

Human immunodeficiency virus/acquired immunodeficiency syndrome and infertility: emerging problems in the era of highly active antiretrovirals

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Objective: To review the effects of human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) in terms of its associated comorbid conditions and the side effects of antiretroviral treatment on fertility.

Design: PubMed computer search to identify relevant articles.

Setting: Research institution.

Patient(s): None.

Intervention(s): None.

Main Outcome Measure(s): None.

Result(s): Biological alterations in reproductive physiology may account for subfertility in patients infected with HIV. Psychosocial factors in patients with HIV infection may affect their reproductive desires and outcomes. Antiretroviral medications may have direct toxicity on gametes and embryos. Available evidence indicates that fertility treatments can be a safe option for couples with HIV-discordant infection status, although the potential risk of viral transmission cannot be completely eliminated.

Conclusion(s): Because their potential reproductive desires are increasingly becoming a concern in the health care of young HIV-infected patients, additional data are needed to address the effect of HIV and its treatments on their fertility and reproductive outcomes. (*Fertil Steril*® 2011;96:546–53. ©2011 by American Society for Reproductive Medicine.)

Key Words: AIDS, fertility, HAART, HIV, infertility, reproduction

From an epidemiologic perspective, acquired immunodeficiency syndrome (AIDS) is a global crisis (1) with approximately 1 million in the United States and >33 million worldwide infected with human immunodeficiency virus 1 (HIV-1), the causative agent (2–7). Fortunately, HIV/AIDS survival has been enhanced by medical therapy with nucleoside analogue reverse transcriptase inhibitors (NRTIs). Presently, drug combinations called highly active antiretroviral therapy (HAART) are the standard of care in the developed world, and this therapeutic boon has improved mortality and morbidity in patients with HIV/AIDS. Importantly, decreased mother-to-child HIV-1 transmission, which in the United States now is essentially absent, was a direct result of prenatal and perinatal antiretroviral therapy in at-risk pregnant women.

Because of the efficacy of therapy, newly diagnosed HIV/AIDS patients are now living with a manageable chronic condition. HIV is most prevalent among persons of reproductive age, about one-third of whom desire to have children. As a result, reproductive desires have emerged as clinically important in patients with HIV/AIDS. We review the effects of the combination of HIV/AIDS, its associated comorbid conditions, and the side effects of antiretroviral treatment on fertility in this unique, growing population.

The following points are addressed in this review:

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1. Potential deleterious effects of HIV-1 infection on fertility in females and males.
2. The impact of comorbidities (e.g., sexually transmitted diseases, drug abuse) on fertility.
3. The impact of antiretroviral therapy on fertility.

Finally, we will expand on issues addressed in prior publications, including fertility treatment in serodiscordant couples, strategies to lower horizontal transmission, and the medicolegal and ethical considerations.

FEMALE INFERTILITY AND HIV-1 INFECTION

Early studies in Sub-Saharan Africa showed that fertility was 25% to 40% lower in HIV-1 infected women than among uninfected controls. This was the first suggestion that HIV/AIDS was associated with fertility defects. However, the general health of patients and particularly those with HIV/AIDS in that geographic region may vary considerably from that in the developed world. Surprisingly, HIV infected teenagers were reported to be more fertile than uninfected controls. This counterintuitive observation was explained by selection for earlier sexual activity in that subset of patients (8). Decreased fertility rates in HIV-infected women have been described in the United States in more recent studies (9).

Biological alterations in reproductive physiology may account for subfertility in HIV-1 infected women. Systemic illness, stress, weight loss, and drug abuse may impact reproductive potential. It should be noted that wasting is considered a major diagnostic criterion for AIDS, as emphasized by the fact that in Africa AIDS may be euphemistically called “slim disease” in lay conversation. On a reproductive endocrinology basis, HIV-infected women are more likely to have protracted anovulation and amenorrhea (10, 11).

The mechanisms underlying this clinical observation are unknown. However, several well-done studies have found no association between HIV infection and amenorrhea after adjusting for age, body mass index, and substance use (12, 13). The number of ovulatory cycles and coital frequency correlate with severity of HIV/AIDS clinical status, obviously impact fertility, and may reflect the degree of wasting and immunosuppression in AIDS. A direct effect of HIV leading to gonadal failure has been proposed in both men and women; however, proof of this hypothesis remains elusive (11, 14).

The testes from men with AIDS have been examined systematically (14); however, this type of study has not been done on ovaries from women with AIDS. Several studies have suggested a link between HIV infection and premature ovarian failure. A small study found elevated serum follicle-stimulating hormone (FSH) levels consistent with menopause in 8% of HIV-infected women aged 20–42 years (15). In a larger study, including 1,139 HIV-infected women and 292 uninfected controls, HIV status had no statistically proven effect on the occurrence of elevated FSH levels among women with amenorrhea. However, HIV-infected women were three times more likely than HIV-negative controls to have prolonged amenorrhea without ovarian failure (11). Another study evaluating biologic measures of reproductive aging including FSH, inhibin B, and antimüllerian hormone levels in 187 HIV-infected women and 76 uninfected controls found no evidence that HIV infection influences ovarian aging (16). Because HIV-infected women are at a high risk for concomitant sexually transmitted diseases that are known to contribute to tubal blockage (17–19), secondary infection could decrease fertility. The incidence of tubal occlusion on hysterosalpingogram has been demonstrated as high as 27.8% among HIV-infected women (20).

After conception, pregnancy-related difficulties may continue. In clinical studies, pregnancy loss is more common among HIV-infected women than uninfected women (18.5% vs. 12.2%) (21). Before HAART was used widely, pregnancy loss rates were reported to be 67% higher among HIV-1 infected women compared with seronegative controls (22). Recently, HAART use before pregnancy has been found to be protective against miscarriage (OR, 0.37; 95% CI, 0.15–0.94) (9). However, a large trial from the United Kingdom and Ireland found a miscarriage rate of 4%, which remained constant from 1990 through 2006 despite evolution of therapy during this period (23).

PSYCHOSOCIAL FACTORS AND INFERTILITY IN HIV/AIDS

Unique psychosocial factors in patients with HIV infection may affect reproductive outcomes. A new diagnosis of HIV is often followed by a decrease of sexual activity in that individual. Studies demonstrate decreased pregnancy and birth rates among HIV-infected women (24, 25), possibly by their own choice. Despite these factors, high-risk behavior and unplanned pregnancies remain prevalent among HIV-infected women (26). Additionally, HIV-infected women are more likely to electively terminate pregnancy. Data from Britain and Ireland indicate a significant increase in the pregnancy termination rate from 3.5 to 6.3 per 100 women years after a new HIV diagnosis, which is consistent across age and ethnic groups (24). In an Australian study, 47% of pregnancies were voluntarily terminated after an HIV diagnosis, a rate more than double that of the general population (25). This suggests that some HIV-infected women terminate pregnancies in light of the challenges that pregnancy, birth, and parenting in the context of HIV infection entail. After the introduction of HAART into clinical practice, several studies

have documented a decrease in the rate of elective pregnancy termination among women with HIV. Townsend et al. (23) reported a significant decrease in terminations from 29.6% in 1990–1993 to 3.4% in 2004–2006 in the United Kingdom and Ireland. The proportion of pregnancies ending in termination decreased from 59.4% to 37.5% after introduction of zidovudine (AZT) prophylaxis in France (27). In a U.S. cohort, Massad et al. (9) reported that HAART users were less likely to electively terminate a pregnancy (OR, 0.33; 95% CI, 0.17–0.67) compared with women receiving no therapy. The HIV-infected women were significantly more likely to electively terminate a pregnancy if it was unplanned, they had lower CD4 counts, or they had an HIV-infected current partner (28).

With the widespread use of HAART, it is possible that behavioral factors and improvement in the overall health and immune status in HIV-1 infected women are sufficient to overcome biological subfertility caused directly by HIV infection *per se*. Patient optimism regarding their response to HAART has been linked to both increased reproductive intention and sexual behavior. Women who planned to have more children had significantly higher HAART optimism scores than women who did not intend to have more children. Sexually active women who reported practicing unprotected intercourse had significantly higher HAART optimism scores than women who were abstinent or practiced protected sexual intercourse (29). Although these may be logical behavioral actions on the part of these patients, more direct studies that evaluate HAART effects on reproductive competence and behavior are needed.

POPULATION DYNAMICS, FERTILITY, AND HIV/AIDS

As may be expected in geographical areas in which HIV-1 infection is prevalent and clinical resources are limited, premature mortality of reproductive-age women, their partners, and their children can lead to alterations of fertility rates at a population level. Additionally, HIV/AIDS is now also recognized as a major cause of global maternal mortality (30).

It is axiomatic to see that the problem of infertility in geographic regions where HIV infection is high relates directly to genesis of a sustainable adult population, an important underpinning for societal progress. Arguably, HIV infection and AIDS impact economic and political stability on a population basis in nations and continents, as suggested in the United Nations report (31). Population dynamics can influence fertility choices at the individual level and vice versa. Awareness of HIV/AIDS may affect fertility intentions of individuals in an entire population. High awareness of AIDS affects the age of sexual debut, coital frequency, use of barrier contraceptives, and rates of remarriage (8, 32–34). Although it is difficult to analyze individual and societal changes in response to the HIV/AIDS pandemic involving reproductive goals and strategies, the value of marriage, sexual and contraceptive practices, and breast feeding have been suggested in both the HIV-1 infected and uninfected population in Sub-Saharan Africa (35).

INTERACTIONS AMONG HIV, NRTIS, AND MITOCHONDRIA IN INFERTILITY

Zidovudine (AZT) and other NRTIs used in HAART are known mitochondrial toxins *in vivo* and *in vitro*. One postulated mechanism of their toxicity posits depletion of mitochondrial DNA (mtDNA) by inhibition of its DNA polymerase and a resultant decrease in polypeptides involved in electron transport (36).

As mentioned previously, NRTIs inhibit HIV-1 reverse transcriptase (37) to reduce viral replication, viremia, and disease manifestations (38). Similarly, antiretroviral nucleosides inhibit mtDNA

synthesis, leading to toxicity (39–45). Our laboratory coined the “pol γ hypothesis” (45, 46) that links inhibition of mitochondrial pol γ (the mtDNA replicase) (47–52), mtDNA depletion, and mtDNA mutation with antiretroviral nucleoside toxicity and tissue damage in the heart, liver, skeletal muscle, and kidney. Defects in mtDNA replication and decreased energetics are caused by AZT (46, 53–58).

This was documented experimentally in vivo using transgenic mouse models of HIV/AIDS (NL4-3 Δ gag/pol TG) with monotherapy and combination antiretroviral nucleoside therapy (56, 57). Our laboratory team showed oxidative stress was integral to the cardiomyopathy (55, 59) from HIV/AIDS, from HIV-1 Tat expressed in cardiac myocytes, and from antiretroviral nucleosides. Conversely, amelioration of oxidative stress prevented cardiomyopathy from antiretroviral nucleosides (60).

On a cell biological basis, mitochondria are central determinants of developmental competence in oocytes and preimplantation embryos (61–66). Based on the pol γ hypothesis of inhibition of mtDNA replication, an individual's reproductive potential may be adversely affected by NRTIs via damage to mitochondrial biogenesis in gametes. Data exist to support this concept. mtDNA depletion has been observed in sperm and oocytes of patients receiving NRTIs (67, 68). Plausibility is further supported, albeit indirectly, by low oocyte mtDNA content in patients with ovarian insufficiency (69). Oocytes with low mtDNA abundance have been shown to have a decreased potential for fertilization (70).

Antiretroviral use has been associated with a lower likelihood of conception in a recent prospective cohort study conducted at six U.S. centers (9). However, another recent study conducted in seven African countries with 4,531 HIV-infected participating women documented a significantly higher pregnancy rate among those receiving antiretroviral therapy (9.0 per 100 person-years compared with 6.5 per 100 person-years among those not on therapy) (71). Specific behavioral and biological mechanisms were not explored. Other factors that independently associated with pregnancy incidence were age, education level, marriage or cohabitation, use and type of contraception, and CD4 counts.

Animal studies provide different information. Some animal studies indicate that HAART may decrease reproductive competence. Direct toxic effects of AZT on developing mouse embryos have been demonstrated both in vivo and in vitro. Data suggest that the critical period of AZT exposure occurs between ovulation and implantation, and AZT has been shown to suppress cell division in the preimplantation mouse embryo, resulting in reduced inner cell mass proliferation, a greater number of resorptions, and fewer fetuses (72, 73). Reproductive toxicity of AZT leading to more resorptions and smaller litter sizes has been reported in rats and rabbits (74, 75).

Although experimental studies have not examined the fertility effects of NRTI in a primate model, several studies have examined the intrauterine effects of NRTIs after the pregnancy has become established. Studies on *Erythrocebus patas* monkeys that were exposed transplacentally to NRTIs have described significant fetal mitochondrial damage. After in utero exposure, AZT was found to be incorporated into fetal mitochondrial DNA from skeletal muscle, liver, kidney, and placenta (76). Mitochondrial toxicity was evidenced by depletion in mtDNA and by OXPHOS enzyme abnormalities in the heart, skeletal muscle, and placenta of AZT-exposed monkey fetuses (77). Examination of fetal blood and umbilical cords taken from retroviral-uninfected monkey infants and from human infants born to HIV-1-infected women revealed NRTI-induced mitochondrial damage (78).

COMORBID CONDITIONS RELATING TO INFERTILITY IN HIV/AIDS

Orchitis and acute epididymitis in HIV-positive men has been reported involving opportunistic infections including cytomegalovirus (CMV), salmonella, toxoplasmosis, *Ureaplasma urealyticum*, *Corynebacterium* sp., *Mycoplasma* sp., and *Mima polymorpha*, fungi, and mycobacteria. Kaposi sarcoma and lymphoma involving the testes have also been described (79–82). Pelvic inflammatory disease in HIV-positive women is more likely to be associated with tuboovarian abscesses; the response to standard treatment is the same as in HIV-negative women (83). The HIV-infected women have higher rates of concomitant *M. hominis*, *Candida*, streptococcal, and human papillomavirus (HPV) infections (82). Most sexually transmitted infections are treated the same way in HIV-positive and HIV-negative women (82).

As many as 50% to 90% of HIV-infected patients may be coinfecting with herpes simplex virus-2 (HSV-2) (84). In the setting of HIV, HSV infections tend to be more severe, take longer to resolve, and may be more resistant to acyclovir (85, 86). In infected patients, HAART reduces the incidence of herpetic ulcers. Also, HSV-2 infection is associated with a twofold to fourfold increased risk of HIV-1 acquisition, and mucosal HIV-1 shedding is increased during mucocutaneous HSV-2 replication (87). Persistent herpetic lesions in a patient receiving antiviral therapy may indicate HSV drug resistance; a lesion present for more than 1 month is considered AIDS defining. Acyclovir-resistant HSV infections are usually also resistant to valacyclovir; foscarnet may be used as the next step in treatment (84). Long-term suppression with acyclovir should be strongly considered because it is both safe and effective (86).

Syphilis and neurosyphilis are more prevalent among HIV-infected patients. Ulcers facilitate HIV transmission. The treatment is similar to that of HIV negative patients (82). HIV-infected women who have chancroid are more prone to treatment failure and may require longer courses of therapy (82). All patients with HIV should be regularly screened for hepatitis C virus (HCV) due to the high coinfection prevalence. Trichomoniasis in HIV-infected women may increase genital shedding of the HIV virus. *T. vaginalis* predisposes women to upper genital tract infections, screening should be performed when initiating care and then annually (82).

Infection with HIV has contributed to a worldwide increase in the incidence of tuberculosis (TB). The genitourinary tract is the second most common site, after the lungs, for TB infection. Tuberculosis can cause infertility and contributes to other poor reproductive health outcomes, especially in the setting of HIV infection. The literature on the subject of genital tuberculosis in HIV-infected patients is lacking (88–90). The recent HPTN 052 study showed promise in reducing HIV-associated disease, particularly tuberculosis, with early initiation of antiretroviral therapy as compared with delayed treatment (91).

MALE INFERTILITY AND HIV/AIDS

Male infertility also can impact reproductive efficacy in HIV/AIDS. Sperm parameters that reflect fertility are significantly impaired in HIV-1 infected men. The standard measurements are adversely affected, including semen volume and sperm motility, concentration, and morphology (92–94). Semen parameters correlate positively with CD4 counts (95), which suggests that patients with full-blown AIDS are less fertile than healthier HIV-1 infected males. Men infected with HIV-1 are more likely to have orchitis, hypogonadism, and leukospermia, which could account for oligospermia and teratozoospermia. Barboza et al. (96) employed atomic force

microscopy to examine sperm morphologic and topographic changes in HIV/AIDS patients receiving HAART and revealed that damage to the spermatozoa was due to HAART rather than the HIV-1 virus. These ultrastructural findings contrast with earlier ones where no adverse effect on sperm resulted from AZT treatment (97). Recent data indicate that HAART significantly decreases total sperm count, progressive motility, and postpreparation count while significantly increasing the proportion of abnormal sperm forms (95).

Hypogonadism, diminished libido, and impotence are major issues in HIV-infected men. Erectile and ejaculatory dysfunction is estimated to affect 60% of men with advanced disease (98). Caution should be used when treating erectile dysfunction with inhibitors of PDE5 in patients who are also taking protease inhibitors as both families of drugs are metabolized by cytochrome P450 3A4 (99–101). In general, the lowest dose of PDE5 inhibitor should be started to avoid the risk of adverse events such as priapism (101).

ENDOCRINE CONSIDERATIONS IN HIV/AIDS

Men tend to have normal testosterone levels early in the course of HIV disease. As the disease progresses to AIDS, testosterone levels decline. Androgen deficiency is particularly common in AIDS wasting syndrome (102). The progressive decline in testosterone has been attributed to both gonadal and extragonadal causes (103–106). Secondary hypogonadism is more commonly seen than primary hypogonadism due to testicular atrophy. However, both may lead to a similar clinical picture. It is important to measure both free and bioavailable testosterone because elevated sex hormone-binding globulin levels have been observed in HIV-infected men (107).

Use of alcohol and illicit drugs may affect testosterone production (108). Side effects of medications used in the treatment of HIV, including glucocorticoids (used as appetite stimulants) and ketoconazole, include suppression of the hypothalamic-pituitary-gonadal axis and inhibition of testosterone synthesis, respectively (109).

Lipodystrophy is common in HIV and remains an important clinical problem. Gynecomastia may be seen in HIV-infected men in association with protease inhibitor use, liver dysfunction, and as part of lipodystrophy (110), as we will discuss in detail. Treatment of symptomatic hypogonadal men with testosterone replacement should be considered after an appropriate investigation of the cause. Benefits of treatment may include improvement in body mass, strength, sexual and cognitive function, bone density, and quality of life (111, 112); these are counterbalanced by the serious side effects. It is important to recall that exogenous androgens inhibit spermatogenesis, so their use in men desiring future fertility may not be appropriate. In HIV-infected women, free testosterone is decreased compared with seronegative women (113). Testosterone replacement may improve weight and quality of life in women with AIDS wasting syndrome (114).

As mentioned previously, lipodystrophy, which is characterized by fat redistribution and insulin resistance, has been reported in both men and women after administration of HAART (115, 116). Hyperandrogenemia in women with lipodystrophy has been reported in association with insulin resistance, dyslipidemia, and an increased luteinizing hormone (LH) to FSH ratio (117). Although these data need to be confirmed, it is plausible that HAART therapy may lead to a phenotype similar to that of polycystic ovary syndrome.

ETHICAL CONSIDERATIONS PERTAINING TO FERTILITY AND HIV

A rapid coevolution of ethical considerations surrounding fertility in HIV-infected patients has taken place simultaneously with dramatic improvements in horizontal and vertical transmission rates and life expectancy. In the early 1990s, many investigators considered pregnancy in the setting of HIV to be morally problematic. A recent ethics committee report from American Society for Reproductive Medicine (ASRM) argues that it is ethical for health care providers to assist fertility-seeking HIV-infected patients after taking all reasonable precautions to limit the risk of HIV transmission (118). Furthermore, this report suggests that health care providers may be legally required to provide fertility services to HIV-infected patients by the Americans with Disabilities Act, as HIV was considered a disability by the U.S. Supreme Court decision in *Bragdon v. Abbott* (119–121).

Patients with HIV infection face multiple barriers to access reproductive care. Infertility specialists are not well versed with the biology of HIV or its therapy. The Centers for Disease Control and Prevention (CDC) have not endorsed intrauterine insemination (IUI) or in vitro fertilization (IVF) for HIV-infected patients; accordingly, physicians may be concerned with liability exposure. In some states, legislation prevents placing material that may harbor HIV into a patient. Finally, irrespective of “universal precautions,” the logistics and costs to outfit embryology and andrology laboratories with separate systems for virally infected patients may be prohibitive (122). Currently, fewer than 3% of U.S. fertility practices provide assisted reproductive services to HIV-infected patients (130).

FERTILITY TREATMENT

An important correlative issue regarding fertility treatment in patients with HIV includes the risk of horizontal HIV transmission in discordant couples and the methods of risk reduction. Fertility options for HIV-infected men and women include unprotected timed intercourse, intrauterine insemination (IUI) with partner or donor sperm, in vitro fertilization with intracytoplasmic sperm injection (IVF/ICSI), embryo donation, and adoption.

In epidemiologic studies, the efficiency of the spread of HIV infection is low, approximately 1 per 500 to 1 per 1,000 episodes of unprotected sexual intercourse. However, the risk factors for transmission—including genital tract infections, trauma with sex, lack of male circumcision, and elevated peripheral blood viral loads—can increase the efficiency of HIV transmission. Bacterial vaginosis, HSV-2, trichomonas, chlamydia, gonorrhea, and syphilis infection all increase HIV transmission risk (123, 124). In the pre-HAART era, the annual HIV transmission rate was 7.2% in couples engaging in unprotected intercourse. In a series of 104 natural conceptions with timed intercourse in HIV-serodiscordant couples, there was a 4.3% seroconversion rate in female partners (125, 126).

A thorough pretreatment evaluation involves obtaining a detailed HIV history that includes recent viral load and CD4, drugs and resistance, disease progression, high-risk behavior, complete infertility evaluation, and Pap smear as well as consultation with perinatology and pediatrics, and the establishment of a social support structure. Patients must understand the importance of risk-reduction treatment and be willing to take reasonable steps toward this goal.

Strategies to reduce the risk of horizontal HIV transmission include optimizing the chance of conception through optimal fertility treatment and suppressing viremia before treatment. Men with elevated peripheral viral loads should be treated with antiretroviral

therapy, and their semen should be tested for HIV RNA. Any sexually transmitted infections should be treated before fertility treatment. Safe sexual practices should be encouraged. A role for chemoprophylaxis with fertility treatment remains to be determined. Recent data indicate that preexposure prophylaxis with vaginal microbicide containing tenofovir can lower women's risk of HIV infection through intercourse by 39% and up to 54% in women with high adherence (127). Another recent trial involving preexposure chemoprophylaxis with combination oral antiretroviral drugs for HIV prevention in men who have sex with men found a 44% reduction in the incidence of HIV transmission (128). Data from the HPTN 052 study, a randomized clinical trial that was ended early after an interim review by an independent data and safety monitoring board, showed that early initiation of antiretroviral therapy for HIV-positive heterosexual people led to a 96% reduction in HIV transmission to the HIV-uninfected partner (91). The uninfected partner should be regularly screened during treatment and subsequent pregnancy. Risk reduction techniques are also used in couples where both partners are HIV positive to reduce the risk of infection with a different strain of HIV.

Fertility centers and sperm banks should follow current U.S. Food and Drug Administration (FDA) mandates: all donors should be screened for high risk factors and clinical evidence of infectious diseases, and should be tested for HIV-1 and HIV-2, hepatitis B virus, hepatitis C virus (HCV), human T-lymphotropic virus types 1 and 2, and cytomegalovirus (129). The current ASRM recommendations should be followed, including infectious disease screening of female recipients and using separate storage tanks for HIV and hepatitis to minimize the risk of cross-contamination (130).

Sperm washing to reduce HIV levels before insemination involves a three-step process. First, the liquefied semen is filtered through a Percoll gradient. Next, the recovered spermatozoa are washed to eliminate seminal plasma and hyperosmotic gradient media. Last, a modified swim-up method recovers highly motile spermatozoa free from leukocytes. Processing is manually performed and hence labor intensive. Although each step is highly effective in reducing viral content, some high-titer samples may exceed the capacity to clear the seminal viral load. The final aliquot of spermatozoa should be tested to exclude HIV RNA contamination, which is done by modified polymerase chain reaction or nucleic acid sequence based amplification; 5% to 10% of samples may contain residual virus after washing. In men with severe dyspermia, the final swim-up step to remove infected leukocytes cannot be performed;

the semen should be tested for HIV DNA. In 9.7% of intrauterine insemination (IUI) cycles performed with fresh sperm in men on HAART with undetectable viral load, detectable HIV was found in either prewash or postwash seminal samples (95).

In a series of 741 HIV-1 serodiscordant couples with all HIV-positive males in which 581 couples met the criteria to allow IUI treatment, a 19% pregnancy rate per cycle was reported; 160 couples had IVF-ICSI, and their pregnancy rate per cycle was 22%. There were no new infections (131). The Centre for Reproductive Assisted Techniques for HIV in Europe has reported outcomes from eight centers of 3,390 ART cycles (2,840 IUI, 107 IVF, 394 ICSI, and 49 FET) using sperm washing; there was no evidence of seroconversion in any uninfected partner or child on follow-up evaluation (132). Investigators at Columbia University recently published their 10 year experience involving 420 ICSI cycles with HIV-positive men. The ongoing pregnancy rate per embryo transfer was 37%. The obstetric outcomes included 41% multiple gestation rate, 5% high-order multiples, and 43% premature infants. There were no maternal or neonatal HIV infections (133). That same group of investigators reported IVF outcomes in 40 HIV-positive women (age range: 27 to 42 years), of whom 38 of 40 were on HAART. Those women had similar pregnancy outcomes to the HIV-negative controls. Throughout pregnancy, the maternal HIV RNA concentrations remained undetectable, and the CD4 counts were stable. All infants remained HIV negative up to 6 months of age (134).

CONCLUSION

Because more young HIV-infected patients are living longer, healthier lives, reproductive issues are increasingly becoming prominent in their health care. It may be concluded that fertility treatment is a safe option for HIV-discordant couples, and may be safer than attempted natural conception. In either case, the potential risk of viral transmission cannot be completely eliminated. Future treatments should be designed to help minimize the risk of HIV transmission and to improve understanding of the effects HIV and its treatments have on fertility and reproductive competence. Finally, complex social and ethical challenges as well as lack of access to care for many HIV-infected patients who desire reproduction need to be addressed at the level of the patient and the health care delivery system.

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