demand for reproductive care is rising.²⁶ Although few centres in the UK are equipped to offer assisted reproduction to HIV positive patients, the needs of these patients are now recognised and increasingly supported by state funding. The main objectives in offering reproductive care are to minimise the risk of viral transmission to the uninfected partner and future child and ensure the safety of healthcare workers and other patients attending the fertility centre.

The risks of timed unprotected intercourse

Conceiving through timed unprotected intercourse carries a transmission risk in both HIV-serodiscordant and HIV-concordant couples. In practice, this risk is difficult to quantify precisely for a heterosexual couple in a stable relationship, limiting intercourse to the fertile time of the month.

- i. **Discordant couples where the man is HIV-positive:** The risk is quoted as 0.1-0.5% per act of intercourse, provided the couple are in a stable monogamous relationship, not engaged in injecting drug use or participating in any other form of high risk activity.^{27 28} Men with negative viral loads such as those on ART, paradoxically, may shed significant virus in semen as viral load in serum and semen are poorly correlated.^{29 30 31} The only prospective study to examine the risk of timed unprotected intercourse in discordant couples trying to conceive was done prior to the widespread use of ART. In this study, timed to the fertile window and four women seroconverted, two during pregnancy and two post partum³². The seroconversions occurred in couples in whom condom use post conception and outside the fertile window was inconsistent. A more recent, retrospective study from Spain 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 77 discordant couples who conceived³³. The study is weakened by the fact that numbers are small and seroconversions were not analysed in couples who failed to conceive. The safety of this approach cannot be improved by inseminating ejaculated semen, which has been first tested for HIV, into the vagina or uterus as the detection of HIV RNA and DNA in ejaculated semen is unreliable³⁴.

Although it is well recognised that timed unprotected intercourse may be the only option for discordant couples unable to access, or finance, risk-reduction options such as sperm washing or donor insemination, the limited data on the safety of this approach should be emphasised and couples discouraged from attempting to conceive in this way, even when the man has an undetectable viral load. Safer options to be considered are sperm washing, and adoption.

- ii. **Discordant couples where the woman is HIV-positive:** The overall risk of HIV transmission from female to male is lower than from male to female through unprotected intercourse³⁵. However, these couples do not have to take this risk to conceive as conception can be achieved safely by collecting sperm in a condom

(which is free of spermicidals) after intercourse and inseminating this into the woman's vagina using a syringe and, if preferred, a quill. This process of self-insemination should be discussed fully with the couple and advice given on how to identify the fertile period in a woman's cycle, using home urinary ovulation detection kits if necessary.

- iii. **When the couple are both HIV-positive:** There is no conclusive data on the overall risk of infection with a different or drug resistant strain of virus in seroconcordant couples who engage in unprotected sex (**see section on HIV super infection**). These couples should be discouraged from attempting to conceive either through timed unprotected intercourse or self-insemination as each may be infected with different strains of HIV and intercourse may lead to superinfection and the transmission drug resistance virus to either partner and/or the future child. Sperm washing is recommended in concordant couples to minimise this risk.

Reproductive options for HIV-positive men and HIV-negative women

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:

- i. **Insemination using donor sperm:** This effectively removes the risk of viral transmission as sperm donors are screened for HIV and other blood-borne viruses. However, it also removes the option of genetic parenting from the infected male.
- ii. **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
- iii. **Adoption:** This is a difficult option for couples as current adoption practice regards HIV in one or both partners as a significant undesirable factor when assessing the suitability of parents requesting to adopt.

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 women HIV-negative, and concordant couples. Semen is centrifuged to separate live sperm, which does not carry HIV, from seminal plasma and non-germinal cells which may carry virus 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, in vitro fertilisation (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^{36 37 38 39 40 41}

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 preparation of a final swim-up. As a quality control for the procedure, and to protect the service from medicolegal action, an aliquot of washed sperm (approximately 100µl) should be tested for detectable HIV RNA prior to the sample being used for treatment.^{42 43} A nucleic acid-based sequence amplification (NASBA, Biomerieux, Basingstoke, Hampshire, UK) or similar commercial assay can be used.⁴⁴ The risk of the sample having detectable HIV is 3-6%.^{45 46 47} This is because in a small proportion of cases, centrifugation fails to remove all the seminal plasma

and leucocytes. The number of washes is limited as repeated centrifuging leads to loss of sperm quality and quantity. 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), in vitro fertilisation (IVF) or intracytoplasmic injection (ICSI) published to date.^{43 48}

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 is done to ensure the viral status of both partners is known at the time of treatment and that any genital lesions or infections can be treated as these can increase the risk of viral transmission⁴⁹ and reduce pregnancy rates. The purpose of the fertility screen is to define the optimum mode of treatment. It is recommended that the male partner has a semen analysis, and the female partner has an endocrine profile and baseline pelvic scan in the early follicular phase of her cycle (day 2-5), a mid-luteal progesterone to measure ovulation and non-invasive test of tubal patency (e.g. hysterosalpingogram), unless there is a history of pelvic pain or infection where laparoscopy is the preferred method for assessing tubal patency⁴².

Most couples electing to have sperm washing are voluntarily infertile and do not have significant fertility issues. For these couples, intrauterine insemination (IUI) is the preferred first line treatment and should be carried out in a natural cycle, unless the woman is anovulatory, where clomifene or injectable gonadotrophins are recommended. Ultrasound follicular tracking is used to time insemination accurately and, where possible, human chorionic gonadotrophin administered to ensure the timing of ovulation is known precisely. Between 3 and 6 cycles of IUI is 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 is not affected by the use of washed sperm as 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 minimise the high costs and risks of multiple pregnancy and ovarian hyperstimulation associated with IVF and ICSI treatment.

Effect of HIV on semen parameters and the outcome of sperm washing IUI

The majority of HIV-positive men have semen parameters within the defined WHO normal range. In the largest analysis of semen parameters in HIV-positive men to date⁵⁰ Nicopoullou and colleagues found all parameters to be significantly impaired compared to HIV-negative controls and that there was 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 use 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 significantly affected IUI outcome. Clinical pregnancy rate was significantly higher in cycles where the man had a low viral load (<1000copies/ml) and where the man was on ARV treatment CD4 count had no impact on IUI outcome. There are insufficient data at present to recommend starting ARV purely to improve IUI success rates and the decision to start medication should be primarily based on the health of the individual.

Management of HIV-positive women

HIV-positive women planning to have children should receive pre-conception counselling on mother to child transmission risks, their long term health and the possible effects of antiretroviral medication on the foetus. They should also receive instructions on how to carry out self-insemination of their partner's sperm at the time of ovulation in order to minimise viral transmission risk through unprotected intercourse.

HIV-positive women appear to have reduced fertility. There is no evidence to suggest an increased incidence of cycle irregularity in positive women, although prospective studies are limited. However a study on positive women undergoing IVF indicates that HIV-positive women have lower IVF success rates than HIV-negative controls due to a reduced response to superovulation.⁵¹ A difference in IVF outcome was not noted in HIV-positive women undergoing ovum donation pointing towards an effect of HIV on ovarian response and ovarian reserve rather than implantation. Retrospective data from Sub-Saharan Africa^{52 53} and prospective data from the UK indicates an increased incidence of tubal infertility in positive women²⁶. For these reasons positive women trying to conceive should be referred for fertility evaluation if they have not conceived within 6 to 12 months of self-insemination. Referral should be earlier if there is a history of pelvic inflammatory disease or they are over 35 years of age.

Reducing risks associated with pregnancy

Minimising risk in HIV-positive women lies primarily in reducing mother to child transmission (MTCT). 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 load⁵⁴. 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 positive women need to monitor all IVF or ICSI cycles in positive women and audit short and long term outcome..

Management of 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. Couples concordant for HIV should be advised to conceive using sperm washing to prevent the risk of superinfection.

Pre-conception counselling

Couples wishing to conceive where one or both partners are infected with HIV should receive reproductive counselling prior to starting treatment. This is 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. During counselling they should also discuss the possibility of treatment failure and how they would cope if they successfully had a child but the infected parent became more seriously ill or died. If they chose to have sperm washing, they have to understand that this is a *risk reduction* method and not *risk free* method as 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 MTCT and the methods used which will reduce this risk to < 2%. They should plan and agree to attend a specialist obstetric unit once pregnant to ensure they receive the best possible advice to minimise MTCT 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 account⁵⁵. Reproductive counselling is particularly pertinent in concordant couples where prognosis and life expectancy in each should be carefully discussed with the HIV physician⁵⁶.

Safety of healthcare workers and non-infected patients

Handling and freezing gametes and embryos from patients who are HIV-positive carries a risk of cross contamination to samples from HIV-negative patients and health workers involved in assisted reproduction. Universal precautions should be employed at all times. It is recommended that samples from patients with known or suspected blood borne viruses are handled in a separate laboratory with equipment (e.g. incubators, flow hoods, cryostorage tanks) dedicated to handling infected samples⁵⁷. This is likely to become mandatory after the implementation of the European Tissue Cells Directive. The Human Fertilisation and Embryology Authority (HFEA), which regulates assisted conception clinics, currently requires all patients undergoing assisted conception to be screened for HIV, hepatitis B and C before undergoing treatment. Gametes and embryos from patients with known viral infections have to be cryopreserved in separate tanks.

Demand for fertility care

It is difficult to estimate the demand for reproductive care amongst HIV-positive patients. A UK audit of demand for assisted reproduction techniques (ART) in HIV-infected patients found that 16% of men and 4% of women attending HIV specialist clinics had enquired about fertility treatment. Following the Human Fertilisation and Embryology Authority recommendation of compulsory HIV, HBV and HCV screening prior to offering ART, 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 minimise cost and travelling.

Key points and recommendations

(based on British Fertility Society Practice and Policy Document 2003⁴²)

- HIV-positive women and their partners planning to have children should receive pre-conceptual counselling on HIV transmission risks, their long term health and the possible effects of antiretroviral medication on the foetus – **IV**.

Management of couples where the male is HIV-positive

- Protected intercourse should be encouraged at all times
- Both partners should undergo a sexual health screen and fertility screen.
- If there are no abnormalities in the female or seminology, the couple should initially be offered natural cycle insemination with washed sperm
- Superovulation with insemination or IVF should be considered if conception has not occurred after 3 – 6 cycles of treatment.
- Sperm washing should be combined with ovulation induction, IVF or ICSI if other fertility factors are identified.

- Sperm should be centrifuged in a density gradient according to published protocols and all samples tested for the presence of HIV RNA before being used for insemination.
- To avoid cycle cancellation due to the sample testing positive post washing, a sample of washed and tested sperm should be frozen as a back up.
- Couples should sign a consent form before treatment confirming they understand the technique 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 6 months after last treatment) and paediatric outcome.

Management of couples where the female is HIV-positive

- Protected intercourse should be encouraged at all times
- Couples should be advised on the method of timed insemination into the vagina of sperm ejaculated into a condom free of spermicides
- Fertility investigations should be initiated when pregnancy is not achieved between 6 and 12 months of self insemination. In women with a history suggestive of tubal disease or anovulation, fertility investigations should be considered earlier.
- Assisted reproductive techniques (IUI, IVF or ICSI) should only be offered within research centres equipped to carry out procedures on patients with HIV and trained to audit outcome, as little is known of the impact of invasive procedures such as intrauterine insemination, oocyte retrieval and embryo transfer on vertical transmission risk
- Treatment should be planned to minimise any risk of multiple pregnancy i.e. controlled superovulation, maximum of two embryos transferred.
- When the male partner is also infected with HIV, sperm should be washed to reduce the risk of transmitting mutated resistant HIV strains to the female partner and offspring.
- Antiretroviral medication should be discussed with the treating HIV physician and adjusted pre-conceptually according to BHIVA recommendations¹². If she is not on medication, a plan should be made to initiate this at the latest by the third trimester. Known teratogenic agents such as efavirenz must 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 couple⁵⁷. The treating HIV physician should be asked to sign the Welfare of the Child form in preference to the GP as 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 injecting drug use.
- Units electing to treat patients infected with HIV on HAART should monitor short and long-term paediatric outcome to identify any potential adverse effects of antiretroviral therapy at the time of conception on the child.

Sexual dysfunction in HIV positive men and women

Men (and women) commonly report sexual difficulties in the presence of HIV. This ranges from the loss of desire, to difficulties in establishing and maintaining partnerships to specific erectile dysfunctions.

Erectile Dysfunction: Investigation and Management

Erectile dysfunction (ED) is a common problem and the prevalence increases with age.⁵⁸ There is some but little evidence that HIV negative MSM are more likely to present with an erectile problem.^{59 60} However there have been many reports of an increased prevalence of erectile difficulties in HIV infected MSM,^{60 61 62 63 64 65} which may contribute to unsafe sex practices⁶². 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 study⁶⁸ identified only protease inhibitors as an associated factor, other studies have confirmed a higher prevalence in patients not on HAART or on non-PI containing combination therapy regimens.^{60 63 64}

The European Association of Urology has recently updated guidelines on the investigation and management of ED⁶⁶ and other recommendations have also been published in the BMJ⁶⁷. An overview of the management of HIV infected men with erectile problems was also published in 2002.^{68 69} 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 antidepressants, anti-psychotics, anabolic steroids, megestrol, lipid lowering agents and recreational drugs including anabolic steroids, alcohol and psychoactive substances have all been implicated.⁷⁰ 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 contra-indicated 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 metabolised by the liver by cytochrome P-450 3A4⁷¹. Interactions with erythromycin, ritonavir, and ketoconazole have all been reported and shown to increase significantly the drug levels of sildenafil or other PDE5Is⁷¹. Therefore other drugs that inhibit this system may be predicted to have a similar effect and should be used cautiously (including all protease inhibitors, other macrolides but not azithromycin⁷² 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 25mg over a 48 hour period. Based on these findings, it is suggested that the vardenafil dose should not exceed 2.5mg in a 72 period, and that the tadalafil dose should not exceed 10mg in 72 hours.⁷³ (<http://www.hiv-druginteractions.org>).

No studies on the effects of the currently licensed NNRTIs on PDE5Is have been published (efavirenz, nevirapine) but inducers of cytochrome P-450 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 concurrently⁷⁴.

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 al⁷⁵ 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. This relationship between high-risk behaviours, possible HIV transmission and PDE5I use has been recently highlighted in the US⁷⁶. 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 antiretroviral agents have been described with other currently available classes of drugs used to treat erectile dysfunction.

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 as 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, and may cause local side effects including urethral pain, and may have a less reliable clinical effect, but may be more acceptable than administration by injection.

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 protease inhibitors, 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 contra-indicated when using PDE5 inhibitors.
- A full recreational drug history is an important part of the assessment of erectile dysfunction. Patients should be counselled on safer sex, possible drug interactions, and contra-indications to PDE5 inhibitor use.

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.

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 ejaculation⁷⁷. Guidelines on the management and investigation of rapid (premature) ejaculation and retarded (delayed) ejaculation have been published by BASHH^{78 79}. The treatment of retarded ejaculation in the context of neuropathy may be extremely difficult and may be exacerbated by concomitant use of antidepressants to treat the neuropathic pain but it may have a psychological cause⁸⁰.

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^{60,79}. Although hormonal abnormalities can affect desire and have also been described in patients on anti-retrovirals^{80 81 82} there has been no causal link firmly established and the individual often cites psychological reasons as the putative cause^{79 80}. However a review of medications that may cause hormonal disturbance (sex steroids, prolactin and thyroid) 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 may have increases in serum estradiol, which may be a cause of loss in sexual desire^{80 81}, and may respond to testosterone therapy⁸³.

With HAART, and with the reduction in the prevalence of late-stage HIV disease, it is likely that the prevalence of hypogonadism has decreased⁸⁴. 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 US, researchers found that 17% of the men had low testosterone levels and another 16% had borderline levels - an increased prevalence relative to the general population⁸⁵. Low plasma testosterone was related to increased age, advanced HIV, higher body mass index, and lipodystrophy. All hypogonadal subjects in this study had evidence of a central origin with decreased follicle-stimulating hormone (FSH) and luteinizing hormone (LH). 63% of those patients who received androgens reported satisfaction with this therapy.

However analysis of a cohort of men with sexual problems published in 2006⁷⁶ did not find hypogonadism to be a common finding (although a raised estradiol was), despite low sexual desire being a common presenting complaint. A questionnaire survey of HIV positive MSM in another central London clinic⁸⁶, showed 41% of sampled men (10/34) 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, TSH, PRL), and an MRI of the pituitary fossa (in particular 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

approximate to normal physiologic 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-physiologic levels. However some of the topical preparations can cause local irritation and the patient may prefer injections.

There is a potential for inducers of cytochrome P-450 3A4 such as ritonavir, to increase the levels of some androgen preparations (<http://www.hiv-druginteractions.org>).

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

Key points and recommendations

- Guidelines for the management of rapid and delayed ejaculation have been issued by BASHH and other organisations^{77 78} and 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 anti-retroviral agents. **III**
- Lowered sexual desire may have a psychological basis (in both men and women) but warrant hormone measurements to exclude an organic cause. **III**

Women and Sexual Dysfunction

Very little has been published on sexual dysfunction and 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)⁸⁷ and therefore presumably problems are under-diagnosed and under-treated.

There are reports of high prevalence rates in women with HIV^{88 89 90 91} 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 antiretroviral therapy 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 use⁸⁷.

It is important that women are asked about any problems, and then an appropriate history and examination performed, and referred to a healthcare provider with expertise in female sexual dysfunction.

Organic causes of FSD are comparable to organic male dysfunctions and may be caused, for example, by neuropathy (HIV or drug induced), endocrine disturbances, and atherosclerosis.⁸⁷

Key points and recommendations

- Female sexual dysfunction 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 referred if necessary. IV
- Psychological issues are often a key component to such problems. III

HIV, cervical and anal pre- cancers and cancers

Cervical intraepithelial neoplasia (CIN) and cervical screening

Introduction

Both cervical cancer and the pre-invasive lesion of the cervix, cervical intraepithelial neoplasia (CIN), are significantly more common in HIV positive women compared to HIV negative women.^{92 93} The risk of having CIN in the setting of HIV appears to be related to the degree of immunosuppression.^{91 94} The development of cancer of the cervix from pre-invasive lesions can take up to 10 years in immunocompetent women and this forms the basis of cytological screening programmes which target detection of such pre-invasive lesions. It is clear that cytological screening is as effective in HIV positive women when compared to HIV negative women.⁹¹

Since 1993, invasive cervical cancer in HIV-positive women has been classified as an AIDS-defining illness.⁹⁵ World wide, cervical cancer is the second most common cancer in women,⁹⁶ 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.⁹⁷

Role of human papilloma virus (HPV)

The role of HPV in the pathogenesis of cervical cancer and CIN is now well established.⁹⁸ Studies have led to the classification of HPV types according to oncogenic risk.⁹⁹ It is known that HIV-positive women have a higher prevalence of cervical HPV infection than HIV-negative and this is further increased in women with lower CD4 counts.¹⁰⁰ HPV infection is also more persistent in HIV-positive women¹⁰¹ particularly with the more oncogenic types.¹⁰²

As 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) has recently been licensed in the USA for use in women. There are no current data around safety or efficacy of such vaccines in HIV-positive patients and studies are awaited.

Impact of HAART on cervical disease

There have been dramatic reductions in morbidity and mortality related to HIV following the introduction of Highly Active Antiretroviral Therapy (HAART).¹⁰³ As women live longer in the post-HAART era, there is potentially longer time for 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 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.^{104 105} Heard et al found that despite regression of CIN with HAART there was

persistence of HPV¹⁰⁶. A further Italian study noted no effect on HPV following initiation of HAART¹⁰⁷ 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 regression¹⁰⁸ and others showing no positive impact.¹⁰⁹ 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.

Cervical screening in HIV infection

Due to 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 [19] 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 little data regarding the prevalence of cervical lesions in sexually active HIV positive adolescents who may have been immunosuppressed for many years. There may therefore be a need for more intense surveillance on a case-by-case basis.

The use of newer screening techniques for cervical screening

Liquid based cytology (LBC) is now the preferred technique for cervical screening and is recommended by the NHSCSP¹¹⁰ and the National Institute of Clinical Excellence (NICE). This technique is currently being rolled out nationally across the NHS Cervical Screening Programme. 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 liquid-based cytology 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.

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 done (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 is limited data on the effect of HAART on the natural history of disease and so management of women should be the same whether receiving therapy or not.- II

Anal cancer

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.¹¹¹ In the general population anal cancer mortality rates are about 30% of these.¹¹⁰ 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 of invasive anal cancer for men and women with HIV infection of 37.9 and 6.8 respectively.¹¹² However, receptive anal intercourse is 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 men who have sex with men (MSM) at the present time remains unclear.^{111,113,114} 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).¹¹⁵ Data from the entire Chelsea and Westminster Hospital, London, HIV+ve cohort showed rates of anal cancer of 60 /10⁶ 1984-2003, which was 120 times higher than an age, sex, and regionally matched population.¹¹⁶ Higher rates of 92 /10⁶ 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.^{117,118} 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.

Natural history

Anal cancer shows many similarities to cervical cancer; in that human papillomavirus (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 & 81% (all men), 95 & 88% (women), and 98% (MSM).^{119,120} 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, 11, can be detected alone in a small minority (~2.5%) of anal cancers [9,10]. It should also be noted that current cigarette smoking is also a significant risk factor for anal cancer, both in men (OR 3.9 [95%CI, 1.9-8.0]) and women (OR 3.8 [95%CI, 2.4-6.2]).¹¹⁹

HPV is a very frequent sexually transmitted infection, which is usually asymptomatic. Prevalence rates of anal HPV infection in HIV-ve MSM are 50-60% across all age groups.¹²¹ Most anogenital HPV infections are transitory, resolving spontaneously within ~9 months, although longitudinal data on anal HPV infections in HIV-ve MSM is sparse to date. In general persistent HPV infections are more frequent in persons over thirty 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, is not known at the present time.

The anal canal has a transformation zone (TZ) at the junction of the anal squamous and rectal columnar epithelia¹²², similar to the cervix, and thus anal cancer probably arises due to high-risk (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.¹²³

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.^{121,124} AIN can be classified as in the original Richart CIN classification, i.e. AIN1, 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 an ~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.^{125,126}

Natural history studies of anal pre-cancer in HIV+ve MSM have been conducted in the pre-HAART era.^{127, 128} Persistent HPV was strongly associated 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 counts.¹²⁹

Are there tests that can detect anal pre-cancer?

Anal warts are frequent encountered 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 HPV11 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.¹²⁸ 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+ve, and where random biopsies from each anal canal quadrant were taken, these showed 16/47 (34%) to have AIN 2/3, and 3/47 (6.4%) to have invasive cancer.¹³⁰

AIN affecting the peri-anal skin, perineum, or natal cleft can produce symptoms of itching and soreness. It also often produces recognisable 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, and many series attest to its utility.^{122,129,131} Colposcopy uses techniques which are similar, but distinct to those used for examination of the cervix.¹³² After visualisation 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, which is similar for the cervix, is the accuracy and reproducibility of these various diagnostic techniques. All have downsides; cytology tends to undercall diagnoses compared to biopsy,^{123,129-131} colposcopic directed biopsies may miss the worst histologic lesion,¹²³ and histopathological reporting may be inaccurate.¹³³

Various ancillary tests could be proposed for the diagnosis of AIN which need further research and evaluation. HPV tests, in particular detection of high risk HPV types, seem a logical proposition, but in reality these are too sensitive and have a very low positive predictive value.¹³¹ Tests with good operational characteristics for 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 liquid based cytology samples.¹³⁴

Are there treatments for anal pre-cancer, and are they effective?

The current definitive treatment for CIN 3 is excision of the cervical transformation zone. Unfortunately the anatomy and complex physiology of the anal canal precludes any similar such 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.^{123,135,136} These include treatments that are evidence-based for genital warts, including podophyllotoxin, trichloroacetic acid, imiquimod, and electrosurgery, although the evidence base for using these treatments for genital warts in HIV infected subjects is much smaller. However, the number of published trials at present that have actually systematically examined treatments for AIN is tiny.^{137,138} There is a particular dearth of data on the outcomes of the medical therapies referred to above.

Chang et al described the outcomes of a single outpatient electrosurgical treatment of AIN 2/3 during the period 1995-1999 performed with sedation and often a field block.¹³⁶ In HIV+ve men over a mean follow-up of 29 months 23/29 (79%) developed a recurrence of their disease. Goldstone et al described the outcomes of outpatient infrared coagulation therapy of localised AIN 2/3 in HIV+ve men during the period 1999-2003 performed under local anaesthesia.¹³⁷ 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 subject.¹³⁹ Although this is could be possible, there is no data to justify the assertion.

There has been debate whether the use of ART affects the prevalence of AIN. A recent study of 92 HIV+ve men used multivariate regression analyses to evaluate risk factors for histological AIN (all grades), and concluded that nadir CD4 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) [30]. Larger studies would allow similar analyses restricted to AIN 2/3.

Current uncertainties on systematic testing for anal pre-cancer in HIV+ve men and women

There are many issues in this area, even in terms of terminology. The term screening should be properly used to describe the application of a preventive technology to an entire population, or a defined subset 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 the sub-groups HIV+ve MSM, heterosexual males, and women.

There are already wide differences of opinion in this area. Whereas one group concluded that testing HIV+ve MSM with anal cytology every 2 years “offers quality-adjusted life expectancy benefits at a cost comparative with other accepted clinical preventive interventions” [29], 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.”¹⁴⁰

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+ve subgroups, MSM, females, and heterosexual males 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 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+ve subgroups, MSM, females, and heterosexual males?

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 to report any lumps noticed in the anal canal – IV

Psychological aspects of HIV and Reproduction

The desire to conceive and parent is universal, for both men and women. 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 for both men and women.

Psychological issues of HIV and Reproduction

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

1. Safer sexual behaviour to prevent transmission of HIV to others and risk behaviours and behavioural patterns
2. Pregnancy and HIV.
3. Fatherhood issues
4. Emotional Health

Safer sexual behaviour to prevent transmission of HIV to others and 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 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 continues¹⁴¹ counselling interventions (with follow up booster sessions) can effectively reduce risk behaviours (and subsequent STI infections).^{142,143} Community based interventions have some effects¹⁴⁴, while there is evidence for and against the efficacy of peer programmes.¹⁴⁵

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 sexually transmitted infections
 - Pregnancy and parenting in the presence of HIV

Ante-natal HIV testing

The availability of interventions to dramatically reduce infant infection has prompted a 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.¹⁴⁶ 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 generalised 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 advised a routine offer of HIV testing in pregnancy. Different centres have either trained all midwifery staff on HIV issues, appointed an HIV specific midwife or counsellor, integrated HIV testing into the routine batter 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 (antiretroviral treatment to prevent mother to child transmission, caesarean section and avoidance of breastfeeding). Treatment choices and decision making is a complex process. This is enhanced by the presence of continuity of care, a dedicated carer knowledgeable in HIV and an opportunity to explore options and revisit decisions.

Couple testing and couple counselling is seen as cost effective,¹⁴⁷ 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 gay and heterosexual) have reproductive concerns and find these difficult to raise in clinics.¹⁴⁸ These concerns should be discussed with HIV positive men and women.

Family Planning and Termination of Pregnancy

HIV provision in family planning and termination clinics lags behind ante-natal provision, with little rationale. Ideal services should make such testing routinely available for all family planning and termination clinic attendees.¹⁴⁹

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 VCT should be counselled on contraception and safer sex as well as prepared for HIV testing. Quality counselling has been shown to be effective.¹⁵⁰ 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 most effective in 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 varied. Evidence suggests that male services are not provided, although the literature suggests that it should be made available and integrated into services.

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 treatments may bring anxiety and emotional upheaval.

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; Goldstein¹⁵¹ noted that approximately 20% of HIV positive parents in the USA had parenting concerns (no similar figures for 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 partum¹⁵²
- Adherence
Parents (particularly mothers) prioritise 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 decision to conceive, treatment options, and parenting decisions. The availability of antiretroviral treatment has had an impact on such decisions and the risk of vertical transmission plays a key role in these decisions^{153 154}
- Custody plans.
Planning for the future is challenging for parents with HIV, noted as being a slow and unstable process. Rotheram-Borus¹⁵⁵ found that 44% of parents died without custody plans, and that parents frequently changed their plans, the majority of which involved family members.

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, hospitalisation, medication side effects, parental illness/absence/death and educational/learning opportunities which 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.

Fatherhood issues

It is trite to assume that reproduction should be totally focussed on women. Men, gay 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.¹⁴⁷ Fatherhood desires are high, although

some studies show that in couples with HIV there may be differences in desires.¹⁵⁶ 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.¹⁵⁷ Decision making, help seeking and resource provision should be made available to men as well as women.

Emotional Health

Sexual and reproductive health, fertility and infertility issues and relationships are all emotionally laden experiences. The mental health literature notes that often progressing through care may result in raised anxiety, mood fluctuation, depression and emotional pain. Furthermore there is some evidence that heterosexual men with HIV are less likely to be referred to mental health provision.¹⁵⁸ There may be additional anxiety linked to the medical process and procedures, 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.

Key points and recommendations

- Psychological considerations are key 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 behavioural aspects of sexual and reproductive health
- An updated understanding of HIV prevention, risk behaviour, reproduction and mother/father perspectives should feed into policy and service provision.

HIV superinfection

Several sexual HIV harm reduction strategies have arisen in the era of ART particularly in the gay community. These include disclosure of status and sero-sorting of partners so that those with the same status may engage in unprotected anal intercourse. As specialised conception services are limited, sero-concordant partners wishing to conceive are often faced with the dilemma of whether to consider unprotected intercourse.

The overall extent to which superinfection occurs has not been quantified and there is concern by some community activists that the risks are often overstated. Because of this it was felt that a section on superinfection should be included in these guidelines to allow for review of the recent literature. Healthcare workers should continue to provide counselling against the possible risks of superinfection and, perhaps more importantly, other sexually transmitted infection for individuals of the same serostatus. It is clear however that PLHA have to balance this advice with other life choices.

The theory of HIV superinfection, defined as re-infection with a second strain of HIV after the first infection has been established through seroconversion, has been mooted since the early years of the HIV epidemic, although the first case reports of apparent superinfection did not occur until 2002.

Superinfection or dual infection?

Multiple infections can occur at three distinct phases of HIV disease. It can occur during primary infection (known as simultaneous infection) if two different strains of HIV infect the same cell. It 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 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.

In order to definitively distinguish between dual infection and superinfection, several criteria must be met. Current research into superinfection has faced several important limitations which calls into question whether any of the case reports so far really are superinfection. In the vast majority of reported cases of superinfection, a source partner for the second virus was not identified. Without a source partner, the timing of exposure cannot be confirmed, and there can be no absolute certainty that the second virus was acquired after seroconversion. In most case reports, therefore, it is possible that the individuals who were apparently superinfected were actually dually infected.

In addition, current limitations in detecting minority populations of viral variants mean that it cannot be virologically proven that the second virus was not present at baseline. Many case reports of apparent superinfection have not been confirmed using ultra sensitive assays to detect dual infection at baseline. For these reasons, some superinfection researchers prefer to label what appears to be superinfection as 'sequentially expressed dual infections'.

Timing of superinfection

The first reported evidence of apparent superinfection came from studies of monkeys in 1987.¹⁵⁹ More recent research suggests that there may be a window of time in which nonhuman primates are susceptible to superinfection. Otten and colleagues¹⁶⁰ found that pig-tailed macaques could be successfully reinfected with a second viral strain up to four weeks after initial infection. Attempts to re infect the macaques were unsuccessful at 8, 12, 14, and 72 weeks after infection. The biological mechanisms that block superinfection after four weeks in this animal model are not yet known.

A similar pattern suggesting a 'window of susceptibility' has been described in superinfection research in humans. Up to 24 cases of apparent superinfection in HIV-infected individuals have been reported.¹⁶⁰⁻¹⁶⁹ In most of these cases, the second virus appeared within the first three-and-a-half years of HIV infection. However, in three cases, the second virus may have appeared up to twelve years after initial infection.^{168, 175-6}

It is currently theorised that the 'window of susceptibility' to superinfection is governed by neutralising antibody response. Smith and colleagues¹⁶¹ and McConnell and colleagues¹⁶² have both presented data suggesting that recently-infected individuals who were apparently superinfected through continued HIV exposure had slower and weaker neutralising antibody responses than recently-infected individuals who were not superinfected through continued HIV exposure.

Risk for superinfection in recent HIV infection

The risk of apparent 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 and colleagues¹⁶⁴ found a 5% incidence rate of HIV-1 clade B superinfection within six to twelve months of initial infection among recently infected gay men with frequent partner change. Similarly, Grant and colleagues¹⁶⁶ estimated a first-year apparent superinfection incidence rate amongst recently infected gay 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 apparent superinfection during the first year of HIV infection may be comparable to the overall incidence of new HIV infections seen amongst high-risk populations.

Risk for superinfection in chronic HIV infection

No apparent superinfection cases have been reported among chronically infected individuals - either untreated or on antiretroviral therapy - in cohort studies. Gonzales and colleagues¹⁶³ looked for superinfection in 718 people - representing 1072 person-years of follow-up - in a clinic cohort, the majority of whom were on antiretroviral therapy found no evidence of it. However, no data on continued HIV exposure was reported. Tsui and colleagues documented high-risk behaviour among injecting drug users (IDUs) over 215 person-years of observation and also found no evidence of superinfection.¹⁶⁴ Grant and colleagues¹⁶⁵ found no evidence of superinfection among HIV-positive couples with genetically distinguishable virus at baseline after 233 person-years of follow-up, representing an estimated 20,859 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 has been HIV-negative.

Two recent case reports suggest that superinfection may still occur in chronically infected individuals, either on or off antiretroviral therapy.

Pernas and colleagues described apparent dual superinfection with drug-resistant virus in an HIV-infected individual at least twelve years after initial infection. The individual admitted high-risk behaviours that included both IDU and unprotected sex. It is not clear from the case report whether the individual was on ART at the time of apparent superinfection.¹⁶⁶

Blick and colleagues described a chronically infected individual becoming apparently superinfected with multidrug-resistant HIV-1 at least seven years after initial infection, and whilst he was taking (non-suppressive) ART. Subsequent formation of a pan-resistant recombinant HIV-1 was observed. In this case, the probable source was identified as the individual's long-term male partner, although both men reported regular unprotected sex and non-IDU drug use with many partners.¹⁶⁷

These recent case reports suggest that although initial HIV infection may provide a degree of protective immunity against superinfection in chronically infected individuals, superinfection may occur at any time regardless of antiretroviral therapy or exposure risk.

Superinfection and drug resistance

At least five of the apparent superinfection cases have reported that a wild-type virus was replaced by a drug-resistant or potentially drug-resistant strain.^{164,167,169 175-6} Data from the Health Protection Agency on acquired primary drug resistance in the United Kingdom¹⁶⁸ suggest that the prevalence of antiretroviral-naïve individuals with HIV in the United Kingdom who are resistant to at least one anti-HIV drug has declined from a peak of 16% in 2002 to 9% in 2004. Although the prevalence of HIV-positive individuals acquiring drug resistant strains of HIV via superinfection is unknown, it is likely to reflect trends in acquired drug resistance amongst HIV-negative individuals. It should be noted, however, that in another three of the reported cases of apparent superinfection, the majority population of drug-resistant virus was replaced by a drug-susceptible strain. However, the initial drug-resistant virus would still be archived in so-called 'sanctuary sites' and may reappear due to selective drug pressure.

Consequently, should superinfection occur it is possible that future antiretroviral therapy may be compromised. In addition, there is a strong possibility that baseline resistance testing - which is currently recommended in all newly diagnosed individuals - may be underreporting minority quasispecies acquired during dual or superinfection.

Superinfection and prognosis

Smith and colleagues¹⁶⁹ reported the immunologic and virologic outcome of a recently-infected gay man initially diagnosed with a drug sensitive strain of subtype B HIV but subsequently apparently superinfected with a strain of subtype B resistant to two classes of antiretroviral drugs. This resulted in a significant increase in the individual's viral load and a fall in his CD4 cell count. Similar outcomes have been reported by Booth and colleagues in similar circumstances¹⁶⁹ and in the more recent case reports by Pernas and colleagues and Blick and colleagues.¹⁷⁵⁻⁶

Even in the absence of drug resistance, it is possible that infection with a second strain of HIV may affect clinical progression, although data are lacking. Gottlieb and colleagues from the University of Washington reported that they had identified four individuals with dual HIV infection that had progressed to AIDS or death within two years of infection.¹⁷⁰ Another study in South African female sex workers found that dual infection may lead to a higher viral load set-point.¹⁷¹

Although dual or superinfection can be associated with a poorer prognosis, it remains unclear whether this is due to viral or host factors.

Key points and recommendations

- The risk of HIV superinfection may diminish with the time from initial infection. Although it appears more likely in the first three years following seroconversion, a risk persists after this. **II**
- All HIV-positive individuals should be counselled regarding the risk of superinfection, particularly those who choose to sero-sort (i.e. have unprotected intercourse with partners who are also HIV-positive). **II**
- Where there is limited access to specialised conception services sero-concordant couples who wish to conceive should be counselled regarding the risk of superinfection. **III**

HIV, Disclosure and Criminalisation

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 health care professionals and all those involved in the care of HIV positive people be 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 review¹⁷² and further guidance will be made available as it published. The briefing paper focuses on the responsibilities and duties of health care 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 is 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 relationship with patients in order to allow them safe space to examine disclosure issues will ultimately lead to far more beneficial outcomes than the threats of litigation.

Further useful information on HIV and criminalization is available on the Terence Higgins Trust website¹⁷³

Key Points and recommendations

- Health care staff should be aware about 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

Sexual and Reproductive Health issues for Women

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 have been made to the management of HIV in pregnancy for which guidelines exist. These are available on the BHIVA website, are updated regularly and should be consulted as appropriate¹⁷⁴.

Contraception for Women with HIV

Introduction

As the health of women and men living with HIV continues to improve with the use of antiretroviral therapy (ART), this may result in changes in decision-making around sexuality and reproduction. 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 FFPRHC documents, which provide evidence based guidance on a variety of contraceptive methods (www.ffprhc.org.uk). In addition, the Clinical Effectiveness Unit of FFPRHC has produced the UK Medical Eligibility Criteria for Contraceptive Use (UKMEC) [2] 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. The eligibility criteria range from 1, with 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)

Table 1

UKMEC Category	Definition of Category
1	A condition for which there is no restriction for use of the method
2	A condition where the advantages of using the method generally outweigh the theoretical or proven risks
3	A condition where the theoretical or proven risks generally outweigh the advantages of using the method
4	A condition, which represents an unacceptable health risk if the contraceptive method is used

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

General Contraception Management

Development of managed care networks or integrated sexual and reproductive health 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 to make an informed choice. Women should be provided with the most effective method of contraception which 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 license 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 antiretroviral therapy.

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 sexually transmitted infections (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 post-exposure prophylaxis following sexual exposure (PEPSE).

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

Table 2

Percentage of users becoming pregnant in first year of use of method, with perfect use of the method

Method	Perfect use
Combined Oral Contraceptive	0.1
Progestogen Only Oral Contraceptive	0.5
Injectable	0.3
Implant	0.05
Male Condom	2
Female Condom	5
Diaphragm	6
Copper Intrauterine Device	0.6
Levonorgestrel Intrauterine System	0.1
Female Sterilisation	0.5
Male Sterilisation	0.1

Barrier methods

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% respectively, 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% respectively can be anticipated.¹⁷⁵ Latex and non-latex male condoms have been shown to offer similar efficacy in pregnancy prevention.¹⁷⁶ Male condom use offers a high degree of protection against HIV sexual transmission¹⁷⁷ and STIs¹⁷⁸ if used correctly. The consistent use of a condom for each episode of vaginal intercourse in sero-discordant couples reduces the risk of HIV transmission by 80%.¹⁷⁹ 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.¹⁸⁰ Laboratory evidence suggests that female condoms also provide protection against STIs^{181,182} although widespread use of female condoms has been limited.

Nonoxinol-9 (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, and does not reduce pregnancy rates, when compared to non-spermicidally lubricated condoms.¹⁸³ Condoms lubricated with N9 are therefore not recommended.¹⁸⁴

Dual protection or “doubling up”, using both barrier and either hormonal or intra-uterine contraception is the most effective way to both prevent pregnancy and to 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 categorises 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.

Diaphragm 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 remains exposed, thus permitting potential viral transmission. In addition, caps and diaphragms are recommended to be used with nonoxinol-9, and as outlined above, 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).

Hormonal Contraception

Hormonal contraceptive methods are amongst the most widely used family planning methods worldwide. They include the combined oral contraceptive pill (COC), the combined

contraceptive patch, the progestogen-only pill (POP), injectable progestogens and the progestogen implant.

Combined oral contraceptive pill (COC)

The combined oral contraceptive pill (COC) is the most commonly used contraceptive method by women in the general UK population aged 16 to 49 years.¹⁸⁵ In current practice, low dose COCs containing 20-35 micrograms (μg) ethinyl oestradiol (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 antiretroviral therapy (ART) and is categorised as UKMEC 1. There is limited evidence suggesting no association between COC use and changes in HIV viral load or CD4 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 risk¹⁸⁶ 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 HIV¹⁸⁷ Hormonal contraceptives cannot replace the ability of barrier methods to prevent transmission of HIV and other sexually transmitted infections and condoms should therefore be recommended in conjunction with any hormonal method.

For women taking HAART, some antiretroviral drugs may potentially reduce the efficacy of hormonal contraception (table 4). A few agents increase contraceptive steroid levels, but more commonly levels are reduced. Antiretroviral drugs such as protease inhibitors (e.g. lopinavir, ritonavir) and non-nucleoside reverse transcriptase inhibitors (e.g. nevirapine) are metabolised 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 combined oral contraception may be reduced by such drugs. Unfortunately, few studies have been published which investigate the pharmacokinetics of oestrogen and progestogen with antiretroviral drugs and none on the effect on contraceptive efficacy. Serum concentrations of ethinylestradiol (EE) were reduced when women taking a 50 μg EE COC were also using ritonavir, but no pregnancies have been documented.¹⁸⁸ 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 ethinylestradiol (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.¹⁸⁹ Some women may opt to use an alternative method of contraception which is not affected by enzyme inducing drugs, such as an intra-uterine method, but this will not be acceptable to everyone. It is important to consider that use of a combined oral contraceptive, even with an enzyme inducer, is likely to confer better contraception than no contraception at all.

The COC is metabolised by the liver and its use in women with cirrhosis is considered UKMEC 3/4. Caution should also be exercised in women abnormal liver function due to co-infection with Hepatitis B and or C or history of alcohol mis-use.

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 TB for example. Use of rifampicin decreases the contraceptive effectiveness of the COC^{190 191} and an alternative or additional contraceptive method should be considered for such women.

Combined contraceptive patch

The transdermal patch delivers ethinyl oestradiol (20ug) and norelgestromin (150ug) daily, and is applied weekly for three weeks followed by a seven-day patch-free interval. A Cochrane systematic review concluded self-reported compliance was better with the patch compared to the COC although overall efficacy is similar for both methods. There are no current 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 combined oral contraception. 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.

Progestogen-only Pill (POP)

Traditional POP 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, not on HAART. Antiretroviral 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.

Long-acting injectable progestogens

These are depot medroxyprogesterone acetate (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. 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 FFPRHC guidance suggests discouraging women at high risk of low bone density from using DMPA¹⁹² HIV infection itself has been found to be associated with reduced bone density¹⁹³, and in addition, 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.

Progestogen-only subdermal 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.¹⁹⁶ Thus concomitant use of HAART reclassifies etonogestrel to category 2 in HIV positive women, and an additional contraceptive method may be recommended.

Intrauterine Contraception

Levonorgestrel intrauterine system (LNG-IUS)

The levonorgestrel-releasing intrauterine system (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 (micrograms) 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 concomitantly, to reduce virus transmission. The majority of women with a 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.

Copper Bearing Intrauterine Devices (Cu-IUD)

Copper bearing intrauterine devices act by preventing fertilisation and inhibiting implantation, and are used for between 5 and 10 years, depending on 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.¹⁹⁴ 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

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 hours of sexual intercourse or insertion of a copper intrauterine device as an alternative if within 5 days (UKMEC1)

Levonorgestrel 1.5mg recently became available in the UK²⁰¹ and replaces previous regimens with 2 doses of 0.75mg. 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 FFPRHC²⁰¹ states that women using liver enzyme-inducing drugs should be advised that an emergency IUD is the preferred option for emergency contraception as 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 (1.5mg), total dose 3mg, as soon as possible and within 72 hours of UPSI. 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 outwith the product licence. Women should be advised of this and this should be documented in the notes.

Table 3: Summary of UKMEC Categories for Use of Common Reversible Methods of Contraception in women with or at risk of HIV

	COC	POP	DMPA	Impl	Cu-IUD	LNG-IUS	Condom	Diaphragm
High risk of HIV	1	1	1	1	2	2	1	3
HIV positive, not using ART	1	1	1	1	2	2	1	3
HIV positive, using ART	2	2	1	2	2	1	1	3

Table 4: Effects of Antiretrovirals on Hormonal Contraception¹⁹⁵

Drug	Effect on hormonal contraception	Notes
NNRTIs		
Efavirenz	Not fully studied – likely reduction in EE and progestogen	FDA Category D Additional or alternative contraceptive methods advised
Nevirapine	Decrease in EE and progestogen concentrations	Additional or alternative contraceptive methods advised
PIs		
Nelfinavir	Decrease in EE and progestogen concentrations	Additional or alternative contraceptive methods advised
Saquinavir		
Fosamprenavir		
Lopinavir		
Atazanavir		
Ritonavir	Decrease EE concentration	Avoid oestrogen-based contraceptives (COC)
Indinavir	No clinically significant interaction	Complex interaction when used with ritonavir
NRTIs		
Abacavir		

Didanosine	No evidence for PK interactions with EE and progestogens identified
Lamivudine	
Emtricitabine	
Zidovudine	
Stavudine	

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 nonoxinol-9 spermicide should be avoided.
- Due to 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 3mg stat is recommended

Sexual and reproductive health issues for men

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 transmission of other STDs from men to women, from women to men and between men.¹⁹⁶
¹⁹⁷ ¹⁹⁸ The use of mineral oil-based lubricants with latex condoms should be discouraged, due to condom damage and increased breakage rates¹⁹⁹ in favour of water-based lubricants that do not contain nonoxynol-9. Although latex and polyurethane condoms such as Avanti™ appear equally efficacious at preventing pregnancy²⁰⁰ no comparative studies looking at HIV transmission has been published. There has been one randomised study that concluded that “thicker” latex condoms marketed for anal sex were no more effective than condoms of normal thickness²⁰¹

The use of microbicides such as nonoxynol-9 can cause a significant increase in genital symptoms and epithelial disruption,^{207, 202} may cause rapid rectal epithelial exfoliation²⁰³ and a major study in high risk women²⁰⁴ and a meta-analysis²⁰⁵ does not show any protection against STDs. Given the effects on the genital epithelium the use of nonoxynol-9 cannot be recommended except in groups at low risk of acquiring STIs and HIV.

Key points and recommendations

- Use of barrier contraceptives should be encouraged to prevent spread of HIV, super-infection 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.*
- The use of mineral oil based lubricants with latex condoms, and use of nonoxynol-9 should be discouraged.

Investigation and Management of Sub-fertility in Men

There is little published data on the direct effect that HIV/AIDS has on fertility and semen quality of infected men. However two studies that have been done have shown little effect of HIV (or hepatitis C virus) on sperm production^{206 207} compared to WHO criteria. One study in the pre HAART era, showed men with advanced disease not on zidovudine monotherapy had reduced sperm counts and an increased percentage in abnormal sperm forms but no significant impairment over CD4 counts of 200²⁰⁸. However there is single case report of reduced semen parameters in an individual whose semen was analysed prior and after HIV-1 seroconversion.²⁰⁹

The effect of specific anti-retroviral agents on human sperm production has not been published. One study²¹⁰ showed no adverse effect of HAART on sperm production but

* These include Medical Defence organisations, Terence Higgins Trust (UK-wide); National AIDS Trust (UK-wide); George House Trust (north-west England); and HIV Scotland (Scotland).

confirmed that those with CD4 counts <200 were more likely to have lower sperm counts. Another study looked at men on HAART requesting assisted reproductive technology 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 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 guidelines²¹¹ in the investigation and management of male sub-fertility in these men. Patients with low CD4 counts or advanced disease with abnormal semen should be advised that optimising anti-retroviral treatment with a rise in CD4 count may improve semen quality^{215, 216,212} 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.

Key points and recommendations

- There is no published evidence that specific antiretroviral agents affect male fertility.
- There is some evidence that men with advanced disease may have abnormal sperm production and therefore optimising 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.

References

- ¹ Mapping the Issues; HIV and other Sexually Transmitted Infections in the United Kingdom: Health Protection Agency 2005 available at http://www.hpa.org.uk/hpa/publications/hiv_sti_2005/default.htm
- ² HPA Annual Report: A Complex Picture :HIV and other Sexually Transmitted Infections in the United Kingdom: 2006 accessed at http://www.hpa.org.uk/publications/2006/hiv_sti_2006/pdf/a_complex_Picture_2006_last.pdf
- ³ A Mocroft, B Ledergerber, C Katlama, O Kirk, P Reiss, A d'Arminio Monforte, B Knysz, M Dietrich, A N Phillips, J D Lundgren, for the EuroSIDA study group Decline in the AIDS and death rates in the EuroSIDA study: an observational study. *Lancet*. 2003 Jul 5;362(9377):22-9
- ⁴ Simms I, Fenton KA, Ashton M, Turner KME et al. The re-emergence of syphilis in the UK: the new epidemic phases. *Sex Transm Dis*. 2005. In press
- ⁵ Nicoll A, Hamers FF. Are trends in HIV, gonorrhoea, and syphilis worsening in Western Europe? *BMJ*2002;324:1324-7.
- ⁶ French P, Ison CA, MacDonald N. Lymphogranuloma venereum in the United Kingdom. *Sex Transm Infect* 2005;81:97-98
- ⁷ Fleming DT, Wasserheit JN. From epidemiological synergy to public health policy and practice: the contribution of other sexually transmitted diseases to sexual transmission of HIV infection. *Sex Transm Inf* 1999;75:3-17.
- ⁸ Stamm WE, Handsfield HH, Rompalo AM, Ashley RL, Roberts PL, Corey L. The association between genital ulcer disease and acquisition of HIV infection in homosexual men. *JAMA* 1988; 260:1429-1433.
- ⁹ Fox KK, del Rio C, Holmes KK, et al. Gonorrhoea in the HIV era: a reversal of trends among men who have sex with men. *Am J Public Health*. 2001;91:959-964
- ¹⁰ data from National Study of HIV in Pregnancy and Childhood (NSHPC) available at <http://www.hpa.org.uk/>
- ¹¹ UK Collaborative Group on Monitoring the Transmission of HIV Drug Resistance: Analysis of prevalence of HIV-1 drug resistance in Primary infections in the United Kingdom *BMJ* 2001;322;1087-1088
- ¹² Hawkins, D.; Blott, M.; Clayden, P.; de Ruiter, A.; Foster, G.; Gilling-Smith, C.; Gosrani, B.; Lyall, H.; Mercey, D.; Newell, M-L.; O'Shea, S.; Smith, R.; Sunderland, J.; Wood, C.; Taylor, G. Guidelines for the management of HIV infection in pregnant women and the prevention of mother-to-child transmission of HIV [HIV Medicine](#), Volume 6, Supplement 2, July 2005, pp. 107-148(42)
- ¹³ Nandwani R on behalf of the Clinical Effectiveness Group of the British Association for Sexual Health and HIV (BASHH). 2006 United Kingdom National Guideline on the Sexual Health of People with HIV: Sexually Transmitted Infections. *International Journal of STD & AIDS* 2006; 17: 594-606
- ¹⁴ Nandwani R, Fisher M on behalf of the MSSVD HIV Special Interest Group. Clinical standards for the screening and management of acquired syphilis in HIV-positive adults. *International Journal of STD & AIDS* 2006; 17: 588-593.
- ¹⁵ 1. Fisher M, Benn P, Evans B et al, Clinical Effectiveness Group (BASHH). UK guideline for the use of post-exposure prophylaxis for HIV following sexual exposure. *Int J STD AIDS* 2006; 17:81-92. sexual intercourse (February 2006): http://www.bashh.org/guidelines/2006/pepse_0206.pdf

-
- ¹⁶ British HIV Association (BHIVA) guidelines for treatment and management of HIV and Hepatitis B co infection available at <http://www.bhiva.org/guidelines/2004/HBV/>
- ¹⁷ British HIV Association (BHIVA) guidelines for treatment and management of HIV and Hepatitis C co infection available at http://www.bhiva.org/pdf/2003/guides/BHIVA_HIV=HCV_coinfection.pdf
- ¹⁸ Rooney, G, Gilson, RJ Sexual transmission of hepatitis C virus infection
Sex Transm Infect 1998 74: 399-404
- ¹⁹ Tedder RS, Gilson RJC, Briggs M et al. Hepatitis C virus: evidence for sexual transmission. *Brit Med J* 1991;302:1299-1302
- ²⁰ Edwin J. Bernard. Sexual Transmission of Hepatitis C. *AIDS Treatment Update* 117 (Sept 2002) at <http://www.aidsmap.com/files/file1000701.pdf> accessed 11/05/07
- ²¹ Letter from Liam Donaldson on sexual PEP accessed 23/03/07 at: <http://www.i-base.org.uk/htb/v7/htb7-5/PEP.html>
- ²² Lyerly, A.D. and J. Anderson, Human immunodeficiency virus and assisted reproduction: reconsidering evidence, reframing ethics. *Fertil Steril*, 2001. 75(5): p. 843-58.
- ²³ Englert, Y., et al., ART in HIV-infected couples. Has the time come for a change in attitude? . *Hum Reprod*, 2001. 16: p. 1309-1315.
- ²⁴ Minkoff, H. and N. Santoro, Ethical considerations in the treatment of infertility in women with human immunodeficiency virus infection. *N Eng J Med*, 2000. 342: p. 1748-1750.
- ²⁵ The ESHRE Ethics and Law Task Force, Taskforce 8: Ethics of medically assisted fertility treatment for HIV positive men and women. *Hum Reprod*, 2004. 19: p. 2454-6.
- ²⁶ Frodsham LCG, B.F., Barton S and Gilling-Smith C Human immunodeficiency virus infection and fertility care in the United Kingdom – demand and supply. . *Fert Steril*, 2006. 85: p. 285-289
- ²⁷ Gray, R.H., et al., Probability of HIV-1 transmission per coital act in monogamous, heterosexual, HIV-1 serodiscordant couples in Rakai, Uganda. *Lancet* 2003. 357: p. 1149-1153.
- ²⁸ De Vincenzi, I., A longitudinal study of human immunodeficiency virus transmission by heterosexual partners. *N Engl J Med* 1994. 331: p. 341-346
- ²⁹ Luizzi, G., et al., Analysis of HIV-1 load in blood, semen and saliva: evidence for different viral compartments in a cross-sectional and longitudinal study. *AIDS*, 1996. 10: p. F51-56.
- ³⁰ Coombs, R.W., et al., Association between culturable human immunodeficiency virus type 1 (HIV-1) in semen and HIV-1 RNA levels in semen and blood: evidence for compartmentalisation of HIV-1 between semen and blood. *J Infect Dis*, 1998. 177: p. 320-30.
- ³¹ Zhang, H., et al., Human immunodeficiency virus type 1 in the semen of men receiving highly active antiretroviral therapy. *N Engl J Med*, 1998. 339: p. 1803-9.
- ³² Mandelbrot, L., et al., Natural conception in HIV-negative women with HIV-infected partners. *Lancet* 1997. 349: p. 850-851.
- ³³ Barreiro, P., et al. Benefit of antiretroviral therapy for serodiscordant couples willing to be parents. 7th International Congress on Drug Therapy in HIV Infection. 2004.
- ³⁴ Dunne, A.L., K.M. Mitch, and e. al.. Analysis of HIV-1 viral load in seminal plasma samples. *J Clin Virol* 2003. 26: p. 239-245.

-
- ³⁵ Mastro TD, De Vincenzi I. Probabilities of sexual HIV transmission. *AIDS*. 1996;10(suppl A):575-582
- ³⁶ Bagasra, O., et al., Detection of HIV-1 proviral DNA in sperm from HIV-1 infected men. *AIDS*, 1994. 8: p. 1669-1674.
- ³⁷ Vernazza, P.L., et al., Quantification of HIV in semen: correlation with antiviral treatment and immune status. *AIDS*, 1997. 11: p. 987-93.
- ³⁸ Quayle, A.J., et al., T lymphocytes and macrophages, but not motile spermatozoa, are a significant source of human immunodeficiency virus in semen. *J Infect Dis*, 1997. 176: p. 960-8.
- ³⁹ Quayle, A.J., et al., The case against an association between HIV-1 and sperm: molecular evidence. *J Reprod Immunology*. *J Reprod Immunology*, 1998. 41: p. 127-36.
- ⁴⁰ Kim, L.U., et al., Evaluation of sperm washing as a potential method of reducing HIV transmission in HIV-discordant couples wishing to have children. *Aids*, 1999. 13(6): p. 645-51.
- ⁴¹ Baccetti, B., et al., HIV particles detected in spermatozoa of patients with AIDS. *J Submicrosc Cytol Pathol* 1991. 23: p. 339-345.
- ⁴² Gilling-Smith, C. and P. Almeida, HIV, hepatitis B and hepatitis C and infertility: reducing risk. *Hum Fertil (Camb)*, 2003. 6(3): p. 106-12.
- ⁴³ Semprini, A.E. and S. Fiore, HIV and reproduction. *Curr Opin Obstet Gynecol*, 2004. 16(3): p. 257-62.
- ⁴⁴ Burgisser, P., et al., Swiss Cohort Study: Performances of five different assays for the quantification of viral load in persons infected with various subtypes of HIV-1. *J Acquir Immun Def Synd*, 2000. 23: p. 138-144.
- ⁴⁵ Marina, S., et al., Pregnancy following intracytoplasmic sperm injection from an HIV-1 seropositive man. *Hum Reprod*, 1998. 13: p. 3247-3249.
- ⁴⁶ Marina, S., et al., Human immunodeficiency virus type I-serodiscordant couples can bear healthy children after undergoing intrauterine insemination. *Fertil Steril*, 1998. 70: p. 35-39.
- ⁴⁷ Gilling-Smith, C., et al., HIV and reproductive care - a review of current practice. *BJOG*, 2006. 113: p. 1-10.
- ⁴⁸ Sauer, M.V., Sperm washing techniques address the fertility needs of HIV-seropositive men: a clinical review. *Reprod Biomed Online*, 2005. 10(1): p. 135-40.
- ⁴⁹ Fleming, D.T. and J.N. Wasserheit, From epidemiological synergy to public health policy and practice: the contribution of other sexual transmitted diseases to sexual transmission of HIV infection. *Sex Trans Inf*, 1999. 75: p. 3-17.
- ⁵⁰ Nicopoullou, J.D., et al., The effect of human immunodeficiency virus on sperm parameters and the outcome of intrauterine insemination following sperm washing. *Hum Reprod*, 2004. 19(10): p. 2289-97
- ⁵¹ Coll, O., et al., Pregnancy and HIV infection: A European consensus on management. *AIDS* 2002. 16((suppl 2)): p. S1-S18.
- ⁵² Brunham, R.C., et al., Chlamydia trachomatis, infertility, and population growth in sub-Saharan Africa. *Sex Transm Dis*, 1993. 20(3): p. 168-73.
- ⁵³ Brunham, R.C., et al., Gonococcal infection and human fertility in sub-Saharan Africa. *Proc Biol Sci*, 1991. 246(1316): p. 173-7.

-
- ⁵⁴ Frodsham, L.C.G., et al., In vitro fertilisation in HIV positive women: risk of mother to embryo viral transmission. *Hum Reprod*, 2004. 9 (Suppl. 1): p. 138.
- ⁵⁵ Frodsham, L.C., J.R. Smith, and C. Gilling-Smith, Assessment of welfare of the child in HIV positive couples. *Hum Reprod*, 2004. 19(10): p. 2420-3
- ⁵⁶ Gilling-Smith, C., Risking Parenthood? Serious viral illness, parenting and welfare of the child, in *Contemporary Ethical Dilemmas in Assisted Reproduction.*, S.F.S. C, Editor. 2006. p. 57-69.
- ⁵⁷ Gilling-Smith, C., et al., Laboratory safety during assisted reproduction in patients with blood-borne viruses. *Hum Reprod*, 2005. 20(6): p. 1433-8. Frodsham, L.C., J.R. Smith, and C. Gilling-Smith, Assessment of welfare of the child in HIV positive couples. *Hum Reprod*, 2004. 19(10): p. 2420-3
- ⁵⁸ Laumann EO, Paik A et al Sexual Dysfunction in the United States: prevalence and predictors. *JAMA* 1999; 281(6): 537-44
- ⁵⁹ Bancroft J. Carnes L et al Erectile and ejaculatory problems in gay and heterosexual men. *Arch Sex Behav* 2005; 34(3): 285-97
- ⁶⁰ Lamba H. Goldmeier D et al Antiretroviral therapy is associated with sexual dysfunction and increased serum oestradiol in men. In *J STD AIDS* 2004; 15(4): 234-7
- ⁶¹ Bancroft J Carnes L et al Unprotected anal intercourse in HIV-positive and HIV-negative gay men: the relevance of sexual arousability, mood, sensation seeking and erectile problems. *Arch Sex Behav* 2005; 34(4): 479-80.
- ⁶² Cove J and Petrak J. Factors associated with sexual problems in HIV-positive gay men. *Int J STD AIDS* 2004; 15(11): 732-6
- ⁶³ Collazos J, Martinez E et al Sexual dysfunction in HIV-infected patients treated with highly active antiretroviral therapy. *J Acquir Immune Defic Syndr* 2002; 31(3): 322-6
- ⁶⁴ Collazos J Mayo J et al Association between sexual disturbances and sexual hormones with specific antiretroviral drugs. *AIDS* 2002; 16(9): 1294-5
- ⁶⁵ Schrooten W, Coleblunders R et al. Sexual Dysfunction associated with protease inhibitor containing highly active antiretroviral therapy. *AIDS* 2001; 15(8): 1019-23.
- ⁶⁶ Wespes E, Amar E, Hatzichristou D, Hatzimouratidis K, Montorsi F, Pryor J, Vardi Y; EAU EAU Guidelines on erectile dysfunction: an update. *Eur Urol.* 2006 May;49(5):806-15. Epub 2006 Feb
- ⁶⁷ Ralph D and McNicholas T. UK Management for erectile dysfunction. *BMJ* 2000 Aug 19-26;321(7259):499-50
- ⁶⁸ Hijazi L, Nandwani R and Kell P. Medical Management of Sexual difficulties in HIV positive individuals. *Int J STD AIDS.* 2002 Sep;13(9):587-92
- ⁶⁹ Goldmeier D, Lamba H. Sexual dysfunction in HIV-positive individuals. *Int J STD AIDS.* 2003 Jan;14(1):63-4
- ⁷⁰ Richardson D, Lamba H, Goldmeier et al. Factors associated with sexual dysfunction in men with HIV infection. *Int J STD AIDS* 2006; 17(11): 764-7
- ⁷¹ Muirhead GJ, Wulff B et al Pharmacokinetic interactions between sildenafil and saquinavir/ritonavir. *Br J Clin Pharmacol* 2000; 50(2): 85
- ⁷² Muirhead GJ, Faulkner S et al The effects of steady state erythromycin and azithromycin on the pharmacokinetics of sildenafil in healthy volunteers. *Br J Clin Pharmacol* 2002; 53 Suppl 1: 37-43S

-
- ⁷³ Sekar V, Lefebvre E, De Marez T et al. Pharmacokinetic interaction between TMC114, a new protease inhibitor, and sildenafil. Forty-Sixth ICAAC, San Francisco, Abstract A-0369, 2006.
- ⁷⁴ Scholler-Gyure M, Debroye C, Vyncke V, et al. Effect of TMC125 on sildenafil pharmacokinetics. Program and abstracts of the 7th International Workshop on Clinical Pharmacology of HIV Therapy; April 20-22, 2006; Lisbon, Portugal. Abstract 45.)
- ⁷⁵ Sherr, L; Bolding, Maguire, M. Elford, J. Viagra use and sexual risk behaviour among gay men in London. *AIDS*. 14(13):2051, September 8, 2000.
- ⁷⁶ Rosen RC, Catania JA, Erhardt AA et al. The Bolger Conference on PDE-5 Inhibition and HIV Risk: Implications for Health Policy and Prevention. *J Sex Med*. 2006 Nov; 3(6):960-75.
- ⁷⁷ Richardson D, Lamba H, Goldmeier G et al Factors associated with sexual dysfunction in men with HIV infection. *Int J STD AIDS* 2006; 17(11): 764-7
- ⁷⁸ Richardson D, Goldmeier D et al Recommendations for the Management of premature ejaculation: of the BASHH special interest group for sexual dysfunction. *Int J STD AIDS* 2006 Jan; 17(1):1-6. Review
- ⁷⁹ Richardson D, Goldmeier D; BASHH Special Interest Group for Sexual Dysfunction Recommendations for the management of retarded ejaculation: BASHH Special Interest Group for Sexual Dysfunction. *Int J STD AIDS*. 2006 Jan; 17(1):7-13. Review
- ⁸⁰ Cove J and Petrak J. Factors associated with sexual problems in HIV-positive gay men. *Int J STD AIDS* 2004; 15(11): 732-6
- ⁸¹ Collazos J Mayo J et al Association between sexual disturbances and sexual hormones with specific antiretroviral drugs. *AIDS* 2002; 16(9): 1294-5.
- ⁸² Collazos J Ibarra S et al Serum prolactin concentrations in patients infected with human immunodeficiency virus. *HIV Clin Trials* 2002; 3(2): 133-8.
- ⁸³ Richardson D, Goldmeier D, Frize G, Lamba H, De Souza C, Kocsis A, Scullard G. Letrozole versus testosterone. a single-center pilot study of HIV-infected men who have sex with men on highly active anti-retroviral therapy (HAART) with hypoactive sexual desire disorder and raised estradiol levels. *J Sex Med*. 2007 Mar;4(2):502-8.
- ⁸⁴ Crum NF, Furtek KJ, Olson PE, et al. A Review of Hypogonadism and Erectile Dysfunction among HIV-Infected Men during the Pre- and Post-HAART Eras: Diagnosis, Pathogenesis, and Management. *AIDS Patient Care and STDs* 2005;19(10):665-671
- ⁸⁵ Crum-Cianflone N, Bavaro M, Hale B, et al. on behalf of the TriSvc AIDS Clin Consortium. Prevalence and risk factors of hypogonadism among HIV-infected men. Program and abstracts of the 13th Conference on Retroviruses and Opportunistic Infections; February 5-8, 2006; Denver, Colorado. Abstract 775.
- ⁸⁶ Elford J, Bolding G, Davis M et al. 'Barebacking' among HIV-positive Gay Men in London. *STI* 2006; 33(7): in press.
- ⁸⁷ Bell C, Richardson D, Wall M et al HIV-associated female sexual dysfunction – clinical experience and literature review. *Int J STD AIDS* 2006 Oct;17(10):706-9
- ⁸⁸ Florence E, Schrooten W, Dreezen C, et al. Prevalence and factors associated with sexual dysfunction among HIV-positive women in Europe. *AIDS Care*. 2004 Jul; 16(5):550-7.

-
- ⁸⁹ Keegan A, Lambert S, Petrak J. Sex and relationships for HIV-positive women since HAART: a qualitative study. *AIDS Patient Care STDS*. 2005 Oct; 19(10):645-54.
- ⁹⁰ Meyer-Bahlburg HF, Nostlinger C, Exner TM, et al. Sexual functioning in HIV+ and HIV- injected drug-using women. *J Sex Marital Ther*. 1993 Spring; 19(1):56-68.
- ⁹¹ Hankins C, Gendron S, Tran TR et al. Sexuality in Montreal women living with HIV. *AIDS Care*. 1997 Jun; 9(3):261-71.
- ⁹² Wright TC Jr, Koulas J, Schnoll F et al. Cervical intraepithelial neoplasia in women infected with human immunodeficiency virus: prevalence, risk factors, and validity of Papanicolaou smears. *Obs and Gynae* 1994; 84: 591-7
- ⁹³ Smith JR, Kitchen VS, Botcherby M et al. Is HIV infection associated with an increase in the prevalence of cervical neoplasia? *Br J Gynae* 1993; 100: 149-153
- ⁹⁴ Schafer A, Friedmann W, Mielke M et al. The increased frequency of cervical dysplasia-neoplasia in women infected with human immunodeficiency virus is related to the degree of immunosuppression. *Am J Obs Gynae* 1991; 164: 593-599
- ⁹⁵ CDC. 1993 Revised CDC HIV classification system and expanded AIDS surveillance definition for adolescents and adults. *MMWR* 1992; 41: 17
- ⁹⁶ Parkin DM, Bray F, Ferlay J, Paisani P. Global cancer statistics, 2002. *CA Cancer J Clin* 2005; 55:74-108
- ⁹⁷ Maiman M, Fruchter RG, Guy L et al. Human immunodeficiency virus infection and invasive cervical cancer. *Cancer* 1993; 71(2): 402-6
- ⁹⁸ Walboomers JM, Jacobs MV, Manos MM et al. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. *J Pathol* 1999; 189: 12-19
- ⁹⁹ Munoz N, Bosch FX, de Sanjose S et al. Epidemiologic classification of human papillomavirus types associated with cervical cancer. *N Engl J Med* 2003; 348: 518-527
- ¹⁰⁰ Palefsky JM, Minkoff H, Kalish LA et al. Cervicovaginal human papillomavirus infection in Human Immunodeficiency Virus-1 (HIV)-Positive and High-Risk HIV-Negative Women. *J Natl Cancer Inst* 1999; 91(3): 226-236
- ¹⁰¹ Sun XW, Kuhn L, Ellerbrock TV et al. Human papillomavirus infection in women infected with the human immunodeficiency virus. *N Engl J Med* 1997; 337(19): 1343-1349
- ¹⁰² Minkoff H, Feldman J, DeHovitz J et al. A longitudinal study of human papillomavirus carriage in human immunodeficiency virus-infected and human immunodeficiency virus-uninfected women. *Am J Obstet Gynecol* 1998; 178: 982-6
- ¹⁰³ Palella FJ Jr, Delaney KM, Moorman AC et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. *N Engl J Med*. 1998; 338(13): 853-60
- ¹⁰⁴ Petry KU, Scheffel D, Bode U et al. Cellular immunodeficiency enhances the progression of human papillomavirus-associated cervical lesions. *Int J Cancer* 1994; 57: 836-840
- ¹⁰⁵ Maiman M, Fruchter RG, Serur E et al. Recurrent cervical intraepithelial neoplasia in human immunodeficiency virus-seropositive women. *Obstet Gynecol* 1993; 82: 170-174
- ¹⁰⁶ Heard I, Schmitz V, Costagliola D et al. Early regression of cervical lesions in HIV-seropositive women receiving highly active antiretroviral therapy. *AIDS* 1998; 12: 1459-1464

- ¹⁰⁷ Lillo FB, Ferrari D, Veglia F et al. Human papillomavirus infection and associated cervical disease in human immunodeficiency virus-infected women: effect of highly active antiretroviral therapy. *J Infect Dis* 2001; 184: 547-551
- ¹⁰⁸ Minkoff H, Ahdieh L, Massad LS et al. The effect of highly active antiretroviral therapy on cervical cytologic changes associated with oncogenic HPV among HIV-infected women. *AIDS* 2001; 15: 2157-2164
- ¹⁰⁹ Moore AL, Sabin CA, Madge S et al. Highly active antiretroviral therapy and cervical intraepithelial neoplasia. *AIDS* 2002; 16: 927-929
- ¹¹⁰ Guidelines for the NHS Cervical Screening Programme.
<http://cancerscreening.org.uk/cervical/publications/nhscsp20.html>
- ¹¹¹ http://www.statistics.gov.uk/downloads/theme_health/MB1_34/MB1_34.pdf
- ¹¹² Frisch M, Biggar RJ, Goedert JJ. Human papillomavirus associated cancers in patients with human immunodeficiency virus infection and acquired immunodeficiency syndrome. *J Natl Cancer Inst* 2000; 92: 1500-1510.
- ¹¹³ Daling JR, Weiss NS, Klopfenstein LL, Cochran LE, Chow WH, Daifuku R. Correlates of homosexual behaviour and the incidence of anal cancer. *JAMA* 1982; 247: 1988–1990.
- ¹¹⁴ Koblin BA, Hessol NA, Zauber AG, et al. Increased incidence of cancer among homosexual men, New York City and San Francisco, 1978–1990. *Am J Epidemiol* 1996; 144: 916–923
- ¹¹⁵ Daling JR, Weiss NS, Hislop TG, et al. Sexual practices, sexually transmitted diseases, and the incidence of anal cancer. *N Engl J Med* 1987;317: 973-977
- ¹¹⁶ Bower M, Powles T, Newsom-Davis T, et al. HIV-associated anal cancer. Has highly active therapy reduced the incidence or improved the outcome? *J Acquir Immune Deficiency Syndrome* 2004; 37: 1563-1565.
- ¹¹⁷ Cleator S, Fife K, Nelson M, et al. Treatment of HIV-associated invasive anal cancer with combined chemoradiation. *Eur J Cancer* 2000; 36: 754-758
- ¹¹⁸ Clark MA, Hartley A, Geh JI. Cancer of the anal canal. *Lancet Oncol* 2004; 5: 149-157
- ¹¹⁹ Frisch M, Fenger C, van den Bruke AJ, et al. Variants of squamous cell carcinoma of the anal canal and perianal skin and their relation to human papillomaviruses. *Cancer Res* 1999; 59: 753-757
- ¹²⁰ Daling JR, Madeleine M, Johnson LG, et al. Human papillomavirus, smoking, and sexual practices in the etiology of anal cancer. *Cancer* 2004; 101: 270-280
- ¹²¹ Chin-Hong PV, Vittinghoff E, Cranston R, et al. Age-specific prevalence of anal human papillomavirus in HIV-negative sexually active men who have sex with men: the EXPLORE study. *J Infect Dis* 2004; 190: 2070-2076
- ¹²² Fenger C, Nielsen VT. Intraepithelial neoplasia in the anal canal. *Acta Path Microbiol Immunol Scand* 1986; 94: 343-349
- ¹²³ Piketty C, Darragh TM, Da Costa M, et al. High prevalence of anal human papillomavirus infection and anal cancer precursors among HIV-infected persons in the absence of anal intercourse. *Ann Intern Med* 2003; 138: 453-459
- ¹²⁴ Abbasakoor F, Boulos PB. Anal intraepithelial neoplasia. *Br J Surg* 2005; 92: 277-290

-
- ¹²⁵ Marfing TE, Abel ME, Gallagher DM. Perianal Bowen's disease and associated malignancies. Results of a survey. *Dis Colon Rectum* 1987;30:782-5
- ¹²⁶ Cleary RK, Schaldenbrand JD, Fowler JJ, et al. Perianal Bowen's disease and anal intraepithelial neoplasia: review of the literature. *Dis Colon Rectum* 1999;42:945-51
- ¹²⁷ Critchlow CW, Surawicz CM, Holmes KK, et al. Prospective study of high grade anal squamous intraepithelial neoplasia in a cohort of homosexual men: influence of HIV infection immunosuppression and human papillomavirus infection. *AIDS* 1995;9:1255-62
- ¹²⁸ Palefsky JM, Holly E, Ralston MR, et al. High incidence of anal high grade squamous intraepithelial lesions among HIV-positive and HIV-negative homosexual and bisexual men. *AIDS* 1998;12:495-503
- ¹²⁹ Brown DR, Schroeder JM, Bryan JT, et al. Detection of multiple human papillomavirus types in condyloma acuminata lesions from otherwise healthy and immunosuppressed patients. *J Clin Micro* 1999; 37: 3316-3322
- ¹³⁰ Papaconstantinou HT, Lee AJ, Simmang CL, et al. Screening methods for high-grade dysplasia in patients with anal condyloma. *J Surg Res* 2005; 127: 8-13
- ¹³¹ Arain S, Walts AE, Thomas P, et al. The anal Pap smear: cytomorphology of squamous intraepithelial lesions. *CytoJournal* 2005; 2: 4
- ¹³² Fox PA, Seet JE, Stebbing J, et al. The value of anal cytology and human papillomavirus typing in the detection of anal intraepithelial neoplasia: a review of cases from an anoscopy clinic. *Sex Transm Inf* 2005; 81: 142-146
- ¹³³ Carter PS, Sheffield JP, Shepherd N, et al. Interobserver variation in the reporting of the histopathological grading of anal intraepithelial neoplasia. *J Clin Pathol* 1994; 47: 1032-1034
- ¹³⁴ Negri G, Moretto G, Menia E, et al. p16INK4a immunocytochemistry in liquid based cervicovaginal specimens with modified Papanicolaou counterstaining. *J Clin Pathol* 2006 Feb 7; Epub
- ¹³⁵ Chin-Hong PV, Palefsky JM. Natural history and clinical management of anal human papillomavirus disease in men and women infected with human immunodeficiency virus. *Clin Infect Dis* 2002; 35: 1127-1134
- ¹³⁶ Fox PA. Human papillomavirus and anal intraepithelial neoplasia. *Curr Opin Infect Dis* 2006; 19: 62-66
- ¹³⁷ Chang GJ, Berry JM, Jay N, et al. Surgical treatment of high-grade anal squamous intraepithelial lesions: a prospective study. *Dis Colon Rectum* 2002; 45: 453-458
- ¹³⁸ Goldstone SE, Kawalek AZ, Huyett JW. Infrared coagulator: a useful tool for treating anal squamous intraepithelial lesions. *Dis Colon Rectum* 2005; 48: 1042-1054
- ¹³⁹ Goldie SJ, Kuntz KM, Weinstein MC, et al. The clinical effectiveness and cost-effectiveness of screening for anal squamous intraepithelial lesions in homosexual and bisexual HIV-positive men. *JAMA*; 281: 1822-1829
- ¹⁴⁰ Wilkin TJ, Palmer S, Brudney KF, et al. Anal intraepithelial neoplasia in heterosexual and homosexual men with access to antiretroviral therapy. *J Infect Dis* 2004; 190: 1685-1691
- ¹⁴¹ Elford J, Bolding G, Sherr L, Hart G High-risk sexual behaviour among London gay men: no longer increasing. *AIDS*. 2005 Dec 2; 19(18):2171-4.
-

-
- ¹⁴² Kamb ML, Fishbein M, Douglas JM Jr, Rhodes F, Rogers J, Bolan G, Zenilman J, Hoxworth T, Malotte CK, Iatesta M, Kent C, Lentz A, Graziano S, Byers RH, Peterman TA. Efficacy of risk-reduction counselling to prevent human immunodeficiency virus and sexually transmitted diseases: a randomized controlled trial. Project RESPECT Study Group. *JAMA*. 1998 Oct 7;280(13):1161-7
- ¹⁴³ Metcalf CA, Malotte CK, Douglas JM Jr, Paul SM, Dillon BA, Cross H, Brookes LC, Deaustine N, Lindsey CA, Byers RH, Peterman TA; RESPECT-2 Study Group. Efficacy of a booster counselling session 6 months after HIV testing and counselling: a randomized, controlled trial (RESPECT-2). *Sex Transm Dis*. 2005 Feb;32(2):123-9
- ¹⁴⁴ Sangani P, Rutherford G, Wilkinson D. Population-based interventions for reducing sexually transmitted infections, including HIV infection. *Cochrane Database Syst Rev*. 2004;(2):CD001220
- ¹⁴⁵ Hart GJ, Williamson LM, Flowers P. Good in parts: the Gay Men's Task Force in Glasgow--a response to Kelly. *AIDS Care*. 2004 Feb;16(2):159-65
- ¹⁴⁶ ref DoH guidelines for HIV testing in pregnancy
- ¹⁴⁷ Postma MJ, Beck EJ, Hankins CA, Mandalia S, Jager JC, de Jong-van den Berg LT, Walters MD, Sherr L. Cost effectiveness of expanded antenatal HIV testing in London. *AIDS*. 2000 Oct 20;14(15):2383-9.
- ¹⁴⁸ Sherr L, Barry N. Fatherhood and HIV-positive heterosexual men. *HIV Med*. 2004 Jul;5(4):258-63
- ¹⁴⁹ Bergenstrom A, Sherr L, Okolo S, HIV testing and prevention: family planning clinic attenders in London. *Sex Transm Infect*. 1999 Apr;75(2):130
- ¹⁵⁰ Bergenstrom A, Sherr L. HIV testing and prevention issues for women attending termination assessment clinics. *Br J Fam Plann*. 1999 Apr;25(1):3-8
- ¹⁵¹ Goldstein RB, Johnson MO, Rotheram-Borus MJ, Kirshenbaum SB, Pinto RM, Kittel L, Pequegnat W, Mickalian JD, Weinhardt LS, Kelly JA, Lightfoot M; National Institute Mental Health Healthy Living Project Team. Psychological distress, substance use, and adjustment among parents living with HIV. *J Am Board Fam Pract*. 2005 Sep-Oct; 18(5):362-73.
- ¹⁵² Rochat TJ, Richter LM, Doll HA, Buthelezi NP, Tomkins A, Stein A. Depression among pregnant rural South African women undergoing HIV testing. *JAMA*. 2006 Mar 22; 295(12):1376-8.
- ¹⁵³ Kirshenbaum SB, Hirky AE, Correale J, Goldstein RB, Johnson MO, Rotheram-Borus MJ, Ehrhardt AA "Throwing the dice": pregnancy decision-making among HIV-positive women in four U.S. cities. *Perspect Sex Reprod Health*. 2004 May-Jun; 36(3):106-13.
- ¹⁵⁴ Sherr L, Fox Z, Lipton M, Whyte P, Jones P, Harrison U; Camden and Islington Steering Group. Sustaining HIV testing in pregnancy- evaluation of routine offer of HIV testing in three London hospitals over 2 years. *AIDS Care*. 2006 Apr;18(3):183-8
- ¹⁵⁵ Rotheram-Borus MJ, Lester P, Wang PW, Shen Q Custody plans among parents living with human immunodeficiency virus infection. *Arch Pediatr Adolesc Med*. 2004 Apr;158(4):327-32
- ¹⁵⁶ Chen J Philips K Kanouse D Collins R Miu A Fertility desires and intentions of HIV positive men and women, *Fam Plann Perspect*. 2001 Jul-Aug;33(4):144-52, 165
- ¹⁵⁷ Paiva V Filipe E Santos N Lima T Segurado A The Right to Love the desire for parenthood among men living with HIV *Reprod health Matters* 2003, nov 11 22; 91-100
-

-
- ¹⁵⁸ Orr G, Catalan J, Longstaff C. Are we meeting the psychological needs of heterosexual men with HIV Disease? *AIDS Care* 2004 Jul 16;5 p 586-93
- ¹⁵⁹ Fultz PN, Srinivasan A, Greene CR, Butler D, Swenson RB, McClure HM. Superinfection of a chimpanzee with a second strain of human immunodeficiency virus. *J Virol.* 1987;61:4026-4029.
- ¹⁶⁰ Otten RA, Ellenberger DL, Adams DR, et al. Identification of a window period for susceptibility to dual infection with two distinct human immunodeficiency virus type 2 isolates in a *Macaca nemestrina* (pig-tailed macaque) model. *J Infect Dis.* 1999;180:673-684. Abstract
- ¹⁶¹ 13. Smith D et al. Lack of neutralizing antibody response to HIV-1 predisposes to superinfection. Thirteenth Conference on Retroviruses and Opportunistic Infections, Denver, abstract 91, 2006.
- ¹⁶² McConnell J et al. Broad neutralization of HIV-1 variants in couples without evidence of systemic superinfection despite exposure. Thirteenth Conference on Retroviruses and Opportunistic Infections, Denver, abstract 92, 2006.
- ¹⁶³ Gonzales MJ, Delwart E, Rhee SY, et al. Lack of detectable human immunodeficiency virus type 1 superinfection during 1072 person-years of observation. *J Infect Dis.* 2003; 188:397-405.
- ¹⁶⁴ Tsui R, Herring BL, Barbour JD, et al. Human immunodeficiency virus type 1 superinfection was not detected following 215 years of injection drug user exposure. *J Virol.* 2004; 78:94-103.
- ¹⁶⁵ Grant RM, McConnell JJ, Herring B, et al. No superinfection among seroconcordant couples after well-defined exposure. Program and abstracts of the 15th International AIDS Conference; July 11-16, 2004; Bangkok, Thailand. Abstract ThPeA6949.
- ¹⁶⁶ Pernas M, Casado C, Fuentes R, et al. A dual superinfection and recombination within HIV-1 subtype B 12 years after primoinfection. *J Acquir Immune Defic Syndr* 2006; 42(1):12-18.
- ¹⁶⁷ Blick G, Kagan RM, Coakley E, et al. The probable source of both the primary multidrug-resistant (MDR) HIV-1 strain found in a patient with rapid progression to AIDS and a second recombinant MDR strain found in a chronically HIV-1-infected patient. *J Infect Dis* 2007; 195(9):1250-1259.
- ¹⁶⁸ Health Protection Agency. HIV Drug Resistance in the United Kingdom: data to end of 2004. *CDR Weekly* 16(4), 2006.
- ¹⁶⁹ Smith DM et al. HIV drug resistance acquired through superinfection. *AIDS* 19: 1251 – 1256, 2005.
- ¹⁷⁰ Gottlieb GS, Nickle DC, Jensen MA, et al. Dual HIV-1 infection associated with rapid disease progression. *Lancet.* 2004; 363:619-622.
- ¹⁷¹ Grobler J, Gray CM, Rademeyer C, et al. Incidence of HIV-1 dual infection and its association with increased viral load set point in a cohort of HIV-1 subtype C-infected female sex workers. *J Infect Dis.* 2004; 190:1355-1359.
- ¹⁷² Anderson J., Chalmers J. Nelson M., Poulton M. Power L, Pozniak A., Reynolds R. HIV transmission, the law and the work of the clinical team. A briefing paper. Available from the BHIVA website <http://www.bhiva.org/>
- ¹⁷³ <http://www.tht.org.uk/informationresources/prosecutions/>
- ¹⁷⁴ BHIVA Guidelines Writing Committee, Guidelines for the management of HIV infection in pregnant women and the prevention of mother-to-child transmission of HIV. *HIV Med* 2005. 6(Suppl 2): p. 107-148 available at <http://www.bhiva.org/>
-

-
- ¹⁷⁵ Faculty of Family Planning and Reproductive Healthcare Clinical Effectiveness Unit. UK Medical Eligibility Criteria for Contraceptive Use. 2006
(<http://www.ffprhc.org.uk/admin/uploads/UKMEC200506.pdf>).
- ¹⁷⁶ Trussell J. Contraceptive Efficacy. In: Hatcher RA, Trussell J, Stewart F, Nelson F et al. (eds), Contraceptive Technology. New York, NY: Ardent Media, 2004
- ¹⁷⁷ Frezieres RG, Walsh TL, Nelson AL, Clark VA, Coulson AH. Evaluation of the efficacy of a polyurethane condom: results from a randomized, controlled clinical trial. Fam Plann Perspect 1999; 31: 81-87
- ¹⁷⁸ Weller S, Davis K. Condom effectiveness in reducing heterosexual HIV transmission. Cochrane Database Syst Rev. 2002; (1): CD003255
- ¹⁷⁹ National Institute of Allergy and Infectious Diseases. Scientific evidence on condom effectiveness for sexually transmitted disease (STD) prevention. Bethesda, Maryland. National Institutes of Health, NIAID, 2001
- ¹⁸⁰ French PP, Latka M, Gollub EL, et al. Use-effectiveness of the female versus male condom in preventing sexually transmitted disease in women. Sex Transm Dis. 2003; 30(5): 440-2
- ¹⁸¹ Faculty of Family Planning and Reproductive Healthcare Clinical Effectiveness Unit. FFPRHC Guidance (January 2007) Male and Female Condoms.
- ¹⁸² Contracept Technol Update. No added STI protection from spermicidal condoms. 1998; 19(8): 105-6
- ¹⁸³ WHO/CONRAD technical consultation on nonoxynol-9, World Health Organisation, Geneva 2001: summary report
- ¹⁸⁴ Dawe F, Meltzer H. Contraception and sexual health, 2001. Office for National Statistics. London, UK: Her Majesty's Stationery Office (HMSO), 2003, i-50.
- ¹⁸⁵ Wang CC, Reilly M, Kreiss JK. Risk of HIV infection in oral contraceptive pill users: a meta-analysis. J Acquir Immune Defic Syndr Hum Retrovirol. 1999; 21: 51-58
- ¹⁸⁶ Morrison CS, Richardson BA, Mmiro F, Chipato T et al. Hormonal contraception and the risk of HIV acquisition. AIDS 2007; 21: 85-95
- ¹⁸⁷ Quellet D, Hsu A, Qian J, et al. Effects of ritonavir on the pharmacokinetics of ethinyl oestradiol in healthy female volunteers. British Journal of Clinical Pharmacology 1998; 46: 111-6
- ¹⁸⁸ Faculty of Family Planning and Reproductive Health Care Clinical Effectiveness Unit. Drug Interactions with hormonal contraception. Journal of Family Planning and Reproductive Health Care 2005; 31(2): 139-151
- ¹⁸⁹ Back DJ, Breckenridge AM, Crawford FE, et al. The effect of rifampicin on the pharmacokinetics of ethynylestradiol in women. Contraception. 1980; 21(2): 135-43
- ¹⁹⁰ Back DJ, Breckenridge AM, Crawford F, et al. The effect of rifampicin on norethisterone pharmacokinetics. Eur J Clin Pharmacol. 1979; 15(3): 193-7
- ¹⁹¹ Gbolade BA. Depo-Provera and bone density. The Journal of Family Planning and Reproductive Healthcare 2002;28:7-11
- ¹⁹² Dolan SE, Huang JS, Kililea MA et al. Reduced bone density in HIV-infected women. AIDS 2004;18

-
- ¹⁹³ Morrison CS, Sekadde-Kigundu C, Sinei SK et al. Is the intrauterine device appropriate contraception for HIV-1-infected women? *BJOG* 2001;108:784-790
- ¹⁹⁴ Faculty Statement from the Clinical Effectiveness Unit on Levonelle® 1500 and the use of liver enzyme inducing drugs (FFPRHC) (April 2006)
- ¹⁹⁵ Liverpool HIV Pharmacology Group. www.hiv-interactions.org. 1999. Department of Pharmacology and Therapeutics
- ¹⁹⁶ Holmes K, Levine R et al Effectiveness of condoms in preventing sexually transmitted infections. *Bulletin of the WHO* 2004; 82:454-461.
- ¹⁹⁷ Ahmed S, Lutalo T et al HIV incidence and sexually transmitted disease prevalence associated with condom use; a population study in Rakai, Uganda. *AIDS* 2001; 15:2171-9.
- ¹⁹⁸ Herbst J, Sherba RT et al A meta-analytic review of HIV behavioural interventions for reducing sexual risk behaviour of men who have sex with men. *J Acquir Immune Defic Syndr* 2005; 39(2): 228-41
- ¹⁹⁹ Voeller B, Coulson AH et al Mineral Oil Lubricants cause rapid deterioration of latex condoms. *Contraception* 1989; 39(1): 95-102
- ²⁰⁰ Gallo MF, Grimes DA et al Non latex vs. Latex male condoms for contraception; a systematic review of randomised controlled trials. *Contraception* 2003; 68(5): 319-26
- ²⁰¹ Golombok S, Harding R and Sheldon J. An evaluation of a thicker versus a standard condom with gay men. *AIDS* 2001 Jan 26; 15(2):267-9.
- ²⁰² Hoffman IF, Taha TE et al Nonoxynol-9 100 mg gel: multi-site safety study from sub-Saharan Africa. *AIDS* 2004; 18(16): 2191-5
- ²⁰³ Phillips DM, Sudol KM et al Lubricants containing N-9 enhances rectal transmission of HIV and other STIs. *Contraception* 2004; 70(2): 107-10
- ²⁰⁴ Van Damme L, Ramjee G et al. Effectiveness of COL-1492, a nonoxynol-9 vaginal gel, on HIV-1 Transmission in female sex workers; a randomised controlled trial. *Lancet* 2002; 360(9338): 971-7
- ²⁰⁵ Wilkinson D, Ramjee G et al. Nonoxynol-9 for preventing vaginal acquisition of sexually transmitted infections by women from men. *Cochrane Database Syst Rev* 2002;(4): CD003939
- ²⁰⁶ Garrido N, Meseuger M et al Semen Characteristics in HIV and HCV seropositive males: predictors of the success of viral removal after sperm washing. *Human Reprod.* 2005; 4:1028-34
- ²⁰⁷ Crittenden JA, Handelsman DJ et al. Semen analysis in human immunodeficiency virus infection. *Fertil Steril* 1992; 57(6): 1294-9
- ²⁰⁸ Politch JA, Mayer KH et al The effects of disease progression and zidovudine therapy on semen quality in human immunodeficiency virus type 1 seropositive men. *Fertil Steril* 1994; 61(5): 922-8
- ²⁰⁹ Van Leeuwen E, Cornelissen M et al. Semen parameters of a semen donor before and after infection with the human immunodeficiency virus type 1: a case report. *Human Reprod* 2004; 19(12): 2845-8
- ²¹⁰ Robbins WA, Witt KL et al Antiretroviral therapy effects on genetic and morphologic endpoints in lymphocytes and sperm of men with human immunodeficiency virus infection. *J Infect Dis* 2001; 184(2): 127-35

²¹¹ National Collaborating Centre for Women's and Children's Health (Commissioned by NICE)
Fertility: Assessment and treatment for people with fertility problems. February 2004.

²¹² Dulioust E. Du AL et al Semen alterations in HIV-1 infected men. Human Reprod 2002; 17(8):
2112-8