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HIV Infection and Infertility

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Abstract

Human immunodeficiency virus (HIV) infection has become a chronic and manageable disease since the availability of combination antiretroviral therapy (cART). Persons living with HIV are living longer with better quality of life. Given that worldwide many HIV-infected individuals are in the reproductive age, fertility and reproductive desire have emerged as clinically important issues among this population. Biological changes caused by HIV, including systemic illnesses, stress, and weight loss, may affect the function of reproductive organs and result in infertility. Newly diagnosed HIV infection may cause psychological trauma and decrease in sexual drive and sexual activity. Several HIV/acquired immune deficiency syndrome (AIDS)-related comorbidities have been reported to be associated with infertility. These include orchitis, acute epididymitis, and pelvic inflammatory disease caused by opportunistic pathogens and coinfections with sexually transmitted infections (STIs) acquired through a similar route of transmission as HIV. The common STIs caused by *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, *Ureaplasma urealyticum*, *Treponema pallidum*, herpes simplex virus-2, and *Trichomonas vaginalis* can damage the reproductive system and cause infertility. Hypogonadism especially in men with AIDS is one of the important endocrine disorders that causes infertility. Although cART provides significant benefits in reducing morbidity and mortality among HIV-infected persons, some antiretroviral drugs, including nucleoside reverse transcriptase inhibitors, are toxic to cellular mitochondria and may affect the mitochondrial biogenesis of sperm and oocytes. HIV-infected individuals may have limited access to reproductive care given the severity of their disease, cost of care, stigmatization, and lack of specific HIV infection/infertility knowledge among their providers.

In the post-cART era, reproductive care has become an important issue to be co-managed with HIV care. Reproductive care includes not only comprehensively managing HIV infection but also minimizing the risk of horizontal HIV transmission in serodiscordant couples, providing suitable options for unprotected timed intercourse, intrauterine insemination with partner or donor sperm, in vitro fertilization with intracytoplasmic sperm injection (IVF/ICSI), embryo donation, and adoption. This chapter reviews potential effects of HIV infection, related opportunistic infections, and physical and psychological comorbidities on fertility; the im-

pact of cART on fertility; and the management of reproductive issues among HIV-infected individuals.

Keywords: HIV, AIDS, Infection, Infertility

1. Introduction

There were approximately 37 million people living with human immunodeficiency virus (PLWHIV) globally at the end of 2014.[1] The course of HIV infection has changed from a deadly disease to a chronic and manageable disease since the introduction of combination antiretroviral therapy (cART) in the 1990s. The estimated life expectancy of a 20-year-old PLWHIV has increased from 30 years during 1996–1999 to 46 years during 2006–2008 according to the UK Collaborative HIV Cohort Study.[2] The increased life expectancy along with improved quality of life has led to increase in reproductive desire among this population.[3] Fertility of PLWHIV can be affected by HIV infection and associated infections. Infections can physically impact the anatomical structure and biological function of the reproductive system, whereas stress and psychiatric disorders related to HIV infection may lessen sexual drive and frequency of sexual intercourse. In addition, socioeconomic factors including limited financial means, difficulty accessing HIV care, and stigmatization can contribute to social withdrawal and reduced reproductive potential among PLWHIV. Management of reproductive health along with cART has become a necessary component of comprehensive HIV care in the post-cART era. The etiologies and epidemiology of HIV-related infertility, factors that may impact fertility, and management options and considerations for infertility among HIV-infected individuals are reviewed in this chapter.

2. Epidemiology of HIV-related infertility

The data on the magnitude and burden of HIV-related infertility derive mostly from studies conducted among HIV-infected women. A previous study using data from case–control studies and theoretical predictions from a model of the proximate determinants of fertility and HIV incidence in African countries demonstrated the 25–40% lower rate of fertility among HIV-infected women compared to HIV-negative women.[4] In a prospective cohort study from the United States during 1994–2002, women with HIV were less likely to conceive than uninfected women (pregnancy rates 7.4 vs.15.2 per 100 person-years, respectively).[5] Using demographic and health surveys between 2003 and 2007, the Joint United Nations Program on HIV/AIDS (UNAIDS) estimated that the global age-specific fertility ratio for HIV-infected women in the reproductive age group of 20–44 years is 0.53 to 0.76 compared to that of women without HIV.[6] A survey study conducted at HIV fertility clinics in the United Kingdom demonstrated a 40% prevalence of tubal factor infertility among HIV-infected women.[7] Despite the infertility in women living with HIV, pregnancy rates among this population have

increased steadily over the past 10 years to between 4 and 6 pregnancies per 100 person-years, varying by region due to the advances in HIV treatment and mother-to-child transmission prevention.[8] This may reflect an increase in reproductive desire and/or unexpected pregnancies and indicate the need for reproductive health care, fertility management, and family planning along with HIV comprehensive care among PLWHIV.

3. HIV effects on fertility

There are several factors associated with HIV infection that can potentially affect fertility in PLWHIV. These factors can be categorized into biological factors, psychological factors, and social factors (Figure 1).

Factors associated with infertility							
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Note: AIDS, acquired immune deficiency syndrome; cART, combination antiretroviral therapy; HIV, human immunodeficiency virus; NRTIs, nucleoside reverse transcriptase inhibitors.

Figure 1. Factors associated with infertility among people living with human immunodeficiency virus

3.1. Biological factors

Demographic characteristics that have been reported to be associated with low rates of pregnancy among HIV-infected women include advanced age, white ethnicity (compared to black ethnicity), having CD4 cell count of less than 100 cells/mm³, and poor adherence to cART. [8-10] Systemic illnesses from HIV and its related comorbidities, stress, and weight loss generally impact the reproductive potential of both sexes.[3] HIV-infected women are more likely than non-HIV-infected women to have protracted anovulation and amenorrhea.[11-14] The number of ovulatory cycles was found to correlate with the severity of immunosuppression and having an AIDS diagnosis. Although there have been no reports of ovarian aging or failure,[15] HIV-infected women may have reduced ovarian reserve.[16] In HIV-infected men, impairment of sperm parameters affecting fertility has been described. The impairment includes lower ejaculation volume, sperm count, and progressive motility (defined as the percent of sperm with forward motility) despite normal morphology compared to non-HIV-infected men.[17-19] Sperm concentration levels, total count, and motility were found to positively correlate with the height of the CD4 cell count, indicating the adverse effect of worsening immunodeficiency on these sperm parameters.[19] Other studies demonstrated that the semen of HIV-infected men was more viscous and contained fewer motile sperm but more round cells.[20] In addition, a study of testicular specimens from autopsy samples (1981–1998) revealed progressive loss of germ cells within the testes with prolonged survival with AIDS.[21] Although recent data indicate that cART significantly decreased total sperm count and progressive motility and increased the proportion of abnormal sperm forms,[22] these adverse effects are balanced by the overwhelming benefits of cART for immune reconstitution, morbidity and mortality reduction, and overall improvement of sperm characteristics associated with higher CD4 cell counts.

3.1.1. Hypogonadism and HIV/AIDS

Hypogonadism was recognized as a relatively common condition early in the HIV epidemic and characterized by a low level of testosterone among HIV-infected men. Hypogonadism can be categorized into primary hypogonadism, which is a disorder of the testes, and secondary hypogonadism, which is a disorder of the pituitary or hypothalamus. Hypogonadism can be associated with various signs and symptoms, including muscle wasting, weight loss, low bone mineral density, and decreased libido.[23] During the early course of HIV disease, men tend to have normal serum testosterone levels. As the disease progresses to AIDS, low serum testosterone levels become more frequent, particularly in those with more advanced immunosuppression (e.g., CD4 cell count less than 100 cells/mm³). Early in the HIV epidemic, 30–50% of symptomatic HIV-infected men had low total serum testosterone levels, which significantly correlated with weight loss and CD4 cell depletion.[24-26] The prevalence of hypogonadism in HIV-infected men has decreased with cART initiation occurring at earlier stages of HIV infection. Effective HIV therapy can normalize testosterone levels over time.[27] Most cases of decreased testosterone levels in HIV-infected men are related to secondary hypogonadism.[24, 28] Other characteristics that have been reported to be associated with low testosterone levels include older age, a detectable HIV RNA level of greater than 10,000 copies/

mL, injection drug use, hepatitis C coinfection, high body mass index, and insulin resistance. [28-31] In addition, several medications commonly used among HIV-infected individuals can affect testosterone levels through varied mechanisms. Systemic glucocorticoids and megestrol acetate can cause hypogonadism by suppressing the hypothalamic–pituitary–gonadal axis, whereas a high dose of ketoconazole (at least 400 mg per day) directly inhibits steroidogenesis. Psychotropic medications can cause hyperprolactinemia and testosterone deficiency, whereas chronic use of alcohol, opiates, and marijuana can impair testosterone production.[32, 33]

Primary hypogonadism	Secondary hypogonadism
<p>Congenital abnormalities</p> <ul style="list-style-type: none"> · Klinefelter’s syndrome · Other chromosomal abnormalities (e.g., 46, XY/XO; 47, XYY) · Mutation in the FSH and LH receptor genes · Cryptorchidism · Disorders of androgen biosynthesis · Myotonic dystrophy · Congenital anorchia · Varicocele <p>Acquired diseases</p> <ul style="list-style-type: none"> · Infectious orchitis · Radiation · Alkylating and antineoplastic agents · Ketoconazole · Glucocorticoids · Dibromochloropropane · Trauma · Testicular torsion · Bilateral orchiectomy · Autoimmune damage · Chronic systemic diseases · Cirrhosis · Chronic kidney disease · Idiopathic 	<p>Congenital abnormalities</p> <ul style="list-style-type: none"> · Congenital GnRH deficiency · Leptin or leptin receptor mutation · Gonadotropin subunit mutations <p>Acquired diseases</p> <ul style="list-style-type: none"> · Hyperprolactinemia · Gonadal steroids · Glucocorticoids · Continuous opiate administration · Critical illness · Chronic systemic illness · Anorexia nervosa · Diabetes mellitus · Obesity · Pituitary adenoma · Metastatic tumor damaging pituitary gland · Sarcoidosis · Hemochromatosis · Tuberculous meningitis · Pituitary apoplexy · Trauma · Idiopathic

Note: FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone.

Table 1. Causes of hypogonadism in males

HIV-infected men with symptomatic hypogonadism may present with loss of facial and body hair, decreased muscle mass and strength, diminished libido, impotence, testicular atrophy, gynecomastia, depression, low energy, and poor concentration.[34] Diagnosis of hypogonadism is made based on a clinical suspicion and low serum testosterone levels (generally less than 300 ng/dL). The screening test of choice is the serum total testosterone concentration (free plus protein-bound fractions). However, in some cases, the total testosterone levels may be normal, whereas the free levels may be low because of the higher sex hormone-binding globulin levels among HIV-infected persons. Thus, in a patient with suspected testosterone deficiency and serum total testosterone concentration in the lower half of the normal range (less than 500 ng/dL), the free testosterone levels should be assessed.[34] Testosterone levels should not be evaluated during an acute illness because of the transient decline of androgen levels related to the acute event. To distinguish between primary and secondary hypogonadism, follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels need to be measured. The elevated FSH and LH levels suggest primary hypogonadism, whereas normal or low levels of FSH and LH are consistent with secondary hypogonadism. Further evaluation should be geared toward diagnosing the possible causes of primary and secondary hypogonadism in HIV-infected men as detailed in Table 1.

3.1.2. Comorbid diseases and HIV/AIDS

3.1.2.1. Sexually Transmitted Infections (STIs)

The impact of STIs on fertility among PLWHIV depends on the local prevalence of the STIs. Given the common route of transmission of causative agents and immunosuppressive status caused by HIV, STIs tend to be more prevalent, to be more severe, to take longer to resolve, and to be more prone to treatment failure in HIV-infected persons compared to the general population. Common causative pathogens for STIs among PLWHIV include bacteria, such as *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, *Ureaplasma urealyticum*, *Mycoplasma hominis*, *Mycoplasma genitalium*, *Treponema pallidum*, *Haemophilus ducreyi*, and *Klebsiella granulomatis*; viruses, such as hepatitis B and C viruses, herpes simplex virus (HSV), and human papillomavirus (HPV); and protozoa, such as *Trichomonas vaginalis*. The underlying pathogenesis for STI-related infertility is direct damage and subsequent anatomical and functional abnormalities of the genital organs, including the testes and epididymis in men and cervix, uterus, fallopian tubes, and ovaries in women. A previous study demonstrated that the DNA of STI pathogens was detected in semen of 45 of 241 asymptomatic men seeking an infertility investigation (19%) and was associated with a decrease in sperm concentration, motile sperm concentration, total sperm count, and neutral alpha-glucosidase concentration.[35]

Gonorrhea is a STI caused by *N. gonorrhoea* and commonly manifests as urethritis in both sexes and pelvic inflammatory disease in women. The reported complications related to fertility of gonorrhea include urethral strictures and subsequent impairment of testicular functions in men.[36] Similarly, *C. trachomatis* can cause urethritis in both sexes and pelvic inflammatory disease in females. Epidemiologic data suggest that *C. trachomatis* may be associated with tubal obstruction and subsequent infertility in women.[37] The impact of *Mycoplasma*, that is, *U.*

urealyticum, *M. hominis*, and *M. genitalium*, on fertility is uncertain. *U. urealyticum* may cause infertility through its effects on sperm chromatin and DNA, whereas *M. genitalium* can attach to spermatozoa and can be transported to the female genital tract.[38, 39] Syphilis is caused by *T. pallidum* and is more prevalent among PLWHIV. Orchitis, epididymitis, and testicular mass have been reported as manifestations of syphilis in HIV-infected men.[40, 41] Although *H. ducreyi* and *K. granulomatis* do not directly affect the reproductive tract, they both cause ulcers and lymphadenopathy around the genital area, which may affect reproductive potential.

Chronic viral hepatitis B and C can cause impairment in sperm concentration, motility, morphology, and viability, whereas HPV primarily affects sperm motility.[42] The presence of HSV DNA in semen has been associated with decreased sperm concentration and reduced motility.[43] In HIV-infected women, chronic HPV infection increases the risk of cervical cancer development and possibly leads to infertility. An important protozoan *T. vaginalis* is the cause of vaginitis, endometritis, adnexitis, and pyosalpinx in women, which can lead to infertility and preterm birth and low birth weight of the newborn.[44] In men, it is associated with complications including urethritis, prostatitis, epididymitis, and infertility through inflammatory damage or interference with sperm function.[44]

3.1.2.2. Opportunistic Infections (OIs)

HIV-infected persons are at increased risk for opportunistic infections (OIs) depending on their degree of immunosuppression. Tuberculosis is a common OI in HIV-tuberculosis endemic locales and its prevalence is higher among PLWHIV compared to non-HIV-infected persons, regardless of the CD4 cell count. Genital tract infection caused by *Mycobacterium tuberculosis* contributes to infertility and poorer reproductive health outcomes in both sexes.³ Salmonellosis, toxoplasmosis, and cryptococcosis can manifest as disseminated infections involving the genital organs. Although cytomegalovirus (CMV) can cause orchitis and epididymitis in HIV-infected men, there are no data on its effect on sperm characteristics.[42] Candidiasis is frequently reported among HIV-infected persons with CD4 cell counts less than 200 cells/mm³. It is the cause of balanitis in men and vaginitis and cervicitis in women, which may affect fertility.

3.1.2.3. Other infections

Other infectious causes of orchitis in both HIV-infected and non-HIV-infected men include bacteria, such as *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Staphylococcus* spp., and *Streptococcus* spp., and viruses, such as mumps, varicella, coxsackievirus, and echovirus.[45] These infections may also contribute to infertility.

3.1.3. Antiretroviral agents

Nucleoside reverse transcriptase inhibitors (NRTIs) remain key components of recommended cART regimens. They inhibit HIV-1 reverse transcriptase, which reduces viral replication and improves disease control. However, these medications also inhibit mitochondrial DNA (mtDNA) synthesis and cause a decrease in polypeptides involved in electron transport, which

can result in cell injury.[46] The degree of mitochondrial toxicity is specific to each NRTI. Theoretically, an HIV-infected person's fertility may be affected by NRTI use via the damage to mitochondrial biogenesis of gametes.³ This is supported by the mtDNA depletion observed in sperm and oocytes of HIV-infected patients taking NRTIs and in low oocyte mtDNA in patients with ovarian insufficiency.[47-49] Data from epidemiologic studies are conflicting regarding the impact of cART on fertility. A prospective cohort from the United States reported the lower likelihood of conception associated with antiretroviral therapy among HIV-infected women,[5] whereas a more recent study from Africa demonstrated significantly higher pregnancy rates among HIV-infected women on cART compared to those not on cART.[50] However, these two studies were conducted in different settings and time, and specific behavioral and biological mechanisms were not explored. Zidovudine (azidothymidine, AZT) is the NRTI drug that has been studied the most. In animal studies, AZT has been shown to suppress cell division in the preimplantation mouse embryo, causing reduction in inner cell mass proliferation, greater number of resorptions, and fewer fetuses.[51, 52] A previous study demonstrated that exposure to NRTI transplacentally caused significant fetal mitochondrial damage in experimental monkeys.[53] Unfortunately, there have been no studies examining fertility effect of NRTIs in humans.

3.2. Psychological factors

Decrease in sexual activity after a new diagnosis of HIV infection is usually observed and may be accompanied by the feeling of guilt and shame and aggravated by the stigma related to HIV infection.[54] Individuals recently diagnosed with HIV infection reported to have decreased desire for or interest in sex relations. They also reported to use condom more consistently during sexual intercourse to avoid transmission of HIV to their partners.[55] Previous studies indicated that HIV-infected women often chose to avoid pregnancy.[56, 57] However, another study revealed that high-risk behaviors, unplanned pregnancies, and pregnancy termination remain prevalent among this population.[58] In the pre-cART era, there was a significant increase in the pregnancy termination rate from 3.5 to 6.3 per 100 women-years following a new HIV diagnosis in the United Kingdom and Ireland[56] and 47% of pregnancies were voluntarily terminated following a new HIV diagnosis in an Australian study.[57] The reasons for pregnancy termination may include challenges of pregnancy, birth and parenting in the context of HIV infection, concerns about increased risks of complications related to pregnancy and delivery, and risk of HIV transmission to the newborn. A previous study reported that unplanned pregnancy, lower CD4 cell count, and having an HIV-infected current partner were factors associated with the decision to terminate a pregnancy.[59] Following the introduction of cART with overall improvement in health and immune status of HIV-infected women, the rates of elective pregnancy termination after a HIV diagnosis were 22%-26% decreased from the pre-cART period.[60, 61] With the success of cART in preventing mother-to-child HIV transmission, HIV infection was reported to have no effect on desire for pregnancy among young urban African Americans aged 15-24 years.[62] Reproductive desire among PLWHIV may now be associated with personal health, cART, concern about HIV transmission, and

social factors. Some HIV-infected persons have an increased desire for children as a way of concealing their HIV-infected status and improving their feelings of self-worth. Others stated that their HIV diagnosis increased their desire for children at an earlier age and some chose to have children following advances in HIV care.[63-65]

3.3. Social factors

The HIV/AIDS epidemic has a significant impact on the economic and political stability of a nation. Awareness of HIV/AIDS at the population level may affect the age of sexual debut, frequency of sexual intercourse, safer sex and contraceptive practices, perceived value of marriage, social norms, and fertility intentions and choices of PLWHIV.³ The dramatic improvement in the life expectancy of PLWHIV and reduction in HIV transmission rates following treatment of the infected partner have changed ethical considerations regarding childbearing in HIV-infected individuals. Early in the HIV/AIDS epidemic, pregnancy in HIV-infected women was considered morally problematic, whereas recently, the Ethics Committee of the American Society for Reproductive Medicine stated that it is ethical for health care providers to assist PLWHIV who seek pregnancy when optimal precautions to prevent HIV transmission are utilized.[66] Despite more opportunities for access to reproductive care, PLWHIV still face multiple obstacles. First, the severity of their disease, level of immunosuppression, presence of OIs, and other comorbid diseases may impair their fertility. Second, their HIV provider may have limited knowledge to counsel them on reproductive health issues, and infertility specialists may have limited expertise in providing care for HIV-infected persons. Third, HIV stigmatization could potentially preclude them from establishing reproductive care. Finally, assisted fertility therapy (AFT) is technically complicated in regard to HIV transmission prevention and costliness and may not be available in all settings.[3]

4. Fertility management

Fertility management for PLWHIV should be comprehensive and involve cART, specific management for factors associated with infertility, and AFT while minimizing the risk of horizontal and vertical transmission of HIV.

4.1. Combination antiretroviral therapy

With advances in the development of antiretroviral agents, cART has become more potent and effective, more tolerable and convenient to administer, and less toxic. Current guidelines recommend that PLWHIV should receive cART when they are willing and able to commit to treatment and understand the benefits and risks of therapy and the importance of adherence, regardless of the CD4 cell count level.[67] The benefits of early cART among persons with a CD4 cell count above 500 cells/mm³ were demonstrated in a recent large-scale randomized trial that showed a reduction in mortality, AIDS-related events, and non-AIDS-related events

in those started on cART immediately versus waiting until the CD4 cell count fell below 350 cells/mm³. [68] The currently recommended initial cART regimens consist of a backbone of two NRTIs and any one drug from the following drug classes: non-NRTI, protease inhibitor with a booster, or integrase inhibitor with or without a booster. [67, 69, 70] The initial cART regimens recommended by different consensus guidelines are shown in Table 2. A patient-specific regimen from these lists will be chosen based on convenience of administration, adverse reactions, local availability, cost, and health plan coverage. The goals of cART are immunologic response, defined as an increase in CD4 cell count, and virologic response, defined as HIV RNA suppression below the lower limit of detection. By extending life expectancy and improving overall health, immunity, and quality of life from cART, cART is expected to improve fertility outcomes. Achieving a sustained virologic response is particularly important to reduce the risk of HIV horizontal and vertical transmission during conception attempts, pregnancy, and delivery.

DHHS 2015	EACS 2015	WHO 2013
ABC + 3TC + DTG	ABC + 3TC + DTG	TDF + FTC/3TC + EFV
TDF + FTC + DTG	TDF + FTC + DTG	
TDF + FTC + EVG/c or TAF + FTC + EVG/c	TDF + FTC + EVG/c	
TDF + FTC + RAL	TDF + FTC + RAL	
TDF + FTC + DRV/r	TDF + FTC + DRV/r	
	TDF + FTC + RPV	

Note: 3TC, lamivudine; ABC, abacavir; DHHS, the U.S. Department of Health and Human Services; DRV/r, ritonavir-boosted darunavir; DTG, dolutegravir; EACS, European AIDS Clinical Society; EFV, efavirenz; EVG/c, cobicistat-boosted elvitegravir; FTC, emtricitabine; RAL, raltegravir; RPV, rilpivirine; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; WHO, World Health Organization.

Table 2. Recommended first-line combination antiretroviral therapy regimens based on consensus guidelines

4.2. Specific management for factors associated with infertility

4.2.1. Management of biological factors

Immunosuppression and wasting syndrome can be improved by cART. In addition, PLWHIV who are taking cART with sustained immunologic and virologic responses will have reduced incidences of OIs, such as tuberculosis, salmonellosis, toxoplasmosis, cryptococcosis, CMV infection, and candidiasis. NRTIs selected for the backbone of a cART regimen should have the least toxicity on mitochondria to minimize the impact on oocytes and sperm. These “safer” NRTIs include tenofovir, abacavir, lamivudine, and emtricitabine. [67, 69, 70] Good general health and less physical stress are associated with normal ovulation and menstrual cycles in HIV-infected women, whereas cART improves overall sperm parameters among HIV-infected men. STIs, OIs, and other infections should be promptly diagnosed and treated to prevent

damage to the genital organs. It is important that sex partners of patients with STIs should be counseled, tested, and treated accordingly.

Hypogonadism should be recognized early, correctly diagnosed, and treated in HIV-infected men. Testosterone treatment is indicated in men with low serum concentrations of testosterone and any of the following signs or symptoms including low libido and/or hypogonadal symptoms, low bone mineral density, low body mass, or weight loss despite virologic response to cART. Prior to initiation of testosterone replacement therapy, patients should be evaluated for coexisting depression and psychosocial stressors along with baseline laboratory studies including complete blood count, a metabolic panel, lipid panel, and a prostate-specific antigen (PSA). Long-term effects of suppression of the hypothalamic–pituitary–gonadal axis, promoting malignancy of the prostate gland and cardiovascular diseases, in those older than 60 years should be carefully monitored. Patients with a history of prostate cancer, a palpable prostate nodule, or an elevated PSA should not be prescribed testosterone replacement therapy.[34, 71] The routes of testosterone administration should be based on the patient's preference and include transdermal patch, gel, and intramuscular injection. For injections, the initial dose is 200 mg every 2 weeks or 100 mg every week. The dose can be titrated based on testosterone levels measured midway between injections aiming for the mid-normal reference range. Testosterone replacement therapy should continue as long as there are symptomatic benefits and no adverse effects.

4.2.2. Management of psychological and social factors

Knowledge about HIV and its epidemiology, routes of transmission, clinical course, long-term prognosis, and benefit of cART is critical to PLWHIV in reducing HIV transmission to their sexual partners and improving their adherence and outcomes. A previous study demonstrated that increased reproductive intention was associated with patient optimism regarding cART efficacy.[72] To overcome the challenges in pregnancy, birth, and parenting, PLWHIV should be informed about the recent advances in antenatal, perinatal, and postnatal care to prevent HIV transmission to their newborns. Family planning counseling should be provided to prepare them for child rearing and to cope with any problems they may face. Issues on reproductive care access for PLWHIV are very new for many developing countries, because the main goals for HIV care in these countries are currently improving access to HIV testing and treatment. Financial burdens, medical coverage, and availability of centers that can provide ART need to be considered when developing and implementing local, regional, and national policies or guidelines for the reproductive care of PLWHIV. In the meantime, physicians who care for PLWHIV should update their knowledge to optimally assess and manage fertility issues among persons with HIV infection. HIV stigmatization may be reduced by campaigns and specific interventions that are appropriate and feasible for each locale.

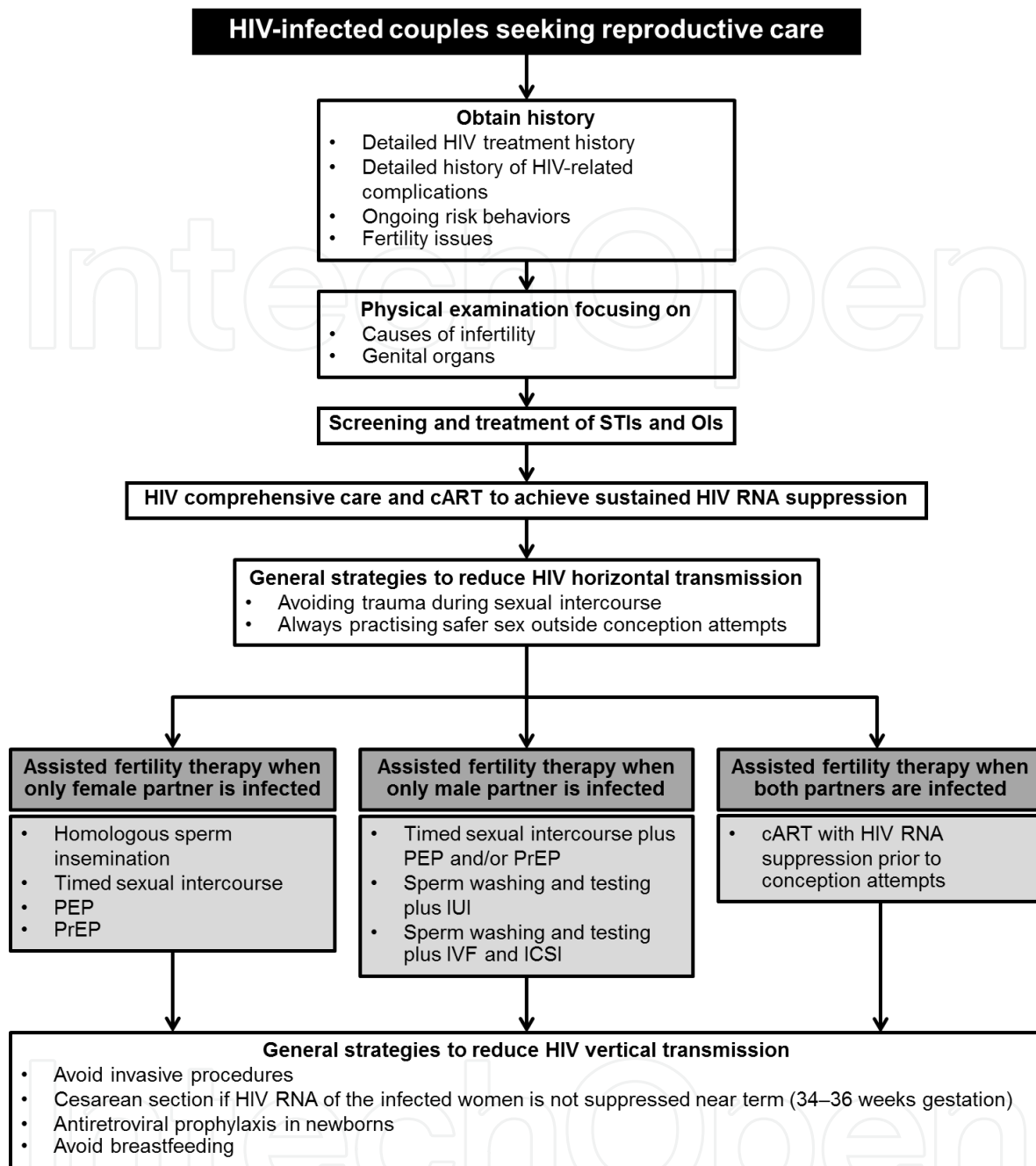
4.3. Assisted fertility therapy

Relevant issues to be considered regarding fertility treatment in PLWHIV include risk of HIV horizontal transmission in serodiscordant heterosexual couples and methods to reduce HIV transmission. Generally, the rate of HIV heterosexual transmission is approximately 1 per

500 to 1 per 1,000 episodes of unprotected sexual intercourse.[3] However, the risk of transmission can increase significantly if there are genital tract infections from STIs or OIs, trauma with sex, lack of male circumcision, and high plasma HIV RNA levels in seropositive persons.[73, 74] Thus, a thorough evaluation is needed before AFT. History including a detailed history of their HIV infection and any associated complications, recent CD4 cell counts and HIV RNA levels, past and current cART regimens, history of antiretroviral drug resistance, ongoing HIV risk behaviors, and fertility problems should be obtained. Physical examination should focus on signs relevant to causes of infertility, genital organs, and Pap smear in women. An HIV-infected partner should be treated with cART until HIV RNA suppression has been achieved prior to AFT. Partners who have STIs need to be treated to reduce transmission risks of HIV and STI-associated pathogens. Trauma during sexual intercourse should be avoided or minimized, and safer sex practices should be encouraged outside the conception attempts. Proposed algorithm for fertility management among HIV-infected couples is shown in Figure 2.

Post-exposure prophylaxis (PEP) with cART in uninfected partners may be used after the unprotected sexual intercourse (conception attempt). Although there have not been well-designed studies in human that assess the efficacy of this intervention, the benefits of HIV transmission reduction have been shown in an animal study and a retrospective study of health care workers exposing to body fluids of HIV-infected persons.[75, 76] The recommended PEP regimens that are also safe if the pregnancy does occur are combined tenofovir, emtricitabine, and ritonavir-boosted atazanavir, ritonavir-boosted darunavir, or raltegravir.[77] PEP should be initiated as soon as possible after HIV exposure but within 48 hours and should be continued for 28 days. Because of its demonstrated efficacy, tenofovir–emtricitabine (TDF/FTC) once daily for pre-exposure prophylaxis (PrEP) administered to the seronegative partner is now the preferred approach to reduce the risk of HIV transmission among serodiscordant couples. Among heterosexual couples, pericoital tenofovir vaginal gel was the first PrEP intervention that showed a 39% efficacy at reducing HIV acquisition among high-risk South African women.[78] Several other randomized controlled trials have demonstrated the benefit of PrEP at reducing HIV acquisition among HIV-negative at-risk individuals including 1) the iPrEx study that demonstrated 44% reduction in the incidence of HIV among men who have sex with men taking daily oral TDF/FTC,[79] 2) the Partners-PrEP study that demonstrated 75% and 67% reduction in the incidence of HIV among serodiscordant couples taking daily oral TDF or TDF/FTC, respectively, in Africa,[80] and 3) the TDF2 study that demonstrated 62% reduction in the incidence of HIV among heterosexual men and women taking daily oral TDF/FTC in Botswana.[81] Pharmacokinetic data suggest that PrEP should begin at least 1 week before unprotected sex for optimal benefit. The uninfected partners who choose to take PEP and/or PrEP need to be regularly screened and monitored for HIV infection and adverse effects of the drugs in PEP and/or PrEP regimens.[67, 77]

In regards to limiting risk of HIV vertical transmission, cART given to HIV-infected women antenatally and avoiding breastfeeding can reduce the rate of transmission from 25–40% to less than 1%.[67] Invasive procedures, such as amniocentesis, chorionic villus sampling, and use of fetal scalp electrodes, should be avoided in HIV-infected women because these can



Note: cART, combination antiretroviral therapy; HIV, human immunodeficiency virus; ICSI, intracytoplasmic sperm injection; IUI, intrauterine insemination; IVF, in vitro fertilization; OIs, opportunistic infections; PEP, post-exposure prophylaxis; PrEP, pre-exposure prophylaxis; RNA, ribonucleic acid; STIs, sexually transmitted infections.

Figure 2. Proposed algorithm of fertility management in HIV-infected couples

increase the risk of fetal/infant exposure to maternal body fluids. Cesarean section instead of normal vaginal delivery can further reduce the risk of maternal-infant transmission in HIV-infected pregnant women whose HIV RNA has not been suppressed following cART. United States guidelines use a HIV RNA level of >1,000 copies/mL at 34–36 weeks gestation as a threshold for recommending Cesarean section, whereas European guidelines recommend a

threshold of >50 copies/mL.[67, 69] Women who achieve virologic suppression near term can proceed with vaginal delivery without increased transmission risk. Antiretroviral prophylactic regimens for newborns of HIV-infected mothers should be prescribed based on the risk of transmission. In general, AZT is recommended for the first 4–6 weeks of life with additional medications added if the mother did not achieve viral suppression. HIV-infected mothers should not breastfeed their babies due to the risk of transmission via breast milk.

4.3.1. AFT when only the female partner is infected

If a woman is HIV infected and her male partner is uninfected, HIV transmission can be avoided by using homologous insemination with the male partner's sperm. However, if this option is not feasible, such as the desire to become pregnant naturally, couples should limit unprotected sexual intercourse to the time of ovulation (timed intercourse) using ovulation kits or basal body temperature monitoring to predict ovulation. These measures allow couples to limit the number of unprotected sexual encounters. In addition, the HIV-infected women should be on cART with a suppressed viral load. The male partner may choose to take PEP and/or PrEP to reduce the risk of HIV transmission; however, these options are not as safe as homologous insemination.[82]

4.3.2. AFT when only the male partner is infected

Conception between an HIV-infected man and his HIV-uninfected female partner is more complicated. The risk of HIV transmission can be reduced by using timed intercourse when the HIV-infected man's plasma HIV RNA is undetectable on cART. However, the HIV transmission of timed intercourse in this setting has been reported to be associated with inconsistent condom use outside the conception attempt.[83] Thus, the practice of timed intercourse alone to prevent HIV transmission to the female partner is not generally recommended in this setting.[82] Additional PEP and/or PrEP may be used to reduce HIV transmission. A study of serodiscordant couples, in which the woman was treated with oral tenofovir taken shortly before and after each unprotected sexual encounter, showed that none of the women became infected with HIV and pregnancy rates reached 75% after 12 attempts. [84] Based on available data, once-daily TDF/FTC for the women would generally be recommended throughout the conception period in countries where resources are available for PrEP.

Sperm preparation and testing prior to intrauterine insemination (IUI) have been described as methods to reduce the chance of HIV transmission to the uninfected female partner. The sperm preparation involves a three-step process.[3, 82] First, the liquefied semen is filtered through a Percoll gradient. Next, the isolated spermatozoa are washed to eliminate seminal plasma and hyperosmotic gradient media. Finally, a modified swim-up method recovers highly motile spermatozoa from leukocytes. After this process, the final sperm specimen is tested by polymerase chain reaction assays for the presence of HIV. If this final specimen tests negative, it is used for insemination. In men with severe dyspermia, the final swim-up step that removes infected leukocytes cannot be performed and thus the semen should be tested for HIV DNA. Utilizing this process, 1,600 inseminations were performed in 513 HIV-uninfected women and

resulted in 228 pregnancies. At 1-year follow-up, none of the children older than 3 months of age and none of the mothers became HIV infected.[85] In addition, studies reviewing worldwide data in 2004 and data from several centers demonstrated no HIV transmission to the uninfected female partners who were inseminated using sperm washing and IUI.[86, 87]

There have been recent data supporting the use of IVF/ICSI to reduce HIV transmission to uninfected women. A 10-year retrospective study of 181 serodiscordant couples undergoing IVF/ICSI, in which sperm was prepared using a modified density-gradient centrifugation and the swim-up method, revealed no HIV infection among the uninfected women and their 170 children.[88] Another study from the Center for Reproductive Assisted Techniques for HIV in Europe reported no evidence of seroconversion in any uninfected partners or children on follow-up.[86] Unfortunately, these techniques are generally prohibitively expensive. Although the data on efficacy and safety of the AFT techniques are encouraging, the potential risk of HIV transmission is not completely eliminated and more studies are required. Until then, serodiscordant couples should also be counseled about other safer options, including using donor sperm, donor embryo, adoption, or not having children.[82] If couples want to have their own biological children, they should be informed about available risk reduction techniques and the availability of centers that can provide effective methods of sperm preparation and testing. Fertility centers should use approved study protocols with informed consent and provide appropriate follow-up of sexual partners and their children.

4.3.3. AFT when both partners are infected

While HIV seroconcordant couples do not have the same concerns about HIV transmission as do HIV serodiscordant couples, the risk of transmission of different strains of HIV between each other or superinfection exists. HIV superinfection in seroconcordant couples has been reported to increase the risk of HIV RNA rebound and decrease in CD4 cell count following immune reactivation.[89] The best way to minimize the risk of superinfection and optimize reproductive outcomes for couples and their offspring is to use cART to achieve HIV RNA suppression in both partners prior to conception attempts.

4.4. Healthcare workers and cross-contamination risks

Healthcare workers are at risk of exposure to blood-borne pathogens, including HIV through patient care. However, if standard universal precautions to prevent the transmission of infectious diseases are followed, the risk of acquiring these pathogens is very small and is not sufficient to deny reproductive services to PLWHIV. To date, there have been no reports of occupational HIV transmission to health care workers performing AFT, suggesting that the risk of transmission is extremely low. Theoretical concerns about contaminating other gametes and embryos stored in the same laboratory from cross-contamination have been raised. To date, no such event has been reported. To avoid this risk, it is recommended that samples from HIV-infected persons be processed in a separate laboratory or designated space within the main laboratory and to use a dedicated storage tank.[82]

5. Conclusions

Reproductive issues have become more relevant among PLWHIV who are living longer and are staying healthier on cART. Fertility outcomes of PLWHIV have been improving for the past decade, although they remain inferior to those of the general population. HIV can impact fertility in many ways that involve biological, psychological, and social factors. Assessing and managing fertility issues in HIV-infected individuals and couples involve the use of cART, diagnosing and correcting causes of infertility, and AFT, which has become more effective and safer. Further studies are needed to address the efficacy and safety of AFT techniques as well as the complex social and ethical challenges of fertility issues of HIV-infected persons. Healthcare workers caring for PLWHIV should be knowledgeable in both HIV infection and reproductive health because they may now be legally and ethically obligated to provide reproductive care and assistance to this population.

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