Assisted Reproductive Technology for Men and Women Infected with Human Immunodeficiency Virus Type 1

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In 2001, the World Health Organization reported 4.3 million new human immunodeficiency virus (HIV) infections in adults globally, 41% of which were in women. During the year 2000, 27% of newly diagnosed HIV infections in the United States occurred in women. In developed countries, the perception of HIV infection has changed from an acute, lethal infection to a chronic illness; the introduction of highly active antiretroviral therapy has decreased morbidity and mortality, and new drug therapies have dramatically decreased perinatal transmission. In view of these advances, some HIV-infected individuals are considering reproduction. Following the lead of organizations in other developed countries, the American College of Obstetricians and Gynecologists has recently endorsed the use of reproductive technology in HIV-infected patients. Which patients should be offered assisted reproduction and what the optimal methods are of decreasing heterosexual and perinatal HIV transmission must be determined.

In the United States, 25% of all new AIDS cases and 35% of HIV-1 infections occur in women [1]. Because the majority of these cases are seen in women who are at the peak of reproductive potential (between the ages of 14–45 years), the optimal recommendation with regard to reproductive choices for this population has always been controversial. At the beginning of the epidemic, the US Centers for Disease Control and Prevention (CDC) advised women known to be infected with HIV-1 to defer pregnancy because of the poor prognosis of the disease, the risk of perinatal transmission, and the possible adverse effects of pregnancy on HIV-infected women [2]. In spite of these recommendations, many of these women chose to become pregnant for cultural or religious reasons [3]. Others conceived without knowing that they were infected with HIV-1. From a public health care perspective, the HIV epidemic raised ethical, scientific, and cost concerns about how to control the spread of the epidemic, how to educate the public about the long-term sequelae of the disease, and how to allocate resources for screening and care.

Two decades later, developed countries have a very different challenge to overcome with regard to HIV infection in the young adult population. The introduction and widespread use of prophylaxis against opportunistic infections and of HAART have decreased morbidity and mortality in this population [4, 5], and the increase in life expectancy has changed the perception of HIV from a lethal disease to a chronic illness. The management of HIV infection during pregnancy has also been revolutionized over the last decade [6, 7]. Perinatal transmission rates have been decreased to 2%–4% with the use of aggressive antiretroviral therapy and the option of additional surgical interventions [6, 8–10]. In developed countries, these questions arise: Should assisted reproductive technology be used to help HIV-infected couples to conceive? Will these treatments avert transmission? If so, who are the optimal candidates for this approach?

Several authors have argued that assisted reproductive technologies should be available for HIV-infected infertile couples [11, 12]. They think that, because of decreased rates of perinatal HIV-1 transmission, offering such techniques to infected individuals balances patient’s autonomy with fetal beneficence,
and they assume that the prognosis for these individuals in the HAART era is favorable [11–14]. Opponents argue that there is no cure for HIV infection and that the risk of horizontal or vertical transmission is not completely abrogated by these techniques. The ethical guidelines provided by the American College of Obstetricians and Gynecologists and by the American Society for Reproductive Medicine concurred that “assisted reproductive technologies should not be denied to HIV-infected couples solely on the basis of their positive serostatus” [13, 14]. However, a detailed analysis of some of the clinical dilemmas and technical challenges that will be encountered when such an approach is implemented has not been provided. From an ethical perspective, we are bound by the dictum “first, do no harm”; as public health advocates, we should strive to decrease the spread of the epidemic; and as physicians, we should select the methods and patients that are likely to benefit from our interventions. Although we presently lack specific guidelines or protocols to manage these cases, the data we review may illustrate the obstacles and limitations that must be overcome to provide optimal recommendations.

**OBSTETRIC ISSUES**

More than 90% of HIV-infected children acquired the infection through perinatal transmission [8]. Although perinatal HIV-1 transmission can occur during early pregnancy, most cases of transmission occur during labor and delivery or through breastfeeding. In developed countries, we have averted transmission through breastfeeding by recommending alternative feeding strategies [7].

In 1994, the landmark Pediatric AIDS Clinical Trials Group Protocol 076 study showed that use of zidovudine during the antepartum, intrapartum, and neonatal periods can decrease perinatal HIV-1 transmission from 25% to 8% [6]. Perinatal transmission can be further decreased to 2%–4% by use of zidovudine chemoprophylaxis, combination antiretroviral therapy, elective cesarean section, or a combination of these approaches [10, 15]. Alternative antiretroviral regimens have been used to decrease transmission from women entering late into the health care system in the United States and women in underdeveloped countries to their children [8, 16, 17]. Most recently, several investigators have reported maternal-fetal transmission rates as low as 0.8%–2% among women whose HIV RNA loads were reduced to <1000 copies/mL or to undetectable levels (<400 copies/mL), regardless of the mode of delivery [15, 18].

In spite of these successes, there are still challenges to overcome in the treatment of HIV-infected women. Some of the antiretroviral medications currently available, such as efavirenz, hydroxyurea, and amprenavir (liquid formula) should be avoided during pregnancy because of concerns of potential teratogenicity [19]. Severe complications of antiretroviral therapy, such as metabolic acidosis, have been reported among pregnant women, leading to recommendations by manufacturers to avoid certain drug combinations during pregnancy if possible [20]. We also recognize that long-term use of HAART can lead to complications such as lipodystrophy and diabetes [5]. The health care provider and the patient who desires to conceive should be aware of treatment contraindications in effect during pregnancy. Regimens that are potentially teratogenic should be changed before conception in women who are trying to get pregnant or during the first trimester, as soon as pregnancy is discovered.

Inadequate treatment regimens or inconsistent adherence to therapy can lead to the development of resistance to antiretroviral therapy among HIV-infected pregnant women [16, 21]. Several investigators have shown genotypic evidence of nucleoside reverse-transcriptase inhibitor– or nonnucleoside reverse-transcriptase inhibitor–resistance mutations in up to 15%–33% of women receiving chemoprophylaxis [16, 21]. Selection of a safe and effective regimen for such patients in future pregnancies could be significantly hindered. Furthermore, the infants born to those women are at risk of perinatal infection with a resistant virus strain [16, 21, 22].

Women living with chronic HIV infection may still experience comorbidities from other viral illnesses, including human papillomavirus, which increases the likelihood of abnormal cervical cytology [23]. Women with high-grade dysplasia or carcinoma in situ should defer conception and should be thoroughly informed of their prognosis. As many as 33% of HIV-infected patients are known to be coinfected with hepatitis C virus (HCV). These individuals are known to have faster development of liver cirrhosis and higher mortality rates, and they are at greater risk of developing liver toxicities if they receive HAART [5, 24, 25]. Higher rates of perinatal HIV transmission have also been reported among women who are coinfected with HIV and HCV [26]. Several authors have also reported an increased risk of perinatal HCV transmission among such patients [27]. Routine liver biopsies in pregnant women are not recommended. The most effective treatment regimens for HCV disease, such as ribavirin, should be considered with caution during pregnancy, because some of these drugs are known to have teratogenic potential and the safety of some is uncertain [28]. HIV-HCV–coinfected women who desire to conceive should first be evaluated by an expert hepatologist with experience in management of HIV-coinfected patients to ascertain disease prognosis before initiation of reproductive technology services [29].

In summary, although the rate of perinatal HIV-1 transmission has been significantly reduced, we recognize that not all women who request reproductive technology services will have good pregnancy outcome—disease or treatment-related comorbidities may interfere. In addition, the use of certain
reproductive technologies in and of itself can increase the risk of poor pregnancy outcomes, such as low birth weight [30].

**ISSUES RELATED TO ASSISTED REPRODUCTION**

“Assisted reproductive technologies,” in the context of this article, is defined as the use of artificial insemination techniques or in vitro fertilization. Documentation that the use of reproductive technologies could result in horizontal transmission [31], coupled with concerns about the short life expectancy of infected individuals, discouraged the use of these treatments for HIV-infected couples until recently. However, the use of assisted reproductive technologies and novel approaches to decrease virus load in genital secretions has resulted in negligible rates of horizontal transmission, thereby challenging the dogma [32–34]. The chance of pregnancy for any fertile couple during a single menstrual cycle is ∼25% [35]. In contrast, in 1998, the pregnancy rate per oocyte retrieval from in vitro fertilization in the United States was ∼35% [36]. Assisted reproduction may be useful in the prevention of HIV transmission for HIV-infection discordant couples, both fertile and infertile, by increasing the chance of conception per cycle and decreasing the number of “exposures” (unprotected intercourse) necessary to conceive.

When providing services for HIV-infected couples, one could potentially encounter 3 distinct case scenarios with different prognoses and technical requirements, as will be discussed below. For any of these case scenarios, issues related to male or female infertility should be managed following standard evaluation and treatment algorithms for the infertile couple, as long as the presenting symptoms are not deemed to be secondary to HIV infection. In case of male infertility and HIV seropositivity, the use of donor semen is always an option.

**Case scenario 1: HIV-positive woman and HIV-negative man.** The main objective for a couple attempting to conceive in which the woman is HIV positive and the man is HIV negative is to avoid horizontal transmission to the male partner and perinatal transmission to the infant. Artificial insemination can be used so that unprotected intercourse is not necessary for such couples. In some cases, intrauterine insemination, with or without ovarian stimulation, will increase the chance of conception [37, 38]. In some instances of severe male infertility, insemination with donor semen is recommended. Infertile women seeking this service might have evidence of anovulation or amenorrhea. These symptoms could be secondary to HIV infection or could be due to other pathological conditions, such as polycystic ovarian syndrome, hypothalamic disorders, or substance abuse. Thus, female partners might require infertility workup and standard management of these symptoms, if the symptoms are judged not to be related to HIV.

An important challenge in providing assisted reproduction services is setting the criteria for deciding which patients will be offered such services. HIV-infected individuals are at increased risk of morbidity due to infection associated with surgery or invasive procedures [39]. Use of antiretroviral therapy or treatment for opportunistic infection also could be associated with drug-related toxicities [5]. Given the lack of knowledge at the present time of the potential complications that HIV-infected women could experience while receiving reproductive services, a conservative approach has been chosen by our group (members of the Division of Maternal-Fetal Medicine and Reproductive Endocrinology, Department of Obstetrics, Gynecology, and Women’s Health, New Jersey Medical School, Newark) with regard to selection of optimal patients for undergoing such treatment. Patients whose health is deemed to be optimal, such as those who do not require antiretroviral therapy or prophylaxis for opportunistic infections or those who have shown adequate tolerance to a treatment regimen, should be given priority until more data are available. Our group has drafted some minimal criteria deemed to be relevant to optimizing perinatal outcomes and minimizing horizontal transmission (table 1). Assisted reproduction services should not be denied to fully informed couples who meet these criteria and who give written informed consent.

**Case scenario 2: HIV-negative woman and HIV-positive man.** When the male partner is HIV positive and the female

<table>
<thead>
<tr>
<th>Table 1. Criteria and recommendations for the use of assisted reproductive technologies among HIV-infected men and women.</th>
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<tr>
<td>Disclosure of serostatus between partners</td>
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<tr>
<td>Preconceptional counseling</td>
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<tr>
<td>Informed consent (risks, benefits, and alternatives must be explained and documented)</td>
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<tr>
<td>Absence of opportunistic infections or prophylaxis</td>
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<tr>
<td>CD4 cell count &gt;350 cells/mm³ and HIV RNA level &lt;50,000 copies/mL</td>
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<tr>
<td>Patients receiving HAART:</td>
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<tr>
<td>HIV RNA level &lt;400 copies/mL</td>
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<td>Regimen without teratogenic drugs</td>
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<tr>
<td>Adequate tolerance to the regimen</td>
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<tr>
<td>Antiretroviral therapy for at least 1 year with appropriate follow-up (stable virus load and CD4 cell count)</td>
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<tr>
<td>Semen samples analyzed for HIV by PCR before insemination (only negative samples should be used)</td>
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<tr>
<td>Close follow-up and appropriate therapy during pregnancy and after birth</td>
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<tr>
<td>Intrapartum zidovudine chemoprophylaxis</td>
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<tr>
<td>Follow-up of the child (strongly recommended)</td>
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<td>HIV-infected women: normal results of Papanicolaou smear or at most low-grade squamous intraepithelial lesion with confirmed colposcopy and appropriate follow-up</td>
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<tr>
<td>HIV–hepatitis C virus–coinfected women: hepatology consultation, stable liver enzymes for &gt;1 year, and no evidence of liver cirrhosis</td>
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partner is HIV negative, the risk of transmission of HIV-1 is to the woman. The minimal inoculum needed for transmission of HIV-1 during assisted reproduction is unknown. Although the mechanisms for horizontal transmission are not completely understood, we know that cell-free or cell-associated virus could be a source of infection. Whether human gametes can be infected by HIV-1 is undetermined and requires further investigation. HIV-1 has been found as free particles in seminal fluid [40, 41] and in the non-sperm cellular fraction of semen [40, 42, 43]. Specifically, infected lymphocyte cells have been observed in ejaculate. These observations persist, although at lower frequencies, among men receiving HAART who have achieved undetectable plasma HIV-1 RNA levels [44]. Thus, therapeutic interventions cannot completely eradicate the virus from the genital compartment. An alternative approach is to remove the HIV-1 from the seminal fluid or from the sperm fraction used for assisted reproduction.

Three basic methods of achieving this are available, and the degree of effectiveness varies. "Sperm washing" refers to the separation of sperm from the seminal fluid by repeated cycles of centrifugation, discarding of the supernatant, and resuspension of the cell pellet in fresh medium each cycle. The final resuspension of cells will contain sperm, as well as seminal WBCs and epithelial cells. Because seminal WBCs are known to be infected with HIV-1 [40, 42, 43], this would not be a safe method of preparing sperm from an HIV-infected man for intrauterine insemination. The "swim-up" technique separates the motile sperm from the nonmotile cells in the sample. After the final centrifugation of the sperm wash, the supernatant is discarded, and a small amount of medium is placed over the final sperm pellet. The preparation is incubated undisturbed for a specified time, during which the motile sperm swim up into the overlying medium. Collection of this medium results in an enriched preparation of motile sperm without the other cellular components. The third technique uses density gradient columns and centrifugation to achieve a final preparation of isolated sperm. Even though a combination of these techniques has been shown to significantly reduce HIV-1 contamination of sperm samples [34, 45, 46], there is no evidence that any of these methods will consistently provide an HIV-free preparation of sperm.

Two groups have published results that use these techniques among HIV-infected men for intrauterine insemination in discordant couples. Semprini et al. [32] included in their study men with advanced disease, as well as asymptomatic subjects. Some of the men were receiving zidovudine monotherapy, and no virus load data were provided. The authors processed the semen samples by a combination of density gradient centrifugation and sperm swim-up. Before insemination, they examined an aliquot of the sperm sample and verified the absence of infected cells by indirect immunofluorescence assay, using monoclonal antibodies. They reported >1000 intrauterine inseminations in 350 discordant couples and no transmissions to the female partner or fetal transmissions in nearly 200 pregnancies [33].

Marina et al. [34] performed a similar study, which included 63 HIV-1–seropositive men without clinical AIDS (CDC classification A1, A2, B1, and B2 [47]). Seventy-six percent of the participants were receiving antiretroviral therapy. The semen samples were processed by a combination of sperm washing, density gradient centrifugation, and sperm swim-up. An aliquot of the final sperm preparation was evaluated via HIV RNA and DNA PCR. Using a more sensitive assay and a modification of the method of Semprini et al. [32], these investigators found that PCR demonstrated HIV RNA but no HIV DNA in 5.6% of the samples tested. Only samples in which PCR found neither HIV DNA nor HIV RNA were used for insemination. Forty-nine percent of the inseminated patients became pregnant, and 37 children were born. Women were assessed up to 6 months after insemination, and neonates were tested for HIV at birth, with negative results in all cases.

Use of similar processing to prepare sperm before in vitro fertilization and intracytoplasmic sperm injection has been reported [48]. Again, there was neither horizontal HIV transmission to the women receiving the embryos nor vertical transmission to children born from these procedures. Collectively, these studies suggest that, with appropriate processing of samples and availability of sensitive assays for HIV-1 detection, horizontal transmission can be avoided. However, we must recognize that the available clinical data are limited.

Case scenario 3: Both man and woman are HIV positive.
The principles for discordant couples are applicable to couples in which both the male partner and the female partner are infected with HIV. Episodes of exposure could be avoided by use of reproductive technologies, and the HIV load in the genital tract could be decreased by use of available techniques. Both approaches could be relevant when there is a concern that HIV superinfection from an infected partner is a real possibility. This case scenario, in which both parents are HIV infected, represents a more complex ethical and medical dilemma. Arguments are ongoing with regard to how to balance patient autonomy with societal concern about an increased risk that the infant will become an orphan at an early age and about the uncertainty of long-term outcomes after exposure to antiretroviral therapies. The optimal management of this case scenario requires further debate. At present, the options available to these couples include the use of reproductive technologies, as described above; the use of donor sperm; deferring pregnancy; and adoption.

LABORATORY ISSUES

Previous clinical experience has shown that exclusion of infected semen samples from clinical use can prevent transmis-
sion to the female partner and the unborn child [30–34]. In addition to available methods, processing of the semen by novel techniques may help decrease or eliminate HIV from samples. For example, use of a “double-tube” gradient centrifugation method to decrease the chance of contamination during processing of the samples has been described [49]. Available and new options should be systematically studied.

Testing of the sperm samples for the presence of HIV after separation from the seminal fluid is a critical step. Currently, PCR is the most sensitive method of detecting HIV in a processed sperm sample before clinical use, but PCR is costly and time-consuming. Reproductive technology laboratories that offer services to HIV-infected couples should establish links with HIV laboratories, which can provide expertise and potentially curtail costs by batch analysis.

Finally, the laboratory can take precautions to decrease the chance of transmission or cross-contamination of HIV-1 [50]. The use of universal precautions in the processing of samples will minimize the chance of transmission of HIV to the laboratory personnel. This applies to the handling of all samples: semen, sperm preparations, follicular fluid at the time of egg retrieval, and human oocytes and embryos. A number of quality-control and infection-control techniques are used today in embryology and andrology laboratories to prevent cross-contamination between samples during processing. In vitro fertilization programs may choose to group infected samples together (e.g., before scheduled laboratory shut-downs) to decrease the chance of cross-contamination from infected to uninfected samples. The laboratory can then be cleaned during the shut-down time, before processing of uninfected samples begins. Other preventive measures may include the use of separate freezers for storing cryopreserved samples from infected and uninfected patients. Because virus cross-contamination has been reported between samples stored in liquid nitrogen [51], storing samples (e.g., sperm or embryos) from infected patients in liquid nitrogen vapor may provide an added margin of safety and help prevent cross-contamination.

CONCLUSION

The changing profile of the HIV epidemic, with increasing infection rates among women and increased survival due to the use of HAART, will continue to pose a challenge to those who provide health care to the HIV-infected population. The role of assisted reproductive technologies in optimizing pregnancy outcomes and reducing heterosexual and perinatal transmission is promising. Ultimately, it is not up to the individual physician to make a biased or arbitrary decision about whether to help these patients conceive. As health care providers and proponents of public health, we must “first, do no harm” and maximize “benefits over risks” for the community as a whole. Preconception counseling and the creation of a multidisciplinary clinical team that includes ethicists, patients living with HIV infection, obstetricians, reproductive endocrinology experts, and infectious diseases specialists will be essential for the success of this approach. Laboratory personnel with experience in reproductive technologies, handling infectious material, and applying novel techniques for virus detection will be needed. Collectively, these individuals should develop treatment algorithms that can be systematically applied and evaluated in terms of effectiveness, cost reduction, and safety and that could serve to create evidence-based guidelines.

We recommend that assisted reproduction techniques that involve the use of sperm from HIV-seropositive men should be performed in centers that have the capacity to screen the processed sample for the presence of HIV before clinical use. These centers should also be able to provide access to all essential elements of care for the HIV-infected men and women who desire to reproduce, from preconceptional counseling to neonatal care.

References
