Reproductive Options for HIV-Serodiscordant Couples

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Abstract

The foundation of a family is a personal enterprise with deep biological and emotional motivations. Family life is a no lesser priority for individuals living with HIV than for others. Moreover, the dramatic reduction in HIV-related morbidity and mortality as a consequence of the widespread use of HAART has led to a growing number of HIV-infected individuals and their partners requiring education and counseling regarding HIV disease and reproduction. After careful evaluation of health status and fertility in both partners, two main alternatives may be considered – natural conception or assisted reproduction techniques. This review discusses the pros and cons of reproductive options in HIV-infected persons and proposes a protocol for their counseling. **(AIDS Reviews 2006;8:158-70)**

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Key words

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Introduction

In the first years of the HIV pandemic, reproductive guidelines strongly stated that HIV-infected patients should avoid pregnancy. For example, the Centers for Disease Control and Prevention (CDC) discouraged any reproductive attempt due to the poor prognosis of HIV infection and the risk of transmission[1]. Similar opinions were shared by the American College of Obstetrics and Gynecology, which recommended HIV-infected women not to become pregnant[2], and the American Society for Reproductive Medicine, which suggested other alternative options such as donor insemination or child adoption[3]. However, even in those early days, many HIV-positive individuals chose to seek pregnancy, assuming the risk of sexual and/or vertical transmission in many instances[4].

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The remarkable changes in the management and prognosis of HIV infection over the last decade have opened up new horizons for HIV-infected persons. The administration of combination triple-antiretroviral regimens allows complete suppression of viral replication and significant improvement of the immune status in most patients. This has dramatically changed the natural history of the infection, which may be now considered a chronic illness for most, at least in developed countries. As a consequence, HIV-infected individuals can look forward to an active life style, both at work and at home.

The positive effect of durable suppression of viral replication with HAART goes beyond the patient's own benefit, and greatly impacts on the risk of sexual and vertical HIV transmission. The early reluctance of many medical and public health authorities to endorse reproductive attempts as a reasonable choice for HIV-infected persons has recently been reconsidered. In 2001 the CDC reviewed their previous statements, encouraging healthcare professionals to "provide information and give support to any reproductive option for HIV-positive patients" when HIV infection was under medical control[5]. Similarly, heterosexual couples are now more likely to consider the possibility of having their own children[6].

For example, one 1998 study examined attitudes concerning parenthood among 1421 HIV-infected sub-

jects. Twenty-nine percent wanted to have children in the near future[7]. Moreover, this desire for parenthood was shared by most HIV-negative partners. The absence of family life and the perception of being in good health seemed to be the most important and independent predictors of the desire for children.

Another 2005 cross-sectional study suggested that HIV-infected women are currently more likely to use reversible contraceptive methods as compared with the pre-HAART era[8]. In fact, the percentage of natural pregnancies (i.e. without artificial reproductive technology) in those women appears to be significantly higher (23%) than it was in the pre-HAART era. In one series, 12% of all women and 26% of those under 30 years of age conceived and bore their youngest child after diagnosis of HIV infection[9]. In another, 12% of HIV-discordant couples admitted that they had attempted conception by practicing unprotected sex during the process of assisted reproduction evaluation[10].

Assisted reproduction technologies have been proposed for HIV-discordant couples in order to minimize the chances of HIV transmission during conception attempts. In the case of HIV-infected male partners, there is experience with "sperm washing" prior to intrauterine insemination. However, the high cost of these techniques together with associated medical management and the limited pregnancy rate achieved are often big hurdles for many of these couples. In this context, and given the proven efficacy of HAART to reduce HIV transmission, a growing number of HIV-positive persons are seeking the chances of natural pregnancy[7].

This review describes the reproductive options in HIV-discordant couples and proposes a work-up protocol to guide pre-conception evaluation, education, and counseling.

Pre-conception counseling

Since HIV infection has become a chronic illness for many HIV-positive persons under HAART, clinicians attending HIV-infected patients should frequently discuss issues regarding reproductive health and family planning in the overall evaluation of clients[6]. Pre-conception control of other incurable but treatable illnesses such us diabetes mellitus[11] are known to enhance pregnancy outcome, and HIV infection is no exception. Expert evaluation and treatment of known risk factors for both lateral and vertical transmission of HIV may also significantly lower the risk of transmission during conception attempts, pregnancy, and delivery. The US Public Health Service[5] and others have emphasized that it is important to ensure that the caregiver's intervention is "nondirective and supportive of any reproductive decision". Current perinatal guidelines clearly state that "healthcare providers should be aware of the complex concerns that HIV-infected couples must consider when making decisions regarding their reproductive options and should be supportive of any decision". The protocol presented here is based on these same principles.

We propose that any HIV-discordant couple planning pregnancy should be evaluated in a standardized manner (Table 1). Firstly, a personal interview with both members of the couple should assess their current understanding of HIV, especially of those aspects related with reproduction, transmission, and survival. Without medical intervention, HIV transmission per heterosexual contact is generally accepted to be very low, around one in 1000 contacts (95% CI, 1/400 to 1/2000)[12]. The probability of infection per heterosexual contact may by higher for women than for men, although there are other factors that play a major role. Among the most important, HIV-RNA plasma concentration is directly correlated with the chances of HIV horizontal transmission[13-15].

In one pivotal study[16], a total of 415 HIV-discordant and stable couples living in Uganda were prospectively followed for an average of 30 months. No HIV-positive subject was receiving any antiretroviral drug. The average rate of sexual contacts was nine per month and consistent condom use was very infrequent (1.2%). The HIV-seroconversion rate during follow-up was 17% for women and 27% for men. However, when considering HIV transmission according to plasma viremia, there were no instances of seroconversion among 51 subjects with viral load < 1500 HIV-RNA copies/ml; also, a greater risk of transmission was seen with increasing HIV-plasma concentrations. These authors concluded that viral load is the chief predictor of the risk of heterosexual transmission of HIV.

The viral load in semen[17] and genital secretions may also be significant when evaluating the risks of HIV sexual transmission. Under normal conditions, the concentration of HIV in semen is lower than in plasma (0.5-0.6-fold)[18]. However, up to 4% of men and 20% of women with undetectable plasma viremia may have detectable concentrations of HIV in sexual fluids[19]. Genital-tract infections such as common bacterial urethritis, vaginitis or vaginosis, *Herpes simplex, Candida or Trichomonas* infections account for most cases of genital HIV shedding in patients with undetectable

Table 1. Proposed protocol to evaluate HIV-serodiscordant couples wanting to be parents

General discusion with the couple
- Risk of HIV transmission, and other infections if present (hepatitis B or C), to the negative partner and/or to the child: even in the best conditions zero risk can never be guarantee
- Other conditions that may modify HIV transmission:
  - Status of HIV infection: CD4 count and viral load
  - Genital tract: infections, disbacteriosis, inflammation, displasia, erosions, etc. (both members of the couple)
  - Tobacco or illicit drug use
  - Stability and duration of couple relationship
- Life expectancy of HIV-positive partner
- Age of the mother: risk for birth defects
- Adverse outcome of pregnancy or teratogenicity due to antiretrovirals
- Reproductive options:
  - Natural conception
  - Self-insemination
  - Assisted reproduction
  - Adoption
  - Accepting no children

Clinical evaluation of each partner
- History: special attention to:
  - HIV status: opportunistic events, CD4 count, viral load
  - Antiretrovirals: adherence, tolerance, experienced in pregnancy, teratogenicity
  - Fertility: menstrual cycles, infertility factors
- General examination
- Pelvic exam: bacterial vaginosis, cervical dysplasia
- Investigations:
  - Hematology and biochemistry. Blood type
  - Screening for: HIV, hepatitis A, B & C, *Cytomegalovirus*, *Herpes simplex*, Rubella, Toxoplasma, Syphilis
  - Culture of genital secretions: *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, *Thichomonas vaginalis*, etc.
- Vaccination status: considerar rubella, varicella, hepatitis A/B

Evaluation of fertile potencial
Especially indicated if history of AIDS, urologic/gynecologic complications of advanced age
- Male partner: spermiogram (count, motility, progression, morphology)
- Female partner:
  - Thyroid hormones
  - LH, FSH, estradiol, progesterone, prolactin
  - Pelvic ultrasound
  - Hysterosalpingogram (if recommended according to past history)

plasma viremia[20]. More importantly, the treatment of genital-tract pathogens is followed by a reduction in the HIV shedding in genital fluids[21]. Thus, current data strongly suggest that reduction in sexual transmission during conception attempts must include both treatment of genital tract infection and inflammatory conditions, and control of plasma viremia.

The risk of vertical transmission of HIV should be carefully discussed[6]. Accumulated experience seems to indicate that when the woman is the one infected, even under the best circumstances (mother receiving HAART with undetectable viremia and high CD4+ counts during pregnancy, perinatal prophylaxis with antiretrovirals to mother and child, etc.) there is still a residual risk of giving birth to an infected child, estimated to be < 1-2%[22,23].

Risks of *in utero* exposure to antiretroviral medications are of concern to clients and caregivers alike. However, to date no teratogenic signal has been detected in prospective registries in the USA[24] and Europe[25]. Although HIV infection itself does not seem to alter the course of pregnancy[26], conflicting data exist regarding the influence of HAART on obstetric outcomes. A large European study, analyzing nearly 4000 newborns from HIV-infected mothers, found a higher risk of preterm birth (OR, 1.4-4.8, median 2.6) in those exposed to HAART, with or without protease inhibitors, as compared with untreated patients[25]. Conversely, other studies have not found any clear relationship between HAART and pregnancy outcomes, low birth weight, or low Apgar scores[27]. There are accumulated data indicating that the use of protease inhibitors du-

ring pregnancy is associated with higher chances for gestational diabetes[28,29].

There is no definitive information either on the safety of nucleos(t)ide analogs given during the course of pregnancy. These drugs are the backbone of most HAART regimens and, as has been clearly established for adults, may cause mitochondrial toxicity in the baby following its good transplacental diffusion. In a French study that recorded data from 2644 newborns exposed *in utero* to nucleos(t)ides, a higher than expected incidence of cardiac, muscular, and neurologic events was identified, although the overall rate was low[30]. Conversely, a meta-analysis pooling data from more than 16,000 children recruited in five different cohorts in the USA found no higher risk for neonatal mitochondrial dysfunction in babies exposed to nucleos(t)ides *in utero*[31]. The European collaborative study rendered similar conclusions[25], as has the ongoing antiretroviral pregnancy registry[24].

The immunologic status of the HIV-positive person is another variable to be taken into account, as the possibility of genital HIV shedding is also greater in subjects with low CD4+ cell counts. The impairment in anti-HIV cellular immunity at the genital compartment may facilitate viral escape, even in patients under antiretroviral therapy[32]. Reduced CD4+ counts are also independently associated with a higher risk of vertical HIV transmission, even after adjusting for viral load and antiretroviral therapy[33]. Women with CD4+ counts < 200 cells/µl are also exposed to a higher incidence of postnatal infections, especially if cesarean section is performed[34]. Therefore, it is advisable that reproductive interventions only be pursued in mothers with a relatively good immune status (preferably > 350 CD4+ T-cells/µl) in order to minimize the risk of HIV transmission and/or complicated outcomes of pregnancy.

Studies in stable couples with one HIV-infected partner indicate that the risk of HIV transmission varies widely from couple to couple. While transmission occurred in some couples after only a few sexual encounters, other couples had many unprotected contacts without HIV transmission[35,36]. The reasons for apparent resistance to HIV transmission are not known, and it is unclear whether the basis is biologic or behavioral. It is possible that either humoral or cellular immunity may protect HIV-seronegative partners from becoming infected, as has been seen in some highly exposed individuals[37-39]. Therefore, couples must understand that we cannot predict in which cases HIV transmission is less likely to occur. For this reason it is advisable to discourage unprotected sexual contacts as consistently as possible but, when considering reproductive attempts, longer duration of the relationship may be a beneficial factor to be taken into account.

Maternal consumption of illicit dugs (heroin, cocaine)[40] or tobacco[41] has been associated with an increased risk of vertical HIV transmission. From all points of view, substance abuse should be strongly discouraged for the sake of good pregnancy outcome and newborn health.

The prognosis of HIV infection has improved very significantly since the advent of HAART. Still, the morbidity and mortality associated to concomitant illnesses, such as chronic viral hepatitis, in HIV-positive persons should be taken into consideration and discussed with the couple[42]. In some cases the priority may be to treat hepatitis C before discussing the chances of pregnancy, since ribavirin precludes temporarily any reproductive attempt due to its teratogenicity.

Finally, all HIV-serodiscordant couples who desire to have children should be informed of the reproductive options available during the first interview. This information should include as possible alternatives: natural conception, assisted reproduction techniques, adoption, or even the acceptance of not having children.

Fertility studies

Any HIV-serodiscordant couple that has decided to pursue pregnancy should be studied to assess upfront their fertile potential. If the HIV-seronegative partner is going to be exposed to HIV infection, it is important to rule out major fertility problems in advance. It has also been recently shown that the rate of pregnancy after *in vitro* fertilization and oocyte donation is lower in HIV-infected women as compared with seronegative women, irrespective of whether the male partner is HIV positive or negative. Only the CD4+ count in the HIV-infected women was related with lower chances of conception[43]. Also, sperm parameters seem to be impaired in HIV-infected patients as compared with seronegative controls; again, the extent of immunodepression seems to be directly correlated with the pathologic findings at the spermiogram[44].

According to our proposed protocol (Table 1), all male partners should have a spermiogram evaluation. For women, basic hormonal tests, pelvic ultrasound and, if recommended based on prior history, hysterosalpingography should be performed. If fertility problems are encountered, the couple should be referred to specialists for further studies. Conversely, couples with a history of recent pregnancy may be candidates

for simpler evaluation of fertility. When no abnormalities in fertility are recognized, the reproductive options for HIV-serodiscordant couples should be considered.

Assisted reproduction techniques

The significant improvement in the life expectancy of HIV-infected persons provided by antiretroviral drugs has allowed these individuals to be considered for assisted reproductive technology. In one study, the proportion of specialists ready to offer these techniques to HIV-positive women with fertility problems increased from 3 to 47% between 1993 and 2000[45].

There are several assisted reproduction interventions to be considered for fertile HIV-serodiscordant couples, which in part depend on the gender of the HIV-infected partner.

HIV-positive woman and HIV-negative man

In this case, the couple has to face the possibility of horizontal and/or vertical HIV transmission. As previously discussed, the latter risk can be significantly reduced by providing effective HAART to the mother so that undetectable plasma viremia is ensured during pregnancy[6]. Any reproductive intervention should wait until this crucial endpoint has been achieved.

Intrauterine insemination is the main option to avoid HIV infection of the seronegative male partner[6]. Due to the cost of this technique or its unavailability in some places, there is a growing number of couples that may opt for self-insemination. Freshly ejaculated semen is obtained after sexual intercourse using a collector that, as with condoms, is not impregnated with spermicides. Self-insemination is performed using a syringe or a disposable Pasteur pipette[46]. On account of to the characteristics of the procedure, there are no published data on the pregnancy rates in couples undergoing self-insemination. For the sake of pregnancy success it is advisable that couples opting for self-insemination receive instruction to identify the most fertile days (calendar calculation, basal temperature, hormonal ovulation test, etc.). Under medical evaluation, there is some experience in Spain with self-insemination during the woman's fertile window and after hormonal ovarian stimulation (del Romero J, personal communication).

HIV-positive man and HIV-negative woman

In this situation the major concern lies in the risk of male-to-female HIV sexual transmission, since babies born from HIV-negative mothers may never acquire HIV from the infected father. For many years, donor sperm insemination was the only alternative to achieve a safe pregnancy in this situation. However, this option is not well accepted by many HIV-discordant couples, whose legitimate desire is to bear their own children.

Accumulated data indicate that human gametes are probably not susceptible for HIV infection. The lack of CD4, CCR5 or CXCR4 receptors (to which HIV attaches when infecting a target cell) in the surface of spermatozoa is a solid argument in favor of this assumption[47,48]. However, there are sporadic reports of recognition of viral particles associated with spermatozoa by electron microscopy, or detection of HIV-DNA by PCR in preparations of spermatozoa. The current view is that the main location of the HIV inoculate in semen is at the seminal plasma (as free virions) and in non-spermatic cells (epithelial cells or lymphocytes)[49,50].

Semen processing techniques used in assisted reproduction have been modified for use in separating spermatozoa from infectious elements in semen[51,52]. The final objective of these "sperm washing" techniques is to obtain a spermatozoa fraction that is free from HIV or HIV-infected cells which, as stated, may be found in seminal plasma or in the non-germinal cell fraction of semen, respectively.

In brief, semen is initially fractionated by gradient centrifugation after which the fraction containing sperm and non-germinal cells is re-suspended and re-centrifuged. The pellet from this second centrifugation is re-suspended in a small volume of buffer for the "swim-up" procedure. In this step, the motile spermatozoa move up into the buffer and are thereby separated from nonmotile non-germinal cells. The motile fraction is collected as the purified sperm preparation. However, there is no absolute certainty that the final concentrate does not contain HIV. For this reason, after the process is completed, an aliquot is analyzed by PCR to rule out the presence of HIV-RNA[53]. Some centers freeze the germinal concentrate while HIV-PCR is performed, although real-time PCR is another alternative to avoid further manipulation of semen. There are protocols that also include the analysis of proviral HIV-DNA[54]. Only seminal samples with negative HIV-PCR results will be used for assisted reproduction procedures.

Once the spermatozoa concentrate has been obtained and the presence of HIV genomic sequences ruled out, there are three main options to achieve a pregnancy:

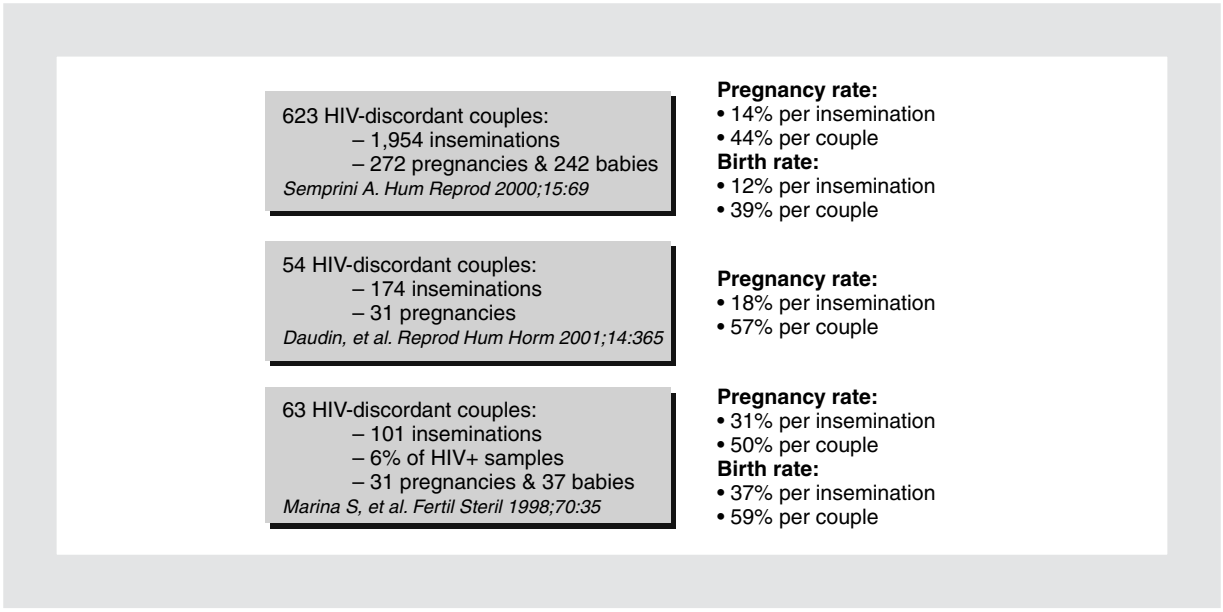

Figure 1. *Main experience with intrauterine insemination (IUI) after sperm concentration in HIV-serodiscordant couples.*

– Intrauterine insemination (IUI).
– *In vitro* fertilization (IVF).
– Intracytoplasmic sperm injection (ICSI).

There is relatively wide experience with the first two techniques in HIV-serodiscordant couples[6]. Semprini, et al. have the largest experience with HIV-negative women undergoing IUI with sperm concentrates from HIV-infected male partners[55]. No cases of horizontal HIV transmission were recorded after more than 4500 inseminations[56]. Similar experiences have been reported by Bujan, et al.[57] and Marina, et al.[58] (Fig. 1). Likewise, no seroconversion events have been recorded in women who have undergone IVF[59] or ICSI[60] in recent years (Fig. 2).

The success of assisted reproductive procedures is still limited. The pregnancy rate per procedure ranges from 15 to 30% for IUI and from 22 to 45% for IVF. The intense manipulation of the semen (centrifugation, swim-up, freezing), often greater than in procedures involving HIV-negative individuals, may contribute to this limited success. The average number of procedures that each couple needs to go through is 3-4 to result in a birth rate per couple of 60-75%. The cost of assisted reproduction techniques is another important consideration for many HIV-discordant couples. These procedures, which are not available in many centers, are expensive (approximately $10,000-17,000 per cycle), which is not affordable by a substantial proportion of HIV-infected persons, many of whom come from a low/medium social strata[61].

A recent survey in Italian centers attending HIV-discordant couples for assisted reproduction has shown that after medical evaluation one third of the couples did not start the insemination process and another third withdrew after a number of failed attempts. Furthermore, one half of couples failing assisted reproduction techniques in a Milan center attempted natural conception by practicing unprotected sex without medical control. Among these, one case of seroconversion was registered[56].

There are technical constraints that contribute to limit the availability of assisted reproduction technology for HIV-infected individuals, as separate laboratory facilities are required to avoid cross-contamination to uninfected patients[45,62]. The number of centers that fulfill specific safety requirements is still few in Europe and the USA. This explains in part why, with few exceptions, assisted reproduction has no public health coverage in Europe for HIV-infected subjects. It is claimed that offering this service to this patient population would further prolong the waiting lists and increase the costs of the procedures. In the particular case of the USA, the CDC has expressed its reluctance to support assisted reproduction procedures for HIV-positive persons, given the report of one case of HIV seroconversion in a woman after being inseminated with her husband's sperm[63].

Assisted reproduction techniques may be especially indicated in the case of HIV-positive male partners under virologic failure and therefore with detectable HIV viremia, although a negative HIV-PCR result from

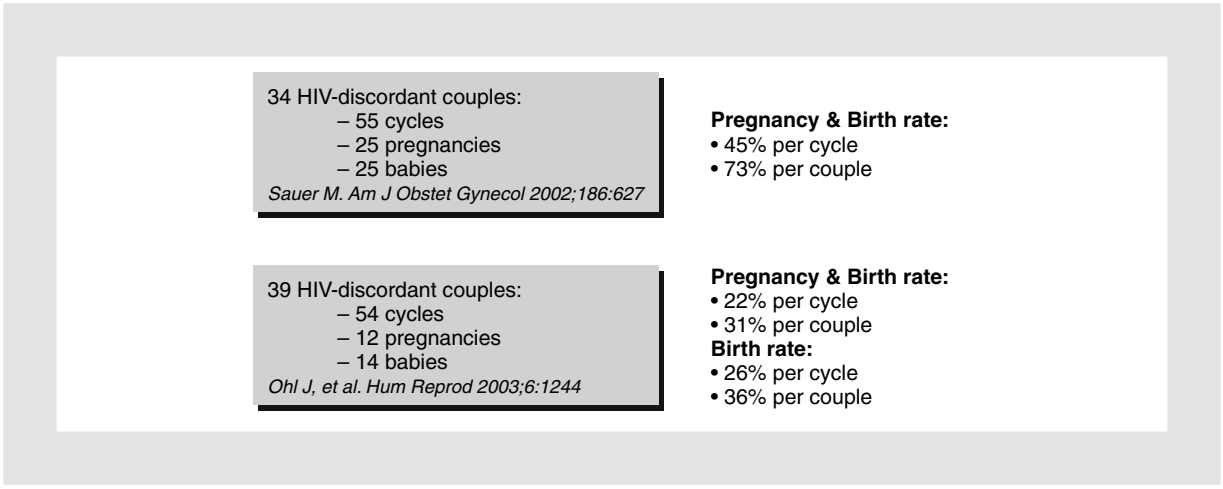

Figure 2. *Main experience with* in vitro *fertilization (IVF) and intracytoplasmic sperm injection (ICSI) after sperm concentration in HIV-serodiscordant couples.*

the spermatozoa concentrate after "sperm wash" may not guarantee non-risk of HIV transmission. Couples should be also referred for assisted reproduction evaluation in the case of fertility impairment.

Natural pregnancy in patients on HAART

Since assisted reproduction techniques are unattainable for a significant number of HIV-positive persons as a consequence of limitations in the public health systems, high cost, low efficacy, and/or ethical concerns, we think it is time to discuss the possibility of natural pregnancy as an alternative option for HIV-serodiscordant couples. However, a careful evaluation of both members of the couple is required, and strict criteria should be met to minimize the chances of HIV transmission.

The steps to be followed before considering natural conception for HIV-discordant couples should be similar to those outlined in the case of choosing for assisted reproduction (Table 1). Among the many issues to be considered, the status of HIV infection is the most important, and attempts at natural conception should be strongly discouraged in those patients with detectable plasma viremia. The low risk of HIV transmission to the negative partner and to the baby if HIV-positive individuals have undetectable viremia under HAART is the minimum criterion for considering natural pregnancy as a reproductive option for HIV-serodiscordant couples. In the case of HIV-positive men, a negative HIV-PCR in semen may be valuable information indicating reduced risk of HIV-transmission.

The effect of HAART on the risk of vertical HIV transmission

Without antiretroviral intervention, the reported rates of HIV vertical transmission are 15-25% in developed countries, and as high as 25-40% according to studies carried out in African or Asian countries, where other medical conditions and prolonged breastfeeding seem to contribute to increase the risk of newborn infections[64]. Several studies using different treatment protocols have shown that the administration of antiretrovirals to the HIV-infected mother during the last weeks of pregnancy (zidovudine, zidovudine/lamivudine, nevirapine, zidovudine/nevirapine) and to the newborn after birth (zidovudine, nevirapine), may significantly reduce the rate of newborn HIV infection[6]. With drug interventions the chances of mother-to-child HIV transmission is at least 50% lower than without any prophylaxis[65].

Other important findings derived from these studies are that the mother's plasma viremia, along with the mode of delivery and the CD4+ count, are all strong and independent predictors of the risk of HIV transmission to the infant[66]. For example, it has been estimated that the rate of vertical HIV transmission is 3.4-fold higher per log of plasma viremia[67].

García, et al.[68] found no cases of newborn infections when assessing 57 pregnant women who had viral loads < 1000 HIV-RNA copies/ml at delivery, irrespective of receiving antiretroviral treatment or not. In this study the rates of vertical HIV transmission were 16.6, 21.3, 30.9, and 40.6% in women with plasma HIV-RNA values of 1000-10,000, 10,000-50,000, 50,000-100,000, and > 100,000 copies/ml, respectively.

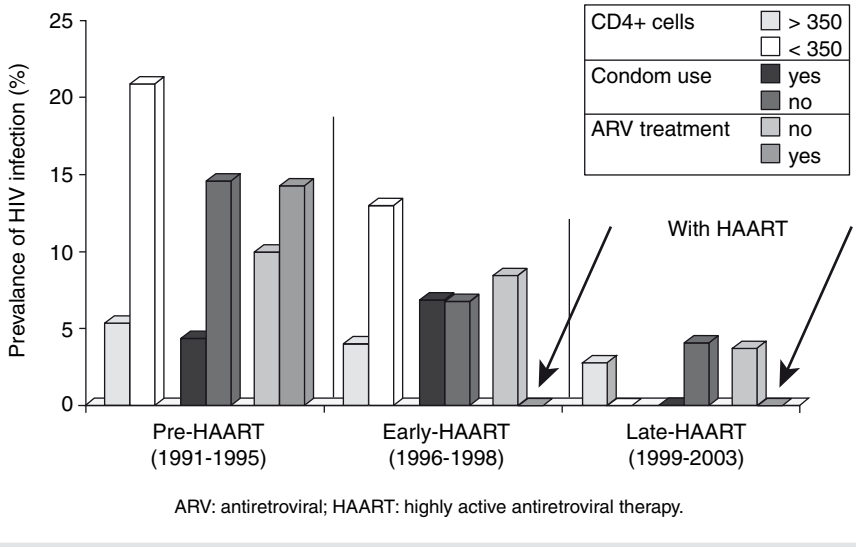

Figure 3. *Rate of heterosexual transmission of HIV in serodiscordant couples according to calendar period, condom use, CD4+ cell count and antiretroviral intervention* (adapted from ref. 77).

However, Ioannidis, et al.[69] found that the risk of vertical HIV transmission in mothers with low plasma viremia (< 1000 HIV-RNA copies/ml) was greatly reduced in those taking antiretrovirals as compared with untreated mothers.

Therefore, it seems that the benefit of antiretroviral therapy for preventing the vertical transmission of HIV is beyond its effect on the mother's plasma viremia.

In developed countries, the current overall rate of perinatal HIV infection is as low as 1-2% as a result of the widespread use of HAART in pregnant HIV-positive mothers[70]. For example, in the North American Women and Infants Transmission Study (WITS) the rate of vertical HIV infection decreased from 7.8% in mothers receiving monotherapy with zidovudine to 1.1% in those under protease inhibitor-containing HAART[23].

In a Spanish study[71], there were seven cases of vertical HIV transmission among 687 pregnancies (incidence rate of 1%). Of note, while more than three quarters of the mothers were under HAART, six of the cases of child infection occurred in mothers with suboptimal viral suppression (three cases of uncontrolled infection during pregnancy, two cases of primary HIV infection during pregnancy, and one case of multidrug-resistant infection with high plasma viremia despite HAART). Also of note, there was no single case of vertical HIV transmission in mothers under HAART with undetectable viremia throughout pregnancy and at the time of delivery.

There are sporadic reports of mothers with undetectable or low plasma viremia giving birth to HIV-infected children[66,72,73]. In these cases, HIV transmission most likely occurred *in utero* rather than at the time of delivery, as is the case for mothers with detectable viremia. Transient viral outbreaks which run unnoticed during the course of pregnancy could explain those anecdotal cases[33]. More rarely, discordance between viral load in plasma and in genital fluids could explain HIV transmission during delivery[74].

In summary, at least for the moment there is no medical intervention or level of viremia that may completely ensure the absence of mother-to-child HIV transmission. Therefore, HIV-infected mothers with undetectable plasma viremia under HAART considering reproductive options should be informed that, even under the best clinical circumstances and irrespective of whether the means to achieve pregnancy is natural or assisted, the risk of HIV infection in the newborn can not be ruled out completely.

The effect of HAART on the risk of sexual HIV transmission

The risk of HIV transmission in unprotected heterosexual intercourse is directly correlated to the level of plasma viremia. In the absence of any antiretroviral intervention, the rate of HIV transmission in hetero-

sexual serodiscordant couples is very low when plasma viremia is < 1500 HIV-RNA copies/ml[16]. This low risk of sexual HIV transmission hypothetically should be recognized in HIV-discordant couples in which the infected partner harbors undetectable viremia under HAART, although data supporting this contention are still limited.

A prospective study in 1994 established a link between zidovudine use and a decrease in the rate of HIV transmission from infected men to their partners[75]. More recently another report concluded that homosexual men have lower infectivity per sexual act after the introduction of HAART[76].

The recent publication of the long-term follow-up of the HIV-serodiscordant Spanish cohort has more specifically established the benefit of HAART for reducing HIV heterosexual transmission[77]. A total of 393 HIV-serodiscordant couples were analyzed according to three periods of time: pre-HAART (1991-1995), early HAART (1996-1998), and late HAART (1999-2003) (Fig. 3). The mean duration of the couples' relationships was 2.7 years. The proportion reporting unprotected coital acts in the preceding six months was 55%. In fact, 45% of the couples had a history of pregnancy and 8.6% were currently expecting a baby. A sharp decline in the incidence of HIV infection in noninfected partners was observed along the three periods of time (10.3, 6.8, and 1.9%, respectively). Importantly, there were no instances of HIV seroconversion in the 60 couples in which the infected partner was under HAART, the mean viral load in this subset of patients being 3.1 HIV-RNA log copies/ml. Having CD4+ counts > 350 CD4+ T-cells/µl was another protective factor for HIV heterosexual transmission.

The first published experience of natural pregnancies in HIV-serodiscordant couples was released by Mandelbrot, et al. back in 1997[78]. A total of 92 HIV-serodiscordant couples, in which the male partner was the one with HIV infection, achieved a natural pregnancy. Only 21 men were under antiretroviral therapy, and no information was available regarding levels of plasma viremia. Couples were instructed to restrict unprotected sex to the most fertile days based on the ovarian cycle. A total of 104 natural conceptions were attained, 17 after only one unprotected sexual contact. On average, five attempts were needed to achieve a pregnancy. There were 92 deliveries, four abortions, and six miscarriages. No cases of HIV seroconversion occurred in women during the first six months of pregnancy. However, there were four cases of seroconversion (3.8%) thereafter, all of them among couples who admitted inconsistent condom use post-conception. Three main conclusions may be drawn from this preliminary experience:

- Natural pregnancy should never be considered outside the framework of undetectable plasma viremia under HAART.
- Unprotected sexual intercourse should be restricted to peri-ovulatory days.
- Unprotected sexual intercourse should be strongly discouraged after pregnancy is attained.

Other medical considerations for serodiscordant couples

In the case of HIV-discordant couples manifesting their will for natural conception, all available risk reduction measures, starting from suppression of HIV viremia, should be discussed. In accordance with the protocol we offer in this review, Vernazza, et al.[56] have proposed that reproductive counseling for couples considering natural conception include the following five measures:

- Suppression of HIV load using HAART.
- Reduction in genital tract infections or inflammation through treatment of sexually transmitted diseases, genital tract infections and the avoidance of practices and products that could irritate the vaginal mucosa.
- Optimization of chances of conception through fertility assessments in both partners and timing on unprotected intercourse.
- Discontinuance of sexual exposure as soon as pregnancy is documented to avoid risk of sexual transmission to the uninfected partner, as well as risk to the fetus should the mother seroconvert during pregnancy.
- Experimental approaches to reduce susceptibility of the uninfected partner (i.e. pre-exposure prophylaxis with antiretroviral drugs or microbicides).

Restriction of unprotected sexual intercourse to woman's fertile days is of major importance to minimize the risk of HIV transmission and to maximize the chances of pregnancy. There are five main methods to identify spontaneous ovulation:

- Calendar calculation according to the length of female menses.
- Analysis of mucous vaginal discharge.
- Monitoring body temperature.
- Determination of sexual hormones in urine (LH and estradiol).
- Serial ovarian ultrasound.

The use of commercial kits to determine the ovulation day based on the concentration of hormones in urine is, for its simplicity and accuracy, the test of choice to be recommended to HIV-serodiscordant couples. Other options may be considered in the case of women with irregular periods. From our point of view, attempts at natural pregnancy should not be done for more than six pinpointed ovulations. If pregnancy has not been achieved after this period the couple should be considered for further fertility studies.

The outcome of natural pregnancies in HIV-serodiscordant couples receiving conception advice in three Spanish HIV reference centers has recently been reviewed[79]. Many of these couples had expressed their desire for parenthood and were informed in advance about the various reproductive options available. All HIV-infected persons had undetectable plasma viremia under HAART, generally for longer than six months, before attempting natural pregnancy. In some cases both members of the couple were assessed in advance and treated, if needed, for concomitant genital infections. Infertility impairments were also discarded by spermiogram and hormonal analyses. Finally, couples seen before pregnancy were advised to have three unprotected sexual contacts on alternate days around the ovulation, estimated on the basis of ovulation tests (calendar calculation or hormonal urine tests in most instances). A total of 62 HIV-discordant couples attained natural pregnancies. In 22 instances the female partner was HIV-positive and in 40 it was the male partner. Overall, 76 natural pregnancies occurred and 68 children were born. There were nine miscarriages, one twin pregnancy, six couples with two consecutive babies, and four couples with three. There were no cases of HIV seroconversion in uninfected partners. However, there was one case of vertical HIV transmission. Of note, 55% of women and 75% of men had chronic hepatitis C; there were no cases of vertical or sexual hepatitis C virus transmission (Table 2).

Table 2. Reproductive outcome in 62 HIV-serodiscordant couples attaining a natural pregnancy while under effective HAART

76 natural conceptions
52 couples with 1 pregnancy
6 couples with 2 consecutive pregnancies
4 couples with 3 consecutive pregnancies
1 twin pregnancy
9 fetal deaths:
– 7 in 30 pregnancies among HIV-positive women (23%)*
– 2 in 42 pregnancies among HIV-negative women (4.7%)*
68 newborns
HIV transmission:
Sexual: No cases in 76 pregnancies
Maternofetal: One case in 23 pregnancies among HIV-positive women

*(OR, 6.1; 95% CI, 1.02-46.68; p = 0.02).
(From ref. 79).

Ethical aspects of reproductive counseling and intervention

Reproductive counseling in HIV-serodiscordant couples raises several ethical questions which might be subject to controversy. While many authors consider that HIV-positive persons under effective HAART represent a low risk for HIV transmission and therefore might be candidates for reproductive procedures[45,80,81], others may argue that HIV transmission can not be absolutely prevented in these patients and, therefore, may still favor not supporting reproductive options in this population.

Vertical and sexual HIV transmissions are the risks that serodiscordant couples have to face when considering parenthood. Vertical HIV transmission is probably of highest concern since the risk remains around 1%, despite the best clinical management of the HIV-infected mother and whether conception is achieved by natural means or is assisted. This ethical dilemma is similar in some aspects to that of couples carrying autosomal recessive diseases (i.e. Tay-Sachs disease, sickle-cell anemia, cystic fibrosis) with the difference that in these latter instances the chances for fetal inherited disease may be as high as 25%. However, balancing this risk with the benefit of parenthood for the couple is considered as ethically acceptable. It has been argued that couples and doctors accepting the risk of transmitting a disease to their offspring do not act unethically if all reasonable precautions to prevent transmission are taken and the parents are prepared to take care of the child regardless of its medical condition[81].

Regarding the possibility of HIV sexual transmission, the epidemiologic evidence is limited, but suggests a low but never absent level of risk when the HIV load is optimally suppressed. There have been sporadic reports of HIV horizontal transmission after both natural and assisted conception. Ideally practitioners should explicitly discuss available data on the safety of assisted reproduction or natural conception, and the effectiveness of proposed risk-reduction strategies. The relative paucity of data on risk of sexual transmission

associated with unprotected sexual intercourse with an HIV-infected partner on HAART should also be noted. Any reproductive attempt should never be done before a standardized evaluation of the HIV-discordant couple, the work-up proposed in this review being one possible option (Table 1). Among the several steps to be followed, it is of special importance that the HIV-positive partner is receiving HAART and shows undetectable plasma viremia. Measures should be taken to rule out causes of infertility and to limit unprotected intercourse to the fertile period of the woman's cycle. It is also crucial to discard out genital infections or disbacteriosis and other causes of local irritation. Attempts at pregnancy should be discouraged outside these conditions, and women should be closely monitored for pregnancy to limit the risk of HIV transmission associated with ongoing sexual exposure. The number of unprotected sexual contacts should be limited, with broader fertility studies being done in the case of pregnancy failure. Within this strict framework, health professionals caring for HIV-infected patients wanting to be parents may play a crucial role in further reducing the risks of HIV transmission, and increasing the chances of attaining pregnancy under the best safety conditions.

Finally, it should be recognized that the debate between natural means or assisted reproduction for attaining pregnancy is at the present moment sterile for many HIV-serodiscordant couples. Although "sperm wash" should further reduce the chances of male-to-female HIV transmission, no comparative studies are available confronting this procedure with natural relationships in couples receiving reproductive counseling and in whom the infected partner has undetectable viremia under HAART. Moreover, the relatively low rate of pregnancy with assisted reproduction techniques and its high cost make this option unaffordable for a substantial proportion of HIV-discordant couples.

The fact that in recent years we are attending a growing number of HIV-infected persons that are considering, when not already trying, to be parents by natural means[45], should encourage HIV doctors to put it upfront rather than just deferring the discussion about this issue. Refusal of counseling will not be acceptable since there is no doubt that medical advice will be helpful in this setting and will reduce the chances of HIV transmission[80,82]. These efforts will be greatly aided by consistent and centralized collection of data on the effectiveness of strategies to prevent sexual transmission so that this information can be incorporated into future counseling guidelines.

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