15

Preconception advice and the optimal management of HIV infection for couples planning pregnancy

Anne Edwards and Yetunde Okunwobi-Smith

The two major aims of preconception care are to identify risks and to take measures to reduce these risks. In terms of HIV, before the development of antiretroviral therapy (ART) the risk of mother to child viral transmission ranged from 15 to 40%[1]. Of equal importance was the high mortality associated with HIV which meant that uninfected children were likely to be left motherless in the first few years of life[2,3]. Faced with these statistics, most physicians actively discouraged HIV positive women from becoming pregnant. The development of ART, however, means that with optimal medical care HIV can be viewed as a chronic infection with a life expectancy approaching normal[4–7]. Unfortunately, this reality is not yet the case in resource limited settings[8].

The use of ART in pregnancy has changed the transmission risk from 15–40% in the untreated woman to less than 2%[9]. Given up to date advice on pregnancy risks and outcomes, patients living with HIV can now make informed choices. This chapter is written to assist physicians to help their patients fulfil their reproductive ambitions.

PREVALENCE OF HIV AND CURRENT EPIDEMIOLOGY

HIV was first identified in the early 1980s when epidemiologists noticed a clustering of cases of Kaposi's sarcoma, a rare skin tumor, in young gay men living in Los Angeles, USA[10]. HIV, the causative agent of the acquired immune deficiency syndrome (AIDS), was subsequently identified[11]. Since then, this new, emergent and, in many cases fatal, sexually transmitted infection (STI) has spread globally. The most significant health consequence is high mortality, especially among those of reproductive, and therefore working, age in the developing world[12]. Most (75–85%) cases of HIV are sexually acquired. The remainder occur as a result of drug use via injection (IDU), mother to child transmission and administration of contaminated blood products[13]. Three different patterns of sexual spread have been described. Pattern 1 is most common in the developed world where HIV has spread mostly amongst men who have sex with men (MSM). In pattern 2 countries, predominantly the developing nations, HIV has spread heterosexually. In pattern 3 countries, the numbers of cases and mode of spread are not always clear (Table 1).

DIAGNOSING HIV INFECTION

Most patients infected with HIV do not have symptoms. In the Western world, where treatment is routinely available, those at risk of HIV are encouraged to come forward for testing, as early diagnosis allows for monitoring

of immune status, and treatment interventions can be timed so that patients may derive the greatest therapeutic benefit. Despite these policies, new diagnoses are still made late in about 42% of African patients residing in the UK. This pattern is likely to be similar to that found in other countries to which native born Africans have emigrated[14,15].

A sexual history and HIV risk assessment is recommended as a routine part of the evaluation of any couple presenting for preconceptional care. Clinicians providing care should be fully aware of the risk factors for HIV, able to undertake a basic HIV risk assessment and feel comfortable explaining the advantages to individuals of knowing their HIV status.

Many Western countries offer HIV testing as part of routine antenatal care[16,17], thus allowing many women to be diagnosed in the early stages of pregnancy. In addition, it is routine in many countries to screen patients requesting treatment for infertility for HIV, again allowing some women to be identified by this route at this time. Unfortunately, neither of these settings is ideal, and in almost all so-called 'unexpected diagnoses' clear risk factors can be identified. An appropriate risk assessment at the preconceptional stage avoids this unsatisfactory situation (Table 2).

After obtaining an adequate sexual history and HIV risk assessment, patients can be encouraged to undergo a full sexual health screen, as the presence of undiagnosed and often asymptomatic STI may affect fertility, pregnancy and the new born child. In this regard, it is especially important to remember that ulcerative and non-ulcerative STI increase the risk of acquisition as well as transmission of HIV. It is for this reason that both partners should be advised to have a STI screen before pregnancy to ensure they are in the best possible sexual health.

Table 1 Risk groups for HIV infection

Risk factor
Men who have sex with men (MSM)*
Country of origin – developing countries such as Africa, Asia, India, Caribbean*
Injecting drug use*
Contaminated blood products either before blood screening or where this is not routinely undertaken*

*Or sexual contact with someone in this risk group

GENERAL REPRODUCTIVE HEALTH IN HIV POSITIVE PATIENTS

Despite all recent advances in treatment, making a diagnosis of HIV is devastating to the patient. Most newly diagnosed women are in the reproductive age range, and some will already have had children whilst others hope for them in the future[18]. Figures 1 and 2 demonstrate the increasing burden of HIV/AIDS in the female population, especially in sub-Saharan Africa.

Because many patients still believe that a diagnosis of HIV infection is at worst a death sentence and at best will mean that they can no longer expect a normal family life, the implications for the individual and her partner(s)

Table 2 Essentials of sexual history taking and HIV risk assessment

*Sexual history**
Partner 1 – timing of last sexual intercourse, with whom and from what country
Use of condoms on this occasion or during the relationship
Duration of the relationship
Partner 2 – timing of past sexual intercourse, with whom and from what country
Use of condoms on this occasion or during the relationship
Duration of the relationship

*History usually repeated to cover any partners in the preceding 6–12 months

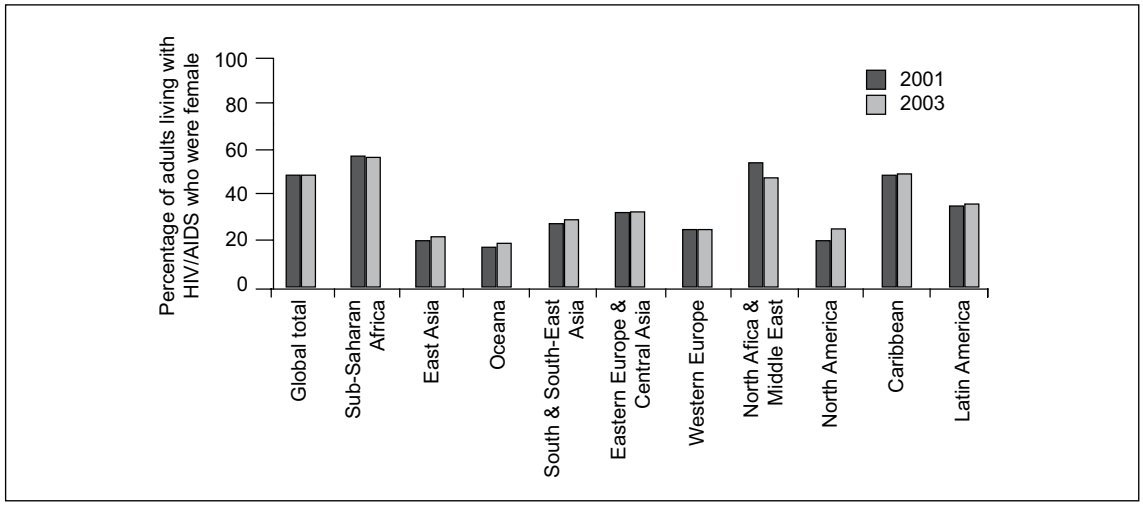

Figure 1 Estimate of percentage of adults (15–49 years) living with HIV/AIDS who were female in 2001 and 2003. (Reproduced with permission from UNAIDS/UNFPA/UNIFEM, 2004[19])

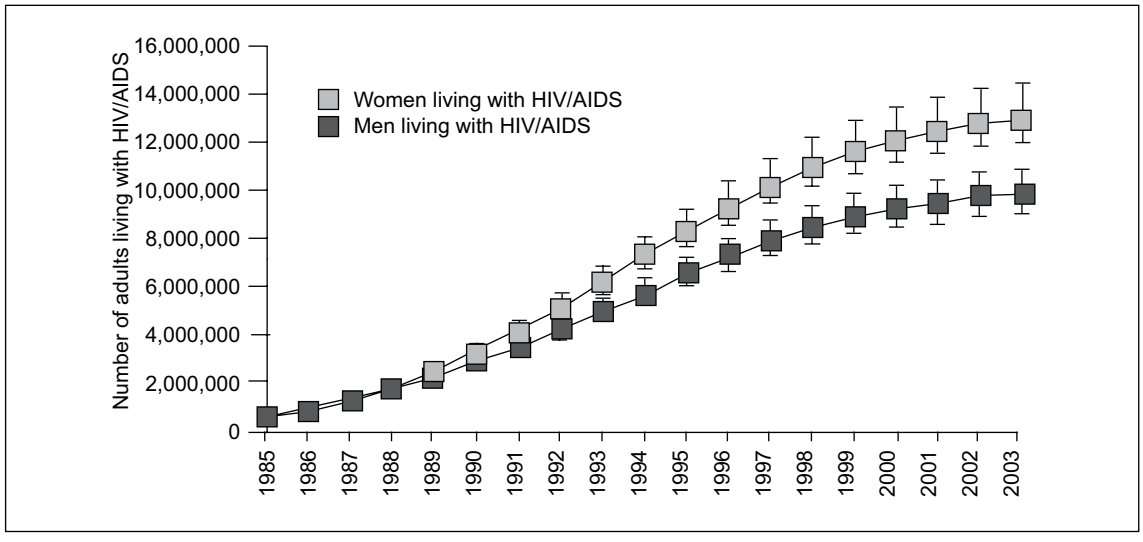

Figure 2 Estmated number of adult (15–49 years) women and men living with HIV/AIDS in sub-Saharan Africa (1985–2003). (Reproduced with permission from UNAIDS/WHO, 2004[20])

and future partners should be a routine part of early discussions. Contact tracing and the testing of current and previous sexual partners should be addressed soon after initial diagnosis. For women of reproductive age, however, such discussions should focus on prevention of onward viral transmission as well as effective contraception. For the newly diagnosed male, the status of their partner(s) and the risk of onward transmission are usually paramount. Figure 3 illustrates estimations of HIV infectivity via different routes of possible transmission. The male condom remains the most effective method of reducing

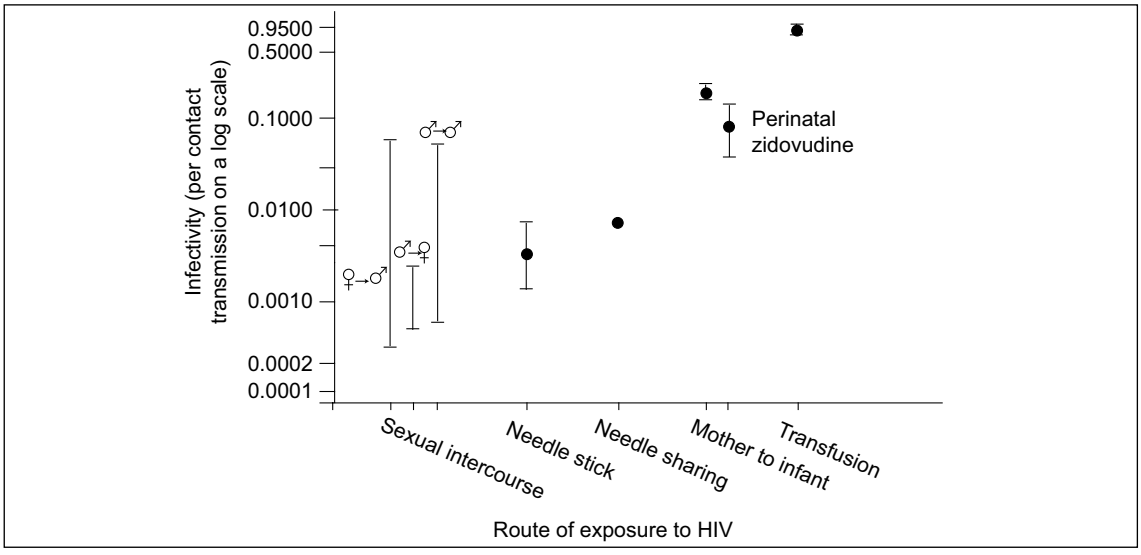

Figure 3 Probability of HIV transmission via different routes. Per contact probability of HIV transmission. The infectivity ranges for sexual contact are derived from a comprehensive review of the literature (lower and upper bounds are from modeling per contact transmission in different study populations with different modeling techniques). Each infectivity estimate for the other routes of infection originates from one representative study. The routes of infection are as follows: sexual intercourse, with ♀→♂ indicating female-to-male transmission, ♂→♀ indicating male-to-female transmission, and ♂→♂ indicating male-to-male transmission; needle stick; needle sharing; transmission from mother to infant with and without perinatal zidovudine treatment; and transfusion. (Reproduced with permission from Royce RA, Sena A, Cates W Jr, Cohen MS. Current concepts: sexual transmission of HIV. *N Engl J Med* 1997;336:1072–8[21]. Copyright 1997: Massachusetts Medical Society. All rights reserved)

virus transmission. For the prevention of an unplanned pregnancy, additional contraceptives methods may be advised.

FERTILITY AND CONTRACEPTION IN THE HIV POSITIVE FEMALE

Contraception

Information about effective contraception is critical for both pre- and post-pregnancy planning. Women should be encouraged to make informed choices regarding contraception and should be given all the information necessary to do so. Most contraceptive methods are safe and effective in HIV positive women who are not taking ART. For those who are on ART, only certain forms of contraception are regarded as effective and patients should be duly informed[22–24]. The use of condoms should be encouraged in addition to other forms of effective contraception for three separate but *related* reasons pertaining to the reduction of: (1) acquiring other STI; (2) transmission of HIV in discordant couples; and (3) possible superinfection in concordant couples. This form of dual protection is often termed 'doubling up'[1]. Table 3 provides a summary of contraceptive choices and their likely efficacy based on guidance from the UK Faculty of Sexual and Reproductive Healthcare.

When a method of contraception fails or unprotected intercourse has occurred, emergency contraception can reduce the risk of an unplanned pregnancy. Women who are not

Table 3 Summary of UK medical eligibility criteria for contraceptive use (UKMEC)

Contraception type	*HIV positive no antiretrovirals*	*HIV positive on antiretrovirals*
Combined oral contraceptive pill	1	2*
Combined contraceptive patch	1	2*
Progesterone-only pill	1	2*
Long-acting injectable progestogens	1	1
Progestogen-only subdermal implants	1	2*
Levonorgestrel intrauterine system	2	1
Copper intrauterine devices	2	2
Diaphragm and caps	3**	3**
Condoms	1	1

UKMEC category: 1, no restriction for use of the method; 2, advantages of using the method generally outweigh the theoretical or proven risks; 3, the theoretical or proven risks generally outweigh the advantages of using the method; 4, an unacceptable health risk if the contraceptive method is used.
*Some antiretrovirals cause a reduction in bioavailability by inducing liver enzymes. Additional use of condoms strongly encouraged.
**Potentially permits transmission of virus

on ART may be offered the progestogen only emergency contraception – levonorgestrel 1.5 mg single dose, for use within 72 hours of sexual intercourse. An alternative is the insertion of a copper intrauterine contraceptive device (IUCD) within 5 days. For women using ART, an emergency IUCD is the preferred option, as this contraceptive method is unaffected by HIV medication. Should the woman be reluctant to use this method, then a double dose of levonorgestrel should be given as soon as possible and within 72 hours; however, use in this manner is outside the product licence.

Fertility

No hard evidence exists to show that women with HIV infection are less fertile than other women. Similarly, asymptomatic women with HIV infection do not experience disorders of menstrual function and ovulation any more frequently than HIV negative women[25,26].

Health before conception

General health should be optimized before conception, because 'early prenatal' care may well be too late for meaningful intervention, and HIV positive women are no exception. Preconception is an opportunity to address risk factors which might result in an adverse outcome for the baby or mother and to discuss possible interventions. Areas that require special attention in HIV positive women, depending on their risk factors for HIV, include diet and weight, alcohol, recreational drug consumption and psychological factors.

Healthy eating and weight management (see Chapters 22 and 30)

Whereas all patients should be encouraged to eat a healthy balanced diet and to exercise regularly, important cultural differences are present in the manner in which HIV and weight are perceived. In the African population, for

example, obesity may be perceived to be a sign of good health, and against this background it may be hard to promote a Western style healthy diet and optimum weight. This difference becomes especially important in women before and during pregnancy.

Nevertheless, issues of weight, both over and under should be specifically addressed. The UK Confidential Enquiries into Maternal and Child Health 2007 (CEMACH) report demonstrated that obese pregnant women with a body mass index of more than 30 were far more likely to die than non-obese women[27]. Under these circumstances, obese women should try to lose weight before conception wherever possible. Adverse outcomes associated with maternal obesity include increased rates of neural tube defects, preterm delivery, diabetes, cesarean sections, and hypertensive and thromboembolic disease[28–31].

Alcohol and/or recreational drug abuse

It is safest to abstain from alcohol entirely when planning pregnancy, as harm can occur early on even before a woman realises she is pregnant. The fetal alcohol syndrome and other alcohol related birth defects can be prevented if women refrain from alcohol consumption before conception. If a woman chooses not to abstain entirely from alcohol, then intake should be restricted to one unit daily[32–34].

Certain areas of the world have experienced HIV epidemics entwined with rising rates of drug abuse[35]. IDU have the highest prevalence rates for HIV, but crack cocaine users and other substance abusers demonstrate substantially elevated rates of infection as well[36]. This is probably related to risky sexual activity while on drugs. The women in this subgroup are particularly vulnerable, as they are open to physical and sexual abuse. Preconceptional counseling provides an opportunity to deal with these issues.

Immunization history

Newly diagnosed HIV positive patients are usually investigated for previous exposure to infections such as cytomegalovirus and toxoplasmosis, both of which display latency and may reactivate in late stage, untreated HIV infection[37]. Newly diagnosed patients are also usually tested for hepatitis C (HCV) infection for which IDU and MSM are the most at risk. In women who may want to become pregnant, this point in time also provides an opportunity to check rubella and hepatitis B status and vaccinate if required. In women infected with hepatitis B, neonates can be protected at birth[38–41].

Safer sex

The consistent and careful use of condoms is crucial for the reduction of HIV transmission and cannot be over emphasized. Risk of HIV transmission in women is particularly high during menstruation and in the presence of genital tract infections or lesions as mentioned above[42].

Psychological well-being

Women with HIV infection are at higher risk of depression than those without the condition. The clinical picture is complex and related in part to the premorbid personality, past history of mental health problems and risk factors for the acquisition of HIV. Depression can impact on compliance with medication and other important health interventions in a manner that is adverse to pregnancy outcome. Because of this, all HIV positive women should undergo a basic mental health assessment as part of preconceptional counseling and, if problems are identified, appropriate expert support can be sought[43].

FERTILITY AND CONTRACEPTION IN HIV POSITIVE MEN

Fertility

Few data are available on the fertility of HIV infected men, although some studies have suggested that such individuals have a reduction in sperm quantity and quality[44,45]; however, this observation is not universal. Using WHO criteria[46], provided the CD4 is greater than 200, others have demonstrated that HIV has little effect on sperm quality or production. On the other hand, men with advanced disease may have abnormal sperm production, and optimizing highly active ART (HAART) may benefit their fertility[1]. No published evidence suggests that specific ARTs affect male fertility.

Contraception

For each act of unprotected intercourse during which the man is HIV positive, the risk of transmission to a negative partner is between 1 in 500 and 1 in 1000[4,47,48]. However, the chance of transmission is cumulative with each act of unprotected intercourse. Therefore, the male condom has been of exceptional importance in the fight against HIV transmission and acquisition, accounting for a decrease in transmission risk by 80–90%[49]. Considering this circumstance alone and irrespective of any desire to avoid an unwanted pregnancy, the use of the condom should be encouraged to prevent the spread of HIV, superinfection (re-infection with a second strain of HIV after the first infection has been established in concordant couples) and co-infection with other STI.

This having been said, education in the proper use of condoms with water-based lubricants not containing nonoxynol-9, rather than oil-based lubricants is of paramount importance, as oil-based lubricants damage latex condoms and increase breakage rates. In contrast, the thickness of condoms does not appear to add any additional benefit with regards to protection[1,50].

PREGNANCY IN HIV POSITIVE WOMEN

Pregnancy is not harmful to women with HIV infection and women should be informed of and reassured by this fact[51–54]. The effect of HIV on pregnancy outcome is discussed below.

Optimal timing of pregnancy

This issue is related to two distinct points, the first being the timing of pregnancy in relation to female fertility and the second being timing in relation to HIV disease status. Patients with HIV infection are offered routine medical follow-up every 3–6 months in those countries where HIV is treated as a chronic and ongoing infection. Unfortunately, such care is not available worldwide. At these visits, the CD4 count (white cells targeted by HIV) and viral load (HIV viral load levels in plasma) are measured and general health reassessed. This information is then used to advise on the timing of ART. Broad indications for starting ART include:

- Symptomatic HIV infection regardless of CD4 count and HIV viral load
- CD4 counts below 350/mm^3 (normal range 500–1000/mm^3)
- Patients with a high viral load (i.e. >30,000 copies/ml)[55].

UK guidelines recommend starting ART in established HIV infection following two consecutive CD4 samples below 350/mm^3 without any obvious explanation for the fall[56]. The guidelines from the International AIDS Society, USA (IAS-USA) are along similar lines[57] as are WHO guidelines[55].

Antiretroviral choice

A wide range of drugs are available for the treatment of HIV[58]. However, the selection of the appropriate agent is an increasingly complex science, and all HIV positive patients, especially those requiring treatment, should be managed by HIV specialists familiar with the complexities and side-effects of ART. If a woman needs to start treatment and there is a possibility of pregnancy in the future, this fact by itself will impact on the choice of drugs. The exact choice of medications is influenced by a number of issues including:

1. The CD4 count at initiation of therapy;
2. The baseline resistance profile, if resources are available to perform this test which is designed to detect the presence of virus which has developed resistance to available drug treatment;
3. The availability and cost of drugs especially in resource-limited settings.

Authoritative sources of further information include the British HIV Association guideline[59], Perinatal HIV Guidelines Working group[60] and WHO Recommendations 2010[61].

Antiretroviral therapy for maternal health

Antiretroviral therapy should be started for the benefit of maternal health if advised by a HIV specialist. If this decision comes at a time when the woman is in the first trimester of pregnancy and yet to start HAART with a CD4 of more than 200 cells/mm^3, then the ART may be delayed until the end of the first trimester[62].

HAART for prevention of mother to child transmission

For women who do not require ART for their own well-being, it should be used to prevent vertical transmission which would be between 15 and 40% without ART[3,63–65] and less than 2% with appropriate intervention. Because vertical transmission can occur at various stages in the peripartum period including delivery and during breastfeeding, these are the main areas where interventions are aimed. When ART is commenced in pregnancy solely to prevent vertical transmission it is termed short term antiretroviral therapy (START). When used in this context ART is stopped in the postpartum period. The optimal timing for initiating START should be before fetal viability, at around 24 weeks' gestation, with the aim of achieving an undetectable viral load (quantum of virus in plasma) before delivery, as this reduces transmission risk to 2%[60]. Women who have persistently low viral loads (<10,000 copies/ml) and require ART only for prevention of mother to child transmission (PMTCT) may opt for zidovudine (ZVD) monotherapy starting at a similar gestational age as described above. An elective cesarean section at 39 weeks' gestation is advocated in these situations. Women on ZDV have a lower incidence of preterm deliveries (PTD) compared to women on multiple antiretrovirals. Although prematurity has been associated with the use of an increasing number of antiretrovirals[58], the huge benefits provided by these agents far outweigh the risk and they should not be withheld.

GETTING PREGNANT

Concordant (both HIV positive) couples

In concordant couples, a theoretical risk of HIV 'superinfection', i.e. transmission of different strains and/or types of HIV with different resistance profiles, is present if condoms are not used[1]. Patients should be made aware of this, counseled against unprotected intercourse and sperm washing advised when attempting to conceive[1,26]. In situations where

this is neither affordable nor available and the couple decide to attempt pregnancy through unprotected intercourse it may be pragmatic to focus advice on the timing of unprotected intercourse during the fertile period. At all other times condoms should be used.

Discordant couples

HIV positive female and HIV negative male

The couple should be advised regarding the use of timed self insemination around the ovulation period. Intercourse should ideally be protected with ejaculation into a non-spermicidal condom. Self insemination of the semen can then be performed with a needleless syringe which is then deposited in the vagina close to the cervix. Turkey basters can be used but clinics often provide women with 10/20 ml syringes. This is well documented and practiced.

HIV positive male and HIV negative female

The main risk in this circumstance is that the woman becomes infected whilst trying to conceive. A number of options can minimize this risk.

Insemination using donor sperm Donor sperm totally excludes the risk of infecting the partner. All sperm donors are screened for blood borne viruses. The drawback of this methodology, however, is that the child conceived will have no genetic relationship to the 'father'.

Sperm washing This is an effective and safe, risk reduction option if undertaken properly as shown by data from Italy and the UK[6]. It is important to inform the couple that this process is not a risk free option, but rather represents a risk reduction option. What is the risk that the sample might be HIV positive after washing? The risk of the washed sample having detectable HIV is 5–6%[66–68]. After washing, 5–6% of semen samples are HIV polymerase chain reaction (PCR) positive using the ultrasensitive assay. This assay detects more than 25 HIV copies/ml. Such samples are obviously discarded. Thus, HIV testing of the washed sample is recommended. The process of sperm washing involves separation of the spermatozoa from the infected seminal fluid and non-sperm cells. The female partner is then inseminated with the washed sperm. Documented success rates of ongoing pregnancies from various centers range from 12.5 to 27.7%[4,68,69].

Use of ART UK and American guidelines discourage unprotected sexual intercourse regardless of the duration of HIV infection and plasma viral load[1,70]. This includes couples where the infected male partner is on ART and has an undetectable viral load, due to the fact that the viral load in semen correlates poorly with that in serum[3,71,72]. Accordingly, men with undetectable plasma viral loads can still transmit HIV in semen where the testes act as a 'sanctuary site'[73].

Adoption This is a final option, although clearly the child will not have a genetic relationship to either parent.

PREGNANCY PROBLEMS IN HIV POSITIVE WOMEN

First trimester

Early referral to an obstetrician is advised, preferably as soon as a pregnancy is confirmed.

Nausea and vomiting

These symptoms are common in early pregnancy and are usually resolved by the second trimester. The occurrence of nausea and vomiting can affect women taking ART; however,

patients should be advised to adjust their pill timing if necessary.

In HIV positive women on ART, a diagnosis of hyperemesis should only be made once all organic causes have been ruled out, especially lactic acidosis, hepatitis and pancreatitis, all of which may be complications of ART. Antiemetics that are safe in pregnancy may be used. There are no known interactions between antiemetics and antiretrovirals.

Miscarriage rate

There is no evidence of an increased risk of miscarriage in HIV positive patients[63,74,75], although the risk of preterm delivery may be increased with increasing numbers of ART. In certain circumstances, as mentioned above, it may be reasonable to use a single ART. However, even with the possible risks of multiple ART use, the benefits of preventing mother to child transmission outweigh the small risk of miscarriage.

Fetal abnormality

HIV is not associated with an increased rate of fetal abnormality. To date, two ART are best avoided in pregnancy: didanosine increases the fetal abnormality rate above the expected background risk, and efavirenz has been associated with congenital malformation in macaques. This drug is contraindicated in pregnancy or in women who may wish to conceive.

Preterm delivery

The risk of preterm delivery is increased with HAART[59]. However, the HIV positive woman presenting with threatened preterm delivery should be managed in the same manner as the HIV negative woman. If preterm rupture of membranes occurs after 34 weeks, delivery should be expedited after an infection screen, paying particular attention to genital infections. Antibiotic coverage is advised.

If there is preterm rupture of membranes at less than 34 weeks, the clinician should balance the risks of fetal prematurity against prolonging the pregnancy. The maternal viral load, HAART and any maternal co-morbidities need to be considered and a multidisciplinary approach is advisable.

Postpartum

Breastfeeding and the mode of delivery can be discussed during preconceptional counseling and in early pregnancy.

Breastfeeding

Because breastfeeding is associated with a two-fold increase in the rate of HIV transmission, it is not advised in resource rich countries[58]. Women should be made aware of this possibility at a stage early enough to discuss any concerns. Pharmacological suppression of lactation can be considered postdelivery if necessary.

Mode of delivery

Elective cesarean section reduces MTCT[58,65]. The final decision on mode of delivery requires a balancing of the risks of maternal complications with benefits. Factors to be considered are the maternal viral load, past obstetric history and use of HAART. Evidence is emerging that viral control and other interventions in the perinatal period may sufficiently reduce risk to enable clinicians to allow vaginal deliveries in some settings where there is optimal control[76,77].

Fetal blood test

In the developed world the neonate will be given ART from birth usually for a period of

1 month[55]. The gold standard test for HIV infection in infancy is an HIV DNA PCR on peripheral blood lymphocytes. The infant is tested at 1 day of life, and 6 and 12 weeks of age. If all tests are negative and the infant is not breastfed, the child is deemed HIV negative. Antibody tests for HIV are only reliable at 18 months because of detectable maternal antibody prior to this age.

CONCLUSION

In the late 1980s and early 1990s HIV was largely untreatable and women were strongly advised not to have children. The development of ART has transformed approaches to care. Patients with HIV can look forward to a much longer and healthier life. They can also consider childbearing with a less than 2% risk of transmission to the child if good preconceptional and antenatal care is provided. The future goal of successful vaccination to prevent primary infection remains elusive but not impossible.

REFERENCES

1. British Association for Sexual Health and HIV. *2007 UK Guidelines for the management of Sexual and Reproductive Health (SRH) of people living with HIV infection*. www.bashh.org/guidelines
2. Masmas TN, Jensen H, Silva D, Hoj L, Sandstrom A, Survival among motherless children in rural and urban areas in Guinea-Bissau. *Acta Paediatr* 2004;93:99–9
3. Michaels D, Levine C. Estimates of the number of motherless youth orphaned by AIDS in the United States. *JAMA* 1992;268:3456–61
4. Gilling-Smith C. Assisted reproduction in HIV-discordant couples. *AIDS Reader* 2000;10:581–7
5. Williams CD, Finnerty JJ, Newberry YG, *et al*. Reproduction in couples who are affected by human immunodeficiency virus: medical, ethical, and legal considerations. *Am J Obstet Gynecol* 2003;189:333–41
6. Gilling-Smith C, Nicopoullos JD, Semprini AE, *et al*. HIV and reproductive care – a review of current practice. *BJOG* 2006;113:869–78
7. Stanwood NL, Cohn SE, Heiser JR, *et al*. Contraception and fertility plans in a cohort of HIV-positive women in care. *Contraception* 2007;75:294–8
8. Sullivan JL.Prevention of mother to child transmission of HIV – What next? *J Acquir Immune Defic Syndr* 2003;34(Suppl 2):S67–72
9. European Collaborative Study. Mother to child transmission of HIV infection in the era of highly active antiretroviral therapy. *Clin Infect Dis* 2005;40:458–65
10. Centers for Disease Control. Pneumocystis pneunomia – Los Angeles. *Morbid Mortal Wkly Rep* 1981;30:250
11. Barre-Sinoussi F, Chermann JC, Rey F, *et al*. Isolation of a T-lymphotropic retrovirus from a patient at risk for AIDS. *Science* 1983;220:868–70
12. Piot P, Plummer FA, Mhalu FS, *et al*. AIDS: an international perspective. *Science* 1988;239:573–9
13. Royce RA, Seña A, Cates W Jr, Cohen MS. Sexual transmission of HIV. *N Engl J Med* 1997;336:1072–8
14. Health Protection Agency. *42% of Africans with HIV in the UK are diagnosed late*. www.hpa.org.uk/webw/HPAweb&HPAwebStandard/HPAweb_C/1225789252997?p=1204186170287
15. Castilla J, Sobrino P, de la Fuente L, Noguer I. Late diagnosis of HIV infection in the era of highly active antiretroviral therapy. *AIDS* 2002;16:1645. www.aidsonline.com
16. CDC. *Revised Recommendations for HIV testing of adults, adolescents and pregnant women in health care settings*. http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5514a1.htm?s_cid=
17. Townsend CL, Cliffe S, Tookey PA. Uptake of antenatal HIV testing in the United Kingdom: 2000-2003. *J Public Health* 2006;28:248–52
18. WHO. *1999 HIV in Pregnancy: A Review*. Geneva: WHO, 1999
19. UNAIDS/UNFPA/UNIFEM. Women and HIV/AIDS: Confronting the crisis. 2004. www.unfpa.org/hiv/women/docs/women_aids.pdf
20. UNAIDS/WHO. Women and AIDS: An extract from the AIDS epidemic update December

2004. 2004. www.data.unaids.org/gcwa/jc986-epiextract_en.pdf
21. Royce RA, Sena A, Cates W Jr, Cohen MS. Current concepts; sexual transmission of HIV. *N Engl J Med* 1997;336:1072–8
22. Chu JH, Gange SJ, Anastos K, *et al*. Hormonal contraceptive use and the effectiveness of highly active antiretroviral therapy. *Am J Epidemiol* 2005;161:881–90.
23. Sinei SK, Morrison CS, Sekadde-Kigondu C, Allen M, Kokonya D. Complications of use of intrauterine devices among HIV-1-infected women. *Lancet* 1998;351:1238–41
24. WHO. *Selected practice recommendations for contraceptive use*. Geneva: World Health Organization, Department of Reproductive Health and Research, 2004
25. Frodsham LC, Boag F, Barton S, *et al*. Human immunodeficiency virus infection and fertility care in the United Kingdom: demand and supply. *Fertil Steril* 2006;85:285–9
26. Harlow S, Schuman P, Cohen M, *et al*. Effect of HIV infection on menstrual cycle length. *J Acquir Immune Defic Syndr* 2000;24:68–75
27. CEMACH. *Saving Mothers' Lives 2003-2005*. CEMACH December 2007. www.cmace.org.uk
28. NHS National Institute for Health and Clinical Excellence. *Maternal and child nutrition*. http://www.nice.org.uk/nicemedia/pdf/PH011quickrefguide.pdf
29. American Academy of Pediatrics and the American College of Obstetricians and Gynecologists. In: Gilstrap L, Oh W, eds. *Guidelines for Perinatal Care*, 5th edn. Washington DC: American Academy of Pediatrics and the American College of Obstetricians and Gynecologists, 2002
30. Kramer MS. Energy/protein restriction for high weight-for-height or weight gain during pregnancy. *Cochrane Database Syst Rev* 2000:CD000080
31. United States Department of Health and Human Services, Public Health Service, National Institutes of Health National Heart, Lung, and Blood Institute Obesity Education Initiative. *Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults*: The Evidence Report. Bethesda, MD: The Department, 1998. NIH Publication NO. 98-4083
32. Royal College of Obstetricians and Gynaecologists. *RCOG Statement No 5*. March 2006. www.rcog.org.uk/files/rcog-corp/uploaded-files/RCOGStatement5AlcoholPregnancy2006.pdf
33. Stratton K, Howe C, Battaglia FC, eds, Committee to Study Fetal Alcohol Syndrome. Institute of Medicine. *Fetal Alcohol Syndrome: Diagnosis, epidemiology, prevention, and treatment*. Washington, DC: National Academies Press, 1996.
34. American College of Obstetricians and Gynecologists. Substance abuse in pregnancy.Technical Bulletin No. 195, July 1994 (replaces No. 96, September 1986). *Int J Gynaecol Obstet* 1994;47:73–80
35. Aceijas C, Stimson GV, Hickman M, Rhodes T, on behalf of the United Nations Reference Group on HIV/AIDS Prevention and Care among IDU in Developing and Transitional Countries. Global overview of injecting drug use and HIV infection among injecting drug users. *AIDS* 2004;18:2295–303
36. Klinkenberg WD, Sacks S. Mental disorders and drug abuse in persons living with HIV/AIDS. *AIDS Care* 2004;16:22–42
37. Luft BJ, Remington JS. Toxoplasmic encephalitis in AIDS. *Clin Infect Dis* 1992;15:211–22
38. Health Protection Agency. *Mapping the Issues; HIV and other Sexually Transmitted Infections in the United Kingdom*. 2005. www.hpa.org.uk/hpa/publications/hiv_sti_2005/default.htm
39. Health Protection Agency. *HPA Annual Report: A Complex Picture :HIV and other Sexually Transmitted Infections in the United Kingdom*. 2006. www.hpa.org.uk/publications/2006/hiv_sti_2006/pdf/a_complex_Picture_2006_last.pdf
40. Centers for Disease Control and Prevention. Control and prevention of rubella: evaluation and management of suspected outbreaks, rubella in pregnant women, and surveillance for congenital rubella syndrome. *MMWR* 2001;50 (RR12)
41. American College of Obstetricians and Gynecologists. Rubella vaccination. Committee opinion no. 281, December 2002. *Int J Gynaecol Obstet* 2003;81:241.
42. Johnson AM. Heterosexual transmission of human immunodeficiency virus. *Br Med J* 1988;296:1017–20

43. Kapetanovic S, Christensen S, Karim R. Correlates of perinatal depression in HIV-infected women. *AIDS Patient Care STDS* 2009;23:101–8
44. Dulioust E, Du A, Costagliola D, *et al*. Semen alterations in HIV-1 infected men. *Hum Reprod* 2002;17:2112–8
45. Nicopoullos JD, Almeida PA, Ramsay JW, Gilling-Smith C. The effect of human immunodeficiency virus on sperm parameters and the outcome of intrauterine insemination following sperm washing. *Hum Reprod* 2004;19:2289–97
46. Crittenden JA, Handelsman DJ, Stewart GJ. Semen analysis in human immunodeficiency virus infection. *Fertil Steril* 1992;57:1294–9
47. Saracco A, Musicco M, Nicolosi A, *et al*. For the Italian partner study. Man to woman sexual transmission of HIV: a longitudinal study of 343 steady partners of infected men. *J Acquir Immune Defic Syndr* 1993;6:497–502
48. Mastro T, De Vincenzi I. Probabilities of sexual HIV transmission. *AIDS* 1996;10(Suppl A):575–82
49. Aaron EZ, Criniti SM. Preconception health care for HIV infected women. *Top HIV Med* 2007;15:137–41
50. Golombok S, Harding R, Sheldon J. An evaluation of a thicker versus a standard condom with gay men. *AIDS* 2001;15:267–9
51. WHO. *HIV in Pregnancy: A Review*. Geneva: WHO, 1999
52. Hocke C, Morlat P, Chene G, *et al* and the Groupe d'épidémiologie clinique du SIDA en Aquitaine. Prospective cohort study of the effect of pregnancy in the progression of human immunodeficiency virus infection. *Obstet Gynecol* 1995;86:886–91
53. Brettle RP, Raab GM, Ross A, *et al*. HIV infection in women: immunological markers and the influence of pregnancy. *AIDS* 1995;9:1177–84
54. Bessinger R, Clark R, Kissinger P, *et al*. Pregnancy is not associated with the progression of HIV disease in women attending an HIV outpatient program. *Am J Epidemiol* 1998;147:434–40
55. WHO. *Safe and Effective: Use of Antiretroviral treatments in Adults with Particular Reference to Resource Limited settings*. 2001. http://apps.who.int/medicinedocs/en/d/Jh2949e/
56. British HIV Association guidelines for the treatment of HIV – 1 – infected adults with antiretroviral therapy 2008. *HIV Med* 2008;9:563–608
57. Hammer SM, Eron JJ, Reiss P, *et al*. Antiretroviral treatment of adult HIV infection. 2008 Recommendations of the International AIDS Society – USA Panel. *JAMA* 2008;300:555–70
58. British Medical Association and the Royal Pharmaceutical Society of Great Britain. *British National Formulary No 57*. March 2009
59. de Ruiter A, Mercey D, Anderson J, *et al*. British HIV Association and Children's HIV Association guidelines for the management of HIV infection in pregnant women 2008. *HIV Med* 2008;9:452–502
60. Perinatal HIV Guidelines working group. Public Health Service Task Force *Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-Infected Women for Maternal Health and Interventions to Reduce Perinatal Transmission in the United States*. April 29 2009:1–90. Available at http://aidsinfo.nih.gov/contentfiles/PerinatalGL.pdf
61. WHO. *Antiretroviral drugs for treating pregnant women and preventing HIV infection in infants: towards universal access. Recommendations for a public health approach*. 2010 version. http://www.who.int/hiv/pub/mtct/antiretroviral/en/index.html
62. Royal College of Obstetricians and Gynaecologists. *Management of HIV in pregnancy*. Guideline No. 39. London: RCOG, 2004
63. Coll O, Fiore S, Floridia M, *et al*. Pregnancy and HIV infection: a European consensus on management. *AIDS* 2002;16(Suppl 2):S1–18
64. European Collaborative Study. Mother to child transmission of HIV infection in the era of highly active antiretroviral therapy. *Clin Infect Dis* 2005;40:458–65
65. The International Perinatal HIV group. Mode of delivery and vertical transmission of HIV-1: A meta-analysis from 15 prospective cohort studies. *N Engl J Med* 1999;340:977–87
66. Gilling-Smith C, Almeida P. HIV, Hepatitis B and Hepatitis C and infertility: Reducing risk. Educational Bulletin sponsored by the Practise and Policy Committee of the BSF. *Hum Fertil* 2003;6:106–12
67. Marina S, Marina F, Alcolea A, *et al*. Human immunodeficiency virus type 1 sero discordant couples can bear healthy children after undergoing intrauterine insemination. *Fertil Steril* 1998;70:35–9

68. Marina S, Marina F, Alcolea R, *et al*. Pregnancy following intracytoplasmic sperm injection from an HIV-1 sero positive man. *Hum Reprod* 1998;13:3247–9
69. Semprini AE, Levi-Setti P, Bozzo M, *et al*. Insemination of HIV-negative women with processed semen of HIV- positive partners. *Lancet* 1992;340:1317–9
70. AIDSinfo. *HIV Guidelines – Adult and Adolescent*. http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf
71. Luizzi G, Chirianni A, Clement M, *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:F51–6
72. Coombs RW, Speck CE, Hughes JP, *et al*. Association between culturable human immunodeficiency virus type 1 (HIV-1) in semen and HIV-1 RNA level in semen and blood: Evidence for compartmentalisation of HIV-1 between semen and blood. *J Infect Dis* 1998;177:320–30
73. Zhang H, Domadula G, Beumont M, *et al*. Human immunodeficiency virus type 1 in the semen of men receiving highly active antiretroviral therapy. *N Engl J Med* 1998;339:1803–9
74. van Benthem BH, de Vincenzi I, Delmas MC, *et al*. Pregnancies before and after HIV diagnosis in a European cohort of HIV-infected women. European Study on the Natural History of HIV Infection in Women. *AIDS* 2000;14:2171–8
75. Massad LS, Springer G, Jacobson L, *et al*. Pregnancy rates and predictors of conception, miscarriage and abortion in US women with HIV. *AIDS* 2004;18:281–6
76. Boer K, Nellen JF, Patel D, *et al* The AmRo study:pregnancy outcome in HIV-1-infected women under effective highly active antiretroviral therapy and a policy of vaginal delivery. *BJOG* 2007;114:148–55
77. Islam S, Oon V, Thomas P. Outcome of pregnancy in HIV-positive women planned for vaginal delivery under effective antiretroviral therapy. *J Obstet Gynaecol* 2010;30:38–40