

Cost and safety of assisted reproductive technologies for human immunodeficiency virus-1 discordant couples

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Abstract

Due to significant advances in the treatment of human immunodeficiency virus type-1 (HIV-1), HIV-1 infection gradually has become a treatable chronic disease. Successfully treated HIV-positive individuals can have a normal life expectancy. Hence, more and more HIV-1 discordant couples in Taiwan and the rest of the world are seeking fertility assistance. Pre-treatment of highly active antiretroviral therapy (HAART) combined with sperm washing and RT-polymerase chain reaction examination for HIV-1 viral load has become the standard procedure to assist them to conceive. However,

in order to reduce the transmission risk to the lowest level for the couple and to diminish the cost of health care for the insurance institutes or government, *in vitro* fertilization (IVF)-intracytoplasmic sperm injection (ICSI) therapy provides the ideal solution for HIV-1 discordant couples with infected men. Intrauterine insemination (IUI) theoretically introduces more than 10^7 times of sperm counts or semen volume to uninfected women vs IVF-ICSI. However, since some regimens of HAART may significantly decrease the sperm motility, compared to IVF-ICSI, IUI only produces 1/5 to 1/2 pregnancy rates per cycle. Given the risk of seroconversion of HIV infection which actually happens after successful treatment, IVF-ICSI for these HIV-1 seropositive men is more cost-effective and should be the first line treatment for these cases.

Key words: Highly active antiretroviral therapy; human immunodeficiency virus-1 discordant; Seroconversion; Intrauterine insemination; Intracytoplasmic sperm injection

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Core tip: For human immunodeficiency virus type-1 (HIV-1)-infected men and uninfected women, highly active antiretroviral therapy, sperm washing and HIV-1 viral load check by RT-polymerase chain reaction have become the standard procedure to enable conception. Although the risk of seroconversion of HIV infection is very low, it remains possible. Intrauterine insemination may introduce more risk of HIV-1 transmission and also possesses less chance of pregnancy compared to *in vitro* fertilization-intracytoplasmic sperm injection (ICSI). Therefore, ICSI may be the preferred choice.

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INTRODUCTION

According to the World Health Organization (WHO)'s data and statistics, more and more people were newly infected with human immunodeficiency virus type-1 (HIV-1), *i.e.*, 2.1 million, in 2013. In the beginning, HIV-1 couples were often discouraged from planning a pregnancy due to its poor prognosis. Nowadays, due to many advances in highly active antiretroviral therapy (HAART) in the last 10 years, the expected age at death of a 35-year-old man could be extended up to 80 years of age^[1]. As a result, many seropositive couples are now looking for ways to safely conceive their own babies.

However, pregnancy by natural conception in HIV-negative women with HIV-infected partners may result in 4.3% seroconversion^[2]. In the stage of lower HIV-1 load, the rate of HIV-1 transmission per coital act could be as low as 0.1% in HIV-1 discordant couples^[3]. This has implications for HIV-1 prevention and for projecting the effects of HAART in this situation. However, the conception rate after a single coital act prior to ovulation is relatively low because the semen volume and sperm motility decreases in HIV-1-infected patients under HAART^[4].

The clinical use of semen washing was first reported in 1992 by Semprini *et al.*^[5] and since then, assisted reproductive technologies, including intrauterine insemination (IUI), *in vitro* fertilization (IVF) and intracytoplasmic sperm injection (ICSI), have widely combined the use of semen washing to help HIV-1-infected discordant couples with an HIV-1-infected man. About 10 years ago, the database of Centers for Reproductive Assistance To HIV couples in Europe reported over 500 infants born following this procedure in 4989 cycles of assisted conception^[6]. More recently, assisted reproductive technology has proved to reduce the risk of HIV-1 transmission of uninfected women and helped these discordant couples to conceive^[7-11].

Therefore, in 2010, the ASRM Committee on Ethics modified their guidelines concerning assisted reproductive technology for these HIV-1 discordant couples as follows^[12]: (1) in couples in which the man is HIV-infected, the use of sperm preparation techniques coupled with either inseminations or IVF with ICSI has proven to be highly effective in avoiding seroconversion of uninfected women and offspring; and (2) fertility clinics, to the extent it is economically and technically feasible, should offer services to HIV-infected individuals and couples who are willing to use risk-reducing therapies. In this article, we would like to discuss which assisted reproductive technology is the most effective and theoretically the safest way to conceive for the couples and most economical for the insurance companies or the government.

HIV-1 SEMEN WASHING

HIV-1 transmission *via* artificial insemination using donor sperm was first reported in 1985^[13] and the risk

remained high, especially in untreated urethritis^[14]. In 1992, Semprini *et al.*^[5] reported a simple method to eliminate the leukocytes from HIV-infected semen for intrauterine insemination. The method is a three-step system: (1) filtering the liquefied semen through a gradient; (2) washing the recovered spermatozoa to remove seminal plasma; and (3) swim-up to collect highly motile spermatozoa. A testing of the final sample by using a polymerase chain reaction (PCR) assay would assure the clearance of HIV-1 virus throughout the washing procedure.

However, the viral burden is an issue. The amount of HIV-1 present in the original semen sample affects the efficiency of the above procedure^[15]. So, in 2004, the Harvard group further decreased HIV-1 RNA copy numbers from 1300 by gradient/swim-up to 200 by double-tube gradient^[16]. Moreover, the amount of motile sperm recovered is superior to Semprini's method. In 2005, Loskutoff *et al.*^[17] used a novel washing method by combining multiple density gradients and trypsin addition for removing HIV-1 from semen, significantly reducing HIV-1 load without affecting sperm quality. Moreover, in 2006, Kato *et al.*^[11] also used an improved swim-up method to collect HIV-free spermatozoa from the semen of HIV-positive males. They demonstrated complete removal of HIV-1 RNA and proviral DNA by nested PCR assay.

Regarding the efficiency of sperm washing in removing HIV-1, the key depends on the seminal viral load. Fiore *et al.*^[15] demonstrated that 5×10^4 copies/mL were generally considered as the upper limit for the standard washing methods. From their study, in semen samples containing 1 and 3×10^6 copies/mL, persistence of viral RNA after standard washing procedures was observed in some of the aliquots tested. In light of this finding, pre-treatment with HAART before sperm washing is rational for these HIV-1 discordant couples.

ASSISTED REPRODUCTIVE TECHNOLOGIES IN HIV-1 DISCORDANT COUPLES (MALE HIV-1 POSITIVE)

Originally, these sperm washing techniques were applied in IUI and some of them even presented with relatively high pregnancy rates (24%-52%)^[7,18]. As we know, different conditions (*e.g.*, women's age) and policies (*e.g.*, high cancellation rates) resulted in different IUI results. Over the past 30 years, our data showed around 10% pregnancy rates for IUI^[19,20] and 45% pregnancy rates for IVF^[21,22]. Since 2003, we have performed IUI in these HIV-1 discordant couples, resulting in 10% clinical pregnancy rates (data not shown) and only 26% in fresh IVF cycles (Table 1). One reason is that some cases are of advanced age and therefore sometimes no embryos or even no oocytes could be obtained. On the other hand, the frozen-thawed cycles have normal pregnancy rates (45%).

Table 1 Results of *in vitro* fertilizations in human immunodeficiency virus type-1 discordant couples with a human immunodeficiency virus type-1-infected male partner at National Taiwan University Hospital from 2005-2014

Results	n
Couples	38
Fresh cycles	72
Age	35.9 ± 4.9
Oocytes retrieved	11.3 ± 7.7
Total 2PN fertilized	6.4 ± 5.1
Clinical pregnancies ¹	19 (26.4%)
Miscarriage	4 (21.1%)
Ectopic pregnancies	2 (10.5%)
Babies born	18
Thawed cycles	20
Clinical pregnancies ²	9 (45.0%)
Miscarriage	0
Ectopic pregnancies	0
Babies born	12
Accumulated pregnancies	23 (60.5%)
Seroconversions	0

¹Per TVOR; ²Per ET.

Semprini and Fiore^[6] favored IUI in the treatment of HIV-1 discordant couples and concluded that "IVF carries a higher pregnancy rate per cycle, but requires ovarian hyperstimulation, egg retrieval under sedation and carries a 20% risk of multi-fatality". Multiple pregnancy is no longer an issue in modern IVF practice since single embryo transfer^[23,24] or elective single embryo transfer was developed^[25,26].

Although combined pre-treatment with HAART, sperm washing and RT-PCR could provide a relatively safe sperm sample for conception in HIV-1 discordant couples, it is not completely virus-free as our HIV-1 assay detection limit is 40 copies/mL at present^[27]. Using more sperm may translate into more volume used or more viruses transmitted. On average, we introduce 40 million spermatozoa into the uterus in IUI, use 0.4 million spermatozoa in the culture dishes for IVF and only one sperm for ICSI. Unless the sperm sample for IUI is extremely concentrated, the volume (means the virus count or the transmission risk of HIV-1) of ICSI will be far less than 1/400000 compared to the IUI procedure.

Furthermore, when HIV-1 RNA is not detectable, is it risk free? Previously, Zhang *et al.*^[28] demonstrated over 50% cases with positive proviral DNA, even HIV-1 RNA less than 50 copies/mL. Therefore, fewer spermatozoa used to conceive (*e.g.*, ICSI) will have the lowest risk of HIV-1 transmission.

COST/BENEFIT

From a model of antenatal screening for HIV-1 infection in Australia, is it cost-effective in a setting of very low prevalence? The answer is "YES" if the prevalence of HIV-1 > 0.004372%^[29]. The expense of massive screening to avoid a new vertical transmission has to be

calculated. Here, HIV-1 discordant couples have already decided to get pregnant. Now, the open question is whether IUI or ICSI is safer?

IVF treatment with ICSI provides 2-5 times higher pregnancy rates compared to IUI, meaning less frequent exposure to HIV-1 in ICSI cycles. Moreover, in single reproductive assistance, IUI involved more than 4×10^7 times of sperm or virus exposure, which may result in the tragedy of HIV-1 seroconversion. That might be a strong reason to choose IVF-ICSI in addition to the theoretical risk. In 1997, Columbia University began offering IVF-ICSI but not IUI to HIV-seropositive men to limit viral exposure to a few motile sperm cells^[30]. Although some worried about more ovarian hyperstimulation syndrome (OHSS) in IVF protocols than in IUI treatment^[9], as a matter of fact that was wrong. The controlled ovarian stimulation protocols are the same and flushing medium into the follicle could remove the most granulosa cells. As we can freeze all embryos and/or use a GnRH agonist to trigger ovulation, the OHSS rates were relatively low in our IVF program. As mentioned, some doctors also criticized the higher multiple pregnancies in IVF cases^[6] which was also actually wrong. Single embryo transfer could assure singleton pregnancy but IUI could not.

If we consider the cost difference between IUI and IVF, it is very trivial (\$2000-15000 USD per IVF course) when compared to the medical fee of long-term HAART (\$28861-40804 USD per person-year) in a new HIV-1 seroconversion^[31]. If we consider the sedation for oocyte pickup, the psychological stress, including more trials and longer waiting of IUI, should also be considered when comparing IVF with ICSI treatment.

CONCLUSION

Modern HAART has prolonged the life expectancy of HIV-1 infected men; moreover, modern assisted reproductive technologies also have helped these couples to conceive successfully and safely. Pre-treatment with HAART, standard sperm washing procedure and controlled ovarian stimulation plus IUI/IVF may provide a promising way to improve pregnancy outcome in these couples. IVF treatment with ICSI in recent years may have given patients higher pregnancy rates and less risk of HIV-1 transmission. Furthermore, accurate HIV-1 assays or even embryo biopsy to verify the status of HIV-1 infection may be the future efforts.

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