Name of journal: *World Journal of Virology*

ESPS Manuscript NO: 14880

Columns: MINIREVIEW

**Cost and safety with assisted reproductive technologies for HIV-1 discordant couples**

Wu MY *et al.* ART for HIV-1 discordant couples

Ming-Yih Wu, Hong-Nerng Ho

**Ming-Yih Wu, Hong-Nerng Ho**, Department of Obstetrics and Gynecology, College of Medicine, National Taiwan University, Taipei 10002, Taiwan

**Author contributions:** Wu MY and Ho HN solely contributed to this paper.

**Conflict-of-interest:** We declare no conflicts of interests.

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**Correspondence to:** **Hong-Nerng Ho, MD,** Department of Obstetrics and Gynecology, National Taiwan University Hospital, No. 7 Chung-Shan South Road, Taipei 10002, Taiwan. hnho@ntu.edu.tw

**Telephone:** +886-2-23123456

**Fax:** +886-2-23116056

**Received:** October 28, 2014

**Peer-review started:** October 29, 2014

**First decision:** December 12, 2014

**Revised:** December 25, 2014

**Accepted:**

**Article in press:**

**Published online:**

**Abstract**

Due to significant advance in the treatment of human immunodeficiency virus type-1 (HIV-1), HIV-1 infection gradually becomes 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 or in the world were 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)-intracytoplasmatic sperm injection (ICSI) therapy provides the ideal solution for HIV-1 discordant couples with men infected. Intrauterine insemination (IUI) theoretically introduces more than 107 times of sperm counts or semen volume to the un-infected 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 are more cost-effective and should be put in the first line treatment for these cases.

**Key words:** Highly active antiretroviral therapy; HIV-1 discordant; Intracytoplasmatic sperm injection; Intrauterine insemination; Seroconversion

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**Core tip:** For human immunodeficiency virus type-1 (HIV-1)-infected men and un-infected women, highly active antiretroviral therapy, sperm washing and HIV-1 viral load check by RT-polymerase chain reaction have become the standard procedure to make them to conceive. 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-intracytoplasmatic sperm injection (ICSI). Therefore, ICSI may be the preferred choice.

Wu MY, Ho HN. Cost and safety with assisted reproductive technologies for HIV-1 discordant couples. *World J Virol* 2015; In press

**INTRODUCTION**

### According to the [World Health Organization](http://www.who.int/%22%20%5Ct%20%22_blank) (WHO)’s data and statistics, more and more people were newly infected with human immunodeficiency virus type-1 (HIV-1), *e.g.*, 2.1 million in 2013. In the beginning, the HIV-1 couples were often discouraged from planning a pregnancy due to its poor prognosis. Nowadays, due to much advance in highly active antiretroviral therapy(HAART) in recent 10 years, the expected age at death of a 35-year-old man could be extended to up to 80 years of age[1]. As a result, many sero-positive 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 their 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. But, the conception rate after single coital act prior to ovulation is relatively low because the semen volume and spermatozoa 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 intracytoplasmatic sperm injection (ICSI) have widely combined the use of semen washing to help the 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 (CREATHE) has 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 the un-infected 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 figure out which one 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 un-treated 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 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, Harvard group has 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 sperms 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, and got 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] has demonstrated that 5x104 copies/mL were generally considered as the upper limit for the standard washing methods. From their study, in semen samples containing 1 and 3 × 106 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 TECHONOLOGIES IN HIV-1 DISCORDANT COUPLES (MALE HIV-1 POSITIVE)**

Originally, this 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 cancelation rates) resulted in different IUI results. Through the past 30 years, our data showed around 10% pregnancy rates of IUI[19,20]; and 45% pregnancy rates of IVF[21,22]. Since 2003, we have performed IUI in these HIV-1 discordant couples and resulted 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 no embryos or even no oocytes could be obtained sometimes. On the contrary, the frozen-thaw cycles have normal pregnancy rates (45%).

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

Although combined pre-treatment with HAART, sperm washing, and RT-PCR could provide a relatively safe sperm sample to conceive in HIV-1 discordant couples, it is not completely virus-free because our HIV-1 assay detection limit is 40 copies/mL at present[27]. More sperms used may translate into more volume used, or more viruses transmitted. In average, we introduce 40 million spermatozoa into the uterus in IUI; and used 0.4 million spermatozoa in the culture dishes for IVF; and picked only one sperm to do 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 IUI procedure.

Furthermore, is there risk-free when HIV-1 RNA is not detectable? Previously, Zhang *et al*[28] demonstrated over 50% cases with positive proviral DNA even HIV-1 RNA less than 50 copies/mL. According to this point, fewer spermatozoa used to conceive (*e.g.*, ICSI) will get 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]. They have to calculate the expense of massive screening to avoid a new vertical transmission. Here, in HIV-1 discordant couples, they have already decided to get pregnant. Now the open question is that which method is safer? IUI or ICSI?

IVF treatment with ICSI provides 2-5 times pregnancy rates compared to IUI, meaning less frequent exposure to HIV-1 in ICSI cycles. Moreover, in single reproductive assistance, IUI involved more than 4x107 times of sperms, or virus exposure, which may result in tragedy of HIV-1 seroconversion. That might have even strong reasons 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 it was wrong. The controlled ovarian stimulation protocols are the same, and flushing medium into the follicle could remove the most granulosa cells. Because we can freeze all embryos and/or using GnRH agonist to trigger ovulation, therefore, the OHSS rates were relatively low in our IVF program. As mentioned, some doctors also criticized the higher multiple pregnancies in IVF cases[6], it 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 on oocyte pickup, the psychological stress including more trials, longer waiting of IUI should be also weighed to comparing IVF with ICSI treatment.

**CONCLUSION**

Modern HAART have 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 the patients more pregnancy rates and less risk of HIV-1 transmission. Further more 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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**P-Reviewer:** Khajehei M, Shih WL **S-Editor:** Ji FF **L-Editor: E-Editor:**

**Table 1 Results of in vitro fertilizations in human immunodeficiency virus type-1 discordant couples with a human immunodeficiency virus type-1-unfected 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 pregnancies1 | 19 (26.4%) |
|  Miscarriage | 4 (21.1%) |
|  Ectopic pregnancies | 2 (10.5%) |
|  Babies born | 18 |
|  |  |
|  Thawed cycles | 20 |
|  Clinical pregnancies2 | 9 (45.0%) |
|  Miscarriage | 0 |
|  Ectopic pregnancies | 0 |
|  Babies born | 12 |
| Accumulated pregnancies | 23 (60.5%) |
| Seroconversions | 0 |

 1Per TVOR; 2Per ET.