Review Article

Human immunodeficiency virus and infertility

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Abstract HIV infection has nowadays become a chronic disease. Antiretroviral drug therapy has improved the life expectancy of these patients. Patients are living longer and those in reproductive group have a desire for conception. HIV infected patients may have infertility. Various treatment strategies are followed so that there is minimal or no risk of HIV transmission to the uninfected partner or their offspring. ART (assisted reproductive techniques) clinics with the necessary resources can offer services to HIV infected patients and couples who are willing to use recommended risk-reducing therapies.

Keywords: Antiretroviral drug therapy, human immunodeficiency virus, infertility

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INTRODUCTION

Human immunodeficiency virus (HIV) is a sexually transmitted infection commonly seen in person of reproductive age. Although there is no cure for HIV infection, nowadays it can be managed as a chronic disease because of the availability of efficacious antiretroviral drug therapy (ART). Patients with HIV are now living longer, with a better quality of life. Since it affects reproductive age group issues of infertility is seen in them at times.

Effect of HIV on fertility

HIV can affect fertility in many ways. Advanced age, ethnicity, CD4 count less than 100cells/mm^3, systemic infection, co morbidities associated with HIV and poor adherence to ART can lead to infertility.

In females

Women infected with HIV have higher rates of sexually transmitted infections like *Mycoplasma hominis*, candida, streptococcus, herpes simplex virus-2 and HPV (Human papilloma virus).[1] Pelvic inflammatory disease seen in them is often associated with tuboovarian abscesses and can damage the reproductive organ leading to infertility.

HIV infected women tends to have amenorrhea and anovulatory cycles. A positive association between HIV and amenorrhea (OR 1.68; *P* value 0.0001) was found in a meta analysis by King et al. They said that the association of amenorrhea to HIV was irrespective of some of the most common HIV-related co morbidities. They also suggested a possible link between amenorrhea and HIV-associated low BMI, due to immune dysregulation.[2]

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Relationship between low CD4 count and menstrual disorder was studied by Watts *et al*.[3] They observed that individuals with very low CD4+ cell counts (median 35 cells/μl) displayed significantly higher rates of amenorrhea than immunocompetent individuals (19 versus 10%). An association between decreased CD4+ cell counts and low Anti mullerian hormome (AMH) levels was seen by Scherzer *et al*.[4] They suggested that CD4+ T cells may have a role in ovarian granulosa cell function. A study done by Santulli *et al*.[5] showed that serum AMH levels, which reflect the ovarian reserve, were lower in women with HIV. They also stated that, age, BMI, CD4þ cell count and viral load were the independent contributors affecting serum AMH levels among women with HIV. Gemmill *et al*.[6] observed HIV-positive women over a 12-month period, and found that HIV-positive women had a 25% average reduction in fecundity compared to HIV-negative women [adjusted FOR (aFOR) = 0.75 (0.62–0.92)]

In males

HIV positive males have orchitis and acute epididymitis due to opportunistic infections like CMV, salmonella, toxoplasmosis, *Ureaplasma urealyticum*, *Corynebacterium*, *Mycoplasma*, fungi and mycobacteria. Kaposi's sarcoma and lymphoma involving the testes have also been described in them.[1]

Impaired semen parameters have been observed in semen of HIV infected males compared to HIV negative males. No association has been observed between semen quality and the type or duration of HAART.[7]

Men with advanced HIV infection were seen to have abnormal sperm or abnormal spermatogenesis.[8] Silent inflammation of the genital tract by HIV and the effects of HAART drugs may lead to dysfunction of prostate and seminal vesicles and thereby resulting in the decreased ejaculate volume.[9] HIV infection can lead to increased production of reactive species of oxygen (ROS) which can decrease the levels of antioxidants present in semen.[10-11] The HIV infected macrophages at times interact with the Leydig cells, resulting in reduction of free testosterone concentrations through the inhibition of steroidogenesis or dysfunction of the hypothalamus. This could lead to a degeneration of the seminal epithelium.[12]

A study has shown that HIV infected patients taking HAART have increased sperm nuclear fragmentation rate compared to HIV patients not receiving HAART.[13] Zhu *et al*.[14] observed that the HIV RNA level was higher in the semen than in the blood of the HIV infected males after HAART, which suggests the potential risk of transmission of HIV to their female partners. The sperm concentration and total sperm motility was lower than the normal value in these males.

Various psychological and social factors like the stigma of being HIV infected, family and community concerns for the health of a potential child are other factors that contribute to infertility in these couples.

Infertility treatment

Effective antiretroviral therapy (ART), pre-exposure prophylaxis (PrEP) with antiretroviral drugs and advancement in assisted reproductive techniques have made it possible to assist the HIV infected couples in reproduction and minimise the risk of viral transmission to an uninfected partner and offspring.

Prior to starting any treatment, these couples should be counselled about the risks for themselves and their offspring. Treatment for infertility can be offered to HIV infected patients with low viral load and who are well controlled with antiretroviral drug therapy or even not currently taking antiretroviral drug therapy. They should be screened for other sexually transmitted infections, and substance abuse. Treatment planned is aimed to achieve pregnancy with a minimal or no risk of transmission to the other partner and the offspring.

The transmission rate of HIV to an uninfected partner is approximately 1 in 500–1,000 episodes of unprotected intercourse.[15] Factors like high viral load in HIV-infected partner or presence of concomitant genital infection, inflammation, or abrasions in HIV-uninfected partner can increase the risk of viral transmission.

There are various ways in which conception can occur in these couples, which either completely eliminate or minimises the risk of HIV transmission between partners.

If a woman is infected with HIV and her male partner is uninfected, homologous insemination with the partner's sperm is advised to avoid the transmission of HIV to the male partner. If this option is not available to the couple, or for other reasons not desired, studies have suggested that the risk of transmission can be minimized by using timed intercourse, combined with either antiretroviral therapy in woman to suppress the viral load to undetectable levels and/or PrEP antiretroviral therapy in the uninfected male.[16] While clinicians would need to emphasize to the couple that this option is not as safe as

homologous insemination, it does represent an alternative option for select couples.

When a couple, where the husband is HIV-infected and the wife is HIV-uninfected tries for conception using condoms except at the time of ovulation, the risk of seroconversion is reduced, but not completely eliminated. Mandelbrot L in their study observed that, of the 92 HIV-uninfected women with HIV infected partners trying to establish pregnancies through timed intercourse, the rate of seroconversion was 4.3%. Two of the women in the study seroconverted during pregnancy and another 2 converted in the postpartum period. All four women reported inconsistent condom use by their partners.[17]

This risk of transmission of HIV infection through unprotected intercourse can be substantially reduced with the use of antiretroviral therapy in the infected partner.[18] A study was done to evaluate the efficacy of PrEP antiretroviral therapy in uninfected female partner during the time conception. Of the 46 serodiscordant couples in which the female received oral tenofovir, none of the women became infected with HIV. The pregnancy rates was 75% after 12 attempts.[19] The US Food and Drug Administration (FDA) has approved the use of antiretroviral therapy for PrEP in such couples.[20]

An interesting study[21] was conducted to assess the residual risk of HIV transmission, cost, and cost-effectiveness of various strategies that can help fertile HIV-uninfected female/HIV-infected male on combination antiretroviral therapy with plasma HIV RNA <50 copies/mL couples to have a child. The strategies included: unprotected sexual intercourse using treatment as prevention; treatment as prevention limited to fertile days (targeting fertile days); treatment as prevention with preexposure prophylaxis (tenofovir/emtricitabine); treatment as prevention and preexposure prophylaxis limited to fertile days; or medically assisted procreation (MAP). It was observed that the HIV transmission risk was highest with treatment as prevention and lowest for MAP (5.4 and 0.0 HIV-infected women/10,000 pregnancies, respectively). Targeting fertile days was more effective than preexposure prophylaxis (0.9 vs 1.8) and associated with lowest costs. They concluded that targeting fertile days was associated with a low risk of HIV transmission in fertile HIV-uninfected female/male with controlled HIV infection couples. The risk is lower with preexposure prophylaxis limited to fertile days, or MAP, but these strategies have an increased cost.

In 1998 Marina[22] was first to report that intrauterine insemination can substantially reduce the chance of HIV transmission to the female partner and child. Semprini[23] described a method using a density gradient and swim-up technique to obtain sperm, which were then tested by PCR assays for the presence of HIV. If the final sperm sample tested negative for HIV, it was used for insemination. With this technique, less than 1% of the samples (6 out of 623) tested positive for the virus. Of the 1,600 inseminations done in 513 HIV-uninfected women, 228 pregnancies were reported. Follow up of 97.5% women at 3 months and 92% at 1 year revealed that all children older than 3 months of age and all mothers remained uninfected.

IVF (In vitro fertilization) with ICSI (intra cytoplasmic sperm injection) can minimise transmission of HIV to uninfected women and her offspring. The first pregnancy achieved in a seronegative woman following in vitro fecundation through intracytoplasmic sperm injection from a man with HIV was reported in 1998.[24] A 10-year retrospective study was done on 181 HIV-discordant couples, using assisted reproductive technology (ART). The couples underwent treatment with IVF with ICSI in which sperm was prepared using a modified density-gradient centrifugation and swim-up method. There were 116 deliveries of 170 neonates (due to a multiple birth rate of 41%), no female seroconversions and no infections in any of the offspring.[25]

A systemic review[26] was done to evaluate the effectiveness of semen washing in HIV discordant couples in which the male partner is infected. Forty single-arm open-label studies among HIV-discordant couples that underwent intrauterine insemination (IUI) or in vitro fertilization (IVF) with or without intracytoplasmic sperm injection (ICSI) using washed semen were studied. It was seen that no HIV transmission occurred in 11,585 cycles of assisted reproduction with the use of washed semen among 3,994 women. Among the subset of HIV-infected men without plasma viral suppression at the time of semen washing, no HIV seroconversions occurred among 1,023 women after 2,863 cycles of assisted reproduction with the use of washed semen. No cases of vertical transmission to infants were reported. Overall, 56.3% of couples (2,357/4,184) achieved a clinical pregnancy with the use of washed semen. They concluded that Semen washing appears to significantly reduce the risk of transmission in HIV-discordant couples desiring children, regardless of viral suppression in the male partner.

A retrospective case-control study[27] was done to compare the efficacy of assisted reproductive technology (ART) in women infected with HIV-1 versus HIV-negative controls. 82 women infected with HIV-1 and 82 women seronegative controls were matched and studied for first IVF cycle only. No statistically significant differences were seen between the two groups for ovarian stimulation data, fertilization rate, or average number of embryos transferred. The clinical pregnancy rate per transfer was statistically significantly lower for the HIV infected women compared to controls (12% vs. 32%), as were the implantation rate (10% vs. 21%) and the live-birth rate (7% vs. 19%). These results suggest that women with controlled HIV-1-infection should be counselled not to delay ART in cases of self-insemination failure or other causes of infertility. Fertility preservation by vitrification of oocytes in women whose pregnancy should be delayed may be an important future consideration.

To compare the outcomes of in vitro fertilization (IVF) for couples where one or both partners were positive for the human immunodeficiency virus (HIV) to matched control couples a study was done by Vankerkem *et al.*[28] The study included 104 couples where the woman was HIV-positive; 90 couples where the man was HIV-positive; and 33 couples where both partners were HIV-positive. For couples involving an HIV-positive man, clinical outcomes were comparable to controls and resulted in the birth of 18 healthy babies after 90 cycles. When the woman was affected, cycle cancelation, number of retrieved oocytes, and on-going clinical pregnancy rates per transfer were statistically reduced. Implantation rates were comparable to those of non-affected controls. Seven healthy babies for 104 cycles were obtained. For a couple in which both partners were HIV-positive, only one healthy birth occurred after 33 cycles. The study concluded that IVF outcomes were similar to controls when men were HIV-positive, were acceptable when women were HIV-positive but were severely reduced when both were HIV positive.

It is seen that while the results of intrauterine insemination seem satisfactory for serodiscordant couples living with HIV, in vitro fertilization results appear to be unfavorable when the woman is infected with HIV. In vitro fertilization results appear to be comparable to those in general population when only the man is infected with HIV. It can be assumed that ovaries are impacted by the treatment and/or the HIV in infected women.[29]

While HIV-seroconcordant couples do not have the same concerns of transmission to an uninfected partner described for those serodiscordant, they are however at an increased risk of HIV superinfection. Some couples in which both partners' viral loads were suppressed to undetectable levels conceived children free of HIV. The child may lose one or both parents to AIDS before he or she reaches adulthood, although recent success with combination antiretroviral therapy has significantly reduced death rates of infected persons.

Ethical issues raised by knowingly risking the birth of a child with HIV

The risk of HIV transmission to offspring when one or both parents are seropositive can be greatly reduced but cannot be completely eliminated. Although recent data does not show instances of vertical transmission using sperm-prepared IUI or IVF with ICSI, theoretically the risk cannot be completely eliminated. Assessing the ethics of assisting such patients to have children includes addressing the question of whether offspring born with HIV are harmed despite the preventive steps taken. This risk raises ethical issues concerning the scope of freedom to reproduce.

HIV and the health professional

Health professional who accidentally inoculated themselves with a patient's blood by a needle stick or were splashed with bloody fluid can be infected with HIV. None of these cases of HIV transmission occurred in the context of current ART.[30] If standard universal precautions to prevent infectious disease transmission are taken, the risk of viral transmission to medical caregivers is very small.

Theoretically, the risk to gametes and embryos could arise through cross-contamination in the laboratory setting, although there is no documentation of contamination of stored human tissue. To avoid the possible cross-contamination, the ASRM Practice Committee recommends that samples from a viral carrier be processed in a separate laboratory or designated space within the main laboratory, utilizing a dedicated storage tank.[31] To date, the lack of any occupational transmissions to ART health-care providers or bystander patients in a treating clinic suggests that the risk to these individuals from providing ART care to an

HIV-infected patient is minimal and potentially nonexistent.

Third-party assisted reproduction for HIV infected intended parents

HIV infected couples may desire for third-party reproduction assistance from a gamete donor or gestational carrier. Professional guidelines counsel against using an HIV-infected gamete donor or gestational carrier for third-party reproduction assistance.[32,33] Since gamete donors and gestational surrogates undergo medical treatment, informed consent of the risks and benefits of treatments should be obtained prior to using their assistance. A gestational carrier who is willing to provide service to an HIV-infected gamete provider should be fully informed of the potential risks to her health. In some jurisdictions, recipients of gametes from HIV-infected donors must sign a specialized written waiver acknowledging the medical risks associated with such a transfer.[34]

CONCLUSION

Human immunodeficiency virus infection has now become a chronic disease. The potential for HIV-infected persons to live long and healthy lives has resulted in increasing numbers of individuals to seek means for creating biologic families. Treatment offered by health-care providers must aim at minimal or no risk of transmission of HIV infection to the uninfected partner and their offspring. ART clinics with the necessary resources can offer services to HIV-infected individuals and couples who are willing to use recommended risk-reducing therapies.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Sexually Transmitted Diseases Treatment Guidelines. MMWR 2010;59:1-110.
2. King EM, Albert AY, Murray MCM. HIV and amenorrhea: a meta-analysis. AIDS 2019;33:483-91. doi: 10.1097/QAD.0000000000002084
3. Watts DH, Spino C, Zaborski L, Katzenstein D, Hammer S, Benson C. Comparison of gynecologic history and laboratory results in HIV-positive women with CD4+ lymphocyte counts between 200 and 500 cells/microl and below 100 cells/microl. J Acquir Immune Defic Syndr Human Retrovirol 1999;20:455-62
4. Scherzer R, Bacchetti P, Messerlian G, Goderre J, Maki PM, Seifer DB, *et al.* Impact of CD4+ lymphocytes and HIV infection on anti-Mullerian hormone levels in a large cohort of HIV-infected and HIV-uninfected women. Am J Reprod Immunol 2015;73:273-84.
5. Santulli P, de Villardi D, Gayet V, *et al.* Decreased ovarian reserve in HIV-infected women. AIDS 2016;30:1083-8.doi:10.1097/QAD.0000000000001025
6. Gemmill A, Bradley SEK, van der Poel S. Reduced fecundity in HIV-positive women. Hum Reprod 2018;33:1158-66. doi:10.1093/humrep/dey065.
7. Savasi V, Parisi F, Oneta M, *et al.* Effects of highly active antiretroviral therapy on semen parameters of a cohort of 770 HIV-1 infected men. PLoS One 2019;14:e0212194. Published 2019 Feb 21. doi:10.1371/journal.pone.0212194
8. Dejucq-Rainsford N, Jegou B. Viruses in semen and male genital tissue-consequences for the reproductive system and therapeutic perspectives. Curr Pharm Des 2004;10:557-75
9. Taylor S, Back DJ, Drake SN, Workman J, Reynolds H, Gibbons SE, *et al.* Antiretroviral drug concentrations in semen of HIV-infected men: differential penetration of indinavir, ritonavir and saquinavir. J Antimicob Chemother 2001;48:351-4
10. Kovalski NN, de Lamirande E, Gagnon C. Reactive oxygen species generated by human neutrophils inhibit sperm motility: protective effect of seminal plasma and scavengers. Fertil Steril 1992;58:809-16.
11. Price TO, Ercal N, Nakaoke R, Banks WA. HIV-1 viral proteins gp120 and Tat induce oxidative stress in brain endothelial cells. Brain Res 2005;1045:57-63. 10.1016/j.brainres.2005.03.031
12. Nazmara Z, Najafi M, Rezaei-Mojaz S, Movahedin M, Zandiyeh Z, Shirinbayan P, Roshanpajouh M, Asgari HR, Hosseini Jafari Lavasani L, Koruji M. The effect of heroin addiction on human sperm parameters, histone-to-protamine transition, and serum sexual hormone levels. Urol J 2018 In press. [PubMed] [Google Scholar]
13. Savasi V, Oneta M, Laoreti A, *et al.* Effects of antiretroviral therapy on sperm DNA integrity of HIV-1-infected men. Am J Mens Health 2018;12:1835-42. doi:10.1177/1557988318794282
14. Zhu XR, Li LH, Fan LX, *et al.* Zhonghua Nan Ke Xue 2018;24:414-418.
15. Mandelbrot L, Heard I, Henrion-Geeant E, Henrion R. Natural conception in HIV-negative women with HIV-infected partners. Lancet 1997;349:850-1.
16. HHS Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission. Recommendations for use of antiretroviral drugs in pregnant HIV-1-infected women for maternal health and interventions to reduce perinatal HIV transmission in the United States. Available at: http://aidsinfo.nih. gov/contentfiles/lvguidelines/PerinatalGL.pdf. Accessed April 9, 2015.
17. Mandelbrot L, Heard I, Henrion-Geeant E, Henrion R. Natural conception in HIV-negative women with HIV-infected partners. Lancet 1997;349:850-1.
18. Cohen MS, Chen YQ, McCauley M, Gamble T, Hosseinipour MC, Kumarasamy N, *et al.* Prevention of HIV-1 infection with early antiretroviral therapy. N Engl J Med 2011;365:493-505
19. Vernazza PL, Graf I, Sonnenberg-Schwan U, Geit M, Meurer A. Preexposure prophylaxis and timed intercourse for HIV-discordant couples willing to conceive a child. AIDS 2011;25:2005-8.
20. Public Health Service; Preexposure Prophylaxis for the Prevention of HIV Infection in the United States–2014. Available at: http://www.cdc.gov/hiv/pdf/PrEPguidelines2014.pdf. Accessed April 9, 2015.
21. Mabileau G, Schwarzinger M, Flores J, *et al.* HIV-serodiscordant couples desiring a child: 'treatment as prevention,' preexposure prophylaxis, or medically assisted procreation? Am J Obstet Gynecol 2015;213:341.e1-341.e3412. doi:10.1016/j.ajog.2015.05.010

22. Marina S, Marina F, Alcolea R, *et al.* Human immunodeficiency virus type 1-serodiscordant couples can bear healthy children after undergoing intrauterine insemination. Fertil Steril 1998;70:35-9. 4.
23. Semprini AE, Levi-Setti P, Ravizza M, Pardi G. Assisted conception to reduce the risk of male-to-female sexual transfer of HIV in serodiscordant couples: an update [abstract]. Presented at the 1998 Symposium on AIDS in Women, Sao Paulo, Brazil, September 14-15, 1998.
24. Marina S, Marina F, Alcolea R, *et al.* Pregnancy following intracytoplasmic sperm injection from an HIV-1-seropositive man. Hum Reprod. 1998;13:3247-9.
25. Sauer MV, Wang JG, Douglas NC, Nakhuda GS, Vardhana P, Jovanovic V, *et al.* Providing fertility care to men seropositive for human immunodeficiency virus: reviewing 10 years of experience and 420 consecutive cycles of in vitro fertilization and intracytoplasmic sperm injection. Fertil Steril 2009;91:2455-60.
26. Zafer M, Horvath H, Mmeje O, *et al.* Effectiveness of semen washing to prevent human immunodeficiency virus (HIV) transmission and assist pregnancy in HIV-discordant couples: a systematic review and meta-analysis. Fertil Steril 2016;105:645-55.e2. doi:10.1016/j.fertnstert.2015.11.028
27. Stora C, Epelboin S, Devouche E, *et al.* Women infected with human immunodeficiency virus type 1 have poorer assisted reproduction outcomes: a case-control study. Fertil Steril 2016;105:1193-201. doi:10.1016/j.fertnstert.2015.12.138
28. Vankerkem P, Manigart Y, Delvigne A, *et al.* In vitro fertilization when men, women, or both partners are positive for HIV: a case-control study. Arch Gynecol Obstet 2017;295:1493-507. doi:10.1007/s00404-017-4374-0
29. Ninive C, Ferraretto X, Gricourt S, *et al.* Prise en charge des couples porteurs du VIH en assistance médicale à la procréation : quels résultats et quelle stratégie en France en2019 ? [Assisted reproductive technologies in HIV patients: Which results and which strategy in France in 2019?]. Gynecol Obstet Fertil Senol 2019;47:362-9. doi:10.1016/j.gofs.2019.02.001
30. Kambin S, Batzer F. Assisted reproductive technology in HIV serodiscordant couples. Sex Reprod Menopause 2004;2:92-100.
31. Practice Committee of American Society for Reproductive Medicine. Recommendations for reducing the risk of viral transmission during fertility treatment with the use of autologous gametes: a committee opinion. Fertil Steril 2013;99:340-6.
32. Practice Committee of the American Society for Reproductive Medicine, Practice Committee of the Society for Assisted Reproductive Technology. Recommendations for gamete and embryo donation: a committee opinion. Fertil Steril 2013;99:47-62.
33. Practice Committee of American Society for Reproductive Medicine, Practice Committee of Society for Assisted Reproductive Technology. Recommendations for practices utilizing gestational carriers: an ASRM Practice Committee Guideline. Fertil Steril 2015;103:e1-8.
34. Cal. Health & Safety Code, Sec. 1644.5. Available at: http://www.leginfo.ca.gov/cgi-bin/displaycode?section¼hsc&group=01001-02000&file=1644-1644.6. Last accessed April 27, 2015.