Recommendations for reducing the risk of viral transmission during fertility treatment with the use of autologous gametes: a committee opinion

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Sexually transmitted infections are of major concern to reproductive specialists. Heading the list are human immunodeficiency virus types 1 and 2 and hepatitis B and C viruses. These pathogens, which may cause incurable chronic infections, can be transmitted through assisted reproductive technologies and from infected mothers to the fetus or newborn. This document replaces the document of the same name, last published in 2020. (Fertil Steril® 2023;120:794–801. ©2023 by American Society for Reproductive Medicine.)

El resumen está disponible en Español al final del artículo.

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SEXUALLY TRANSMITTED VIRUSES CAN CAUSE CHRONIC LIFELONG INFECTIONS

The past two decades of intensive virus research have provided cure strategies for hepatitis C (1) but not for human immunodeficiency virus (HIV) types 1 and 2 or hepatitis B virus (HBV). There is a substantial body of information on mechanisms and risk factors underlying sexually transmitted infections, suggesting risk reduction strategies to prevent transmission. Sensitive and precise diagnostic tests allow the early detection and monitoring of viral infections, and new antiviral drugs make it possible to manage many chronic viral infections. HIV-infected individuals, in particular, are now living healthier, longer lives and, in ever-increasing numbers, are choosing to have children. The Centers for Disease Control and Prevention (CDC) have concluded that people with HIV who take antiretroviral therapy as prescribed and achieve and maintain an undetectable viral load have effectively no risk of transmitting HIV through sex (2).

The guidance in this document provides strategies, on the basis of scientific principles and clinical experience, for reducing the risk of viral transmission in couples seeking fertility treatment. Recommendations are aimed at the following: reducing viral load in an infected partner(s); reducing exposure and susceptibility in a noninfected partner; and promoting honest, detailed discussions with patients about available scientific evidence and risk reduction strategies to provide a basis for informed consent. Clinics in Europe and North America have incorporated these principles into practice with encouraging results (3, 4).

EXISTING SCREENING/TESTING GUIDELINES

Sexually intimate partners are excluded from United States Food and Drug Administration-mandated screening and testing for viral infections (5). However, couples proceeding with assisted reproductive technologies (ARTs) are advised to undergo viral screening. Such screening can help ensure that appropriate precautions are taken to minimize risk of viral transmission to partners and offspring and allow for adequate segregation and storage of specimens to minimize the risk of cross-contamination. Intimate couples in which one or both partners are positive for HIV, HBV, or hepatitis C virus (HCV) should have the opportunity to undergo ART procedures at all fertility centers (6). This document does not address all viral diseases because they are related to...
fertility care. For example, the American Society for Reproductive Medicine (ASRM) has separate publications with recommendations for Zika infections and West Nile virus (7, 8).

**REQUIREMENTS FOR TREATMENT**

Couples in which one or both partners are infected with a sexually transmissible pathogenic virus should receive in-depth preconception counseling on the risks of sexual and vertical transmission of their infections. In many cases, the viral infection can be treated effectively, so the risk of transmission during intercourse is eliminated. Thus, this should be first-line therapy for discordant couples.

In discordant couples for whom the viral infection cannot be treated effectively or when the couple has an infertility diagnosis (e.g., low sperm counts), ART may be required for conception. Informed consent should be explicit and as thorough as possible, emphasizing little or no risk of transmission when specific risk reduction strategies are followed. In-depth medical and obstetric care should be provided, ideally, by a multidisciplinary medical team that includes an expert in infectious disease. Counseling and education concerning safe-sex practices, such as condoms, throughout fertility treatment, pregnancy, and the postpartum period should be provided and emphasized. Serial diagnostic testing of the uninfected partner is recommended throughout treatment and pregnancy and for both mother and infant during the first year after birth.

**VIRUS-SPECIFIC RISK REDUCTION STRATEGIES**

Table 1 summarizes highlights of virus-specific transmission risk and risk reduction strategies during ART (9–11).

**Human Immunodeficiency Virus**

Human immunodeficiency virus type 1 and HIV-2 are retroviruses that infect T lymphocytes and other immune cells primarily. Human immunodeficiency virus type 1 and HIV-2 have the same modes of transmission and put women at risk of acquiring opportunistic infections and progressing to acquired immunodeficiency syndrome (AIDS). Infection with HIV-1 leads to AIDS and death in most individuals if left untreated. Immunodeficiency associated with HIV-2 infection may be less severe and develop more slowly.

Human immunodeficiency virus and AIDS are endemic in Sub-Saharan Africa and Southeast Asia and are prevalent throughout the world in high-risk groups, including users of unscreened blood products, intravenous drug users, sex workers, and men who have sex with men. Human immunodeficiency virus is transmitted both sexually and vertically through blood, semen, vaginal secretions, and breast milk. The rate of HIV heterosexual transmission is relatively low (approximately 1 per 1,000 acts of unprotected intercourse) (12). Risk factors for HIV transmission include genital tract infections and ulceration, sexual practices that induce trauma or bleeding, and a lack of male circumcision (13).

The rate of HIV transmission is highly associated with peripheral blood viral load and is lowest in individuals with peripheral viral loads that are undetectable (14).

HPTN 052, a phase 3 randomized trial, demonstrated a 93% reduction of HIV transmission within serodiscordant couples (where one person is HIV-infected and the other is not) when the HIV-infected partner was taking antiretroviral therapy (15). Ongoing research now supports the CDC statement that people with HIV who take antiretroviral therapy as prescribed and achieve and maintain an undetectable viral load have effectively no risk of transmitting HIV through sex (4, 16, 17).

Human immunodeficiency virus viremia should be minimized in the infected partner (peripheral blood viral load <40 copies/mL) through the use of highly active antiretroviral therapy to reduce levels of HIV in semen. When there is no diagnosis of infertility, the couple can attempt to conceive by means of intercourse. It is highly recommended that both partners undergo a sexual health screening. Bacterial vaginosis and infections with herpes simplex virus type 2, *Trichomonas vaginalis*, *Chlamydia trachomatis*, *Neisseria gonorrhoea*, and *Treponema pallidum* can increase HIV-1 transmission (18) and should be treated. Practices and behaviors that lacerate mucosal surfaces and other risk factors for HIV transmission should be avoided (19).

When there is a diagnosis of infertility, both partners should undergo a fertility assessment. Ovulation induction, intrauterine insemination (IUI), or in vitro fertilization (IVF) with either insemination or intracytoplasmic sperm injection
should be recommended on the basis of the diagnosis of infertility. Risk reduction techniques have been used for couples where both partners are HIV-infected to reduce the risk of superinfection of the female partner with different strains of HIV or drug-resistant HIV (20). In situations where the female partner is HIV-positive, IUI and IVF eliminate the risk of viral transmission to their partner effectively. In situations where the male partner is HIV-positive, a sperm wash protocol should be used to enrich motile sperm and reduce or eliminate HIV-infected white blood cells and free virus in the fraction isolated for insemination (21, 22). The CDC estimated that 8–141 women were infected through donor insemination from 1980 to 1984 before stricter donor screening and semen quarantine practices were implemented (23). Because HIV is found primarily in white blood cells and as cell-free virions in semen (24), sperm wash techniques that separate motile sperm from the round cell and seminal fluid fractions can reduce HIV levels before insemination markedly (25). A systemic review of 40 studies of 1,023 HIV-negative women undergoing 2,863 IUI or IVF and intracytoplasmic sperm injection procedures with sperm from their HIV-positive partners revealed no cases of seroconversion in the women and no infected infants (21). A second systemic review from 2016 showed no HIV transmission in 8,212 IUI cycles and 1,254 IVF cycles among HIV-discordant couples (26). Trauma to the cervix or uterus during the IUI or IVF procedure must be minimized.

Sperm wash procedures involving density-gradient centrifugation followed by a sperm swim-up step have been used to separate motile sperm free from HIV and HIV-infected somatic cells (25, 27). A modified method for limiting contamination of the sperm during the gradient separation is the double-tube method with the use of a product called Prolnser (Nidacron) (25). This product includes a second tube that serves as a channel to retrieve the sperm pellet without coming into contact with the gradient material along the sidewalls of the tube, which may be contaminated with white blood cells or free virus. Quantitative assessment of HIV in semen before and after the double-tube gradient method indicates that >99.99% of HIV-1 RNA is removed (25). Similar sperm preparation techniques have been used to separate HCV from sperm (22) and may be useful for other viral infections where the majority of virus is found in free form or associated with semen somatic cells (i.e., white blood cells, epithelial cells).

The uninfected partner in a discordant couple should be tested for HIV at 3-month intervals during fertility treatments and pregnancy. Approaches such as pre-exposure prophylaxis (PREP) with antiretroviral drugs (28–30) and locally applied vaginal estrogen gels (31) may further reduce the susceptibility of the uninfected female partner. Those who do not wish to conceive should use condoms and consider PREP. Pre-exposure prophylaxis with the use of tenofovir and emtricitabine, rapidly acting antiretroviral drugs with long half-lives, is endorsed in serodiscordant couples (32); when both couples are seropositive, PREP may still be recommended to reduce the risk of contracting a different viral stain. When HIV infection is detected in the female partner during pregnancy, she should be referred to an obstetric service experienced in managing HIV-infected women. Use of antiretroviral drugs during pregnancy and/or labor, use of cesarean section in individuals with a detectable viral load, and avoidance of breastfeeding can reduce the risk of vertical transmission of HIV to <2% (33).

**Hepatitis B**

Hepatitis B virus, a double-stranded DNA virus, is a major cause of acute and chronic hepatitis, cirrhosis, and hepatocellular cancer. Hepatitis B virus is one of the most common infectious diseases in the world; it has been estimated that 350 million people worldwide are HBV carriers (34–36). Hepatitis B virus can be transmitted parenterally, sexually, vertically, and via other routes of mucosal exposure. Approximately 25% of regular sexual contacts with HBV-infected persons will become seropositive for HBV (35), and HBV has been transmitted through artificial insemination (36). Health care workers ran a high occupational risk of HBV infection before universal precautions and HBV immunization were introduced in the workplace. Universal safety precautions and vaccination with the HBV vaccine, available since 1982, are the most effective ways to reduce the risk of HBV infection (37).

Hepatitis B virus-infected individuals run a high risk of coinfection or superinfection with hepatitis D virus (HDV), a circular replication-defective RNA virus that requires the presence of HBV for replication (38). Approximately 25% of chronic HBV carriers are coinfected with HDV, which increases their risk of cirrhosis from 15% to 80%. The vertical transmission of HDV has been documented. Because HBV is needed for HDV replication, measures to prevent the transmission of HBV, such as vaccination of uninfected partners and newborns, prevent the transmission of HDV.

All couples being evaluated for IVF should be screened for HBV via hepatitis B surface antigen (HBSAg). In couples who are discordant for HBV infection, the partner who is seronegative for HBSAg and has no evidence of immunity on additional serologic testing (i.e., is negative for hepatitis B surface antibody and core antibody) should be vaccinated against HBV. When discordant partners have good antibody titers, there is no recommendation for further risk-reducing treatments. Attempts to conceive, including fertility treatments, may be initiated once the vaccinated partner’s antihepatitis B surface antibody titer is positive. A modified sperm wash to reduce the viral load is not required after the female partner is immunized against HBV.

All HBSAg-positive HBV-infected women should be offered a referral to a hepatologist to determine whether they are immune-tolerant or have immune-active disease. Immune-tolerant individuals are carriers of the virus with normal alanine transaminase and aspartate transaminase levels and do not have active hepatitis. Immune-active disease (previously termed chronic active hepatitis) occurs in those individuals who have elevated liver function tests associated with chronic hepatitis. For the immune-tolerant patient with HBV, the current recommendations are to treat individuals with HBV DNA viral levels >200,000 IU/mL with appropriate antiviral therapy. Treatment should be
initiated at 28–32 weeks of gestation and continued up to 3 months postpartum. Patients with immune-active disease should be treated on the basis of the usual recommendations for all nonpregnant women with appropriate antiviral therapy as determined by the hepatologist.

Cesarean section is not indicated owing to insufficient data to support its benefit to prevent vertical transmission. All infants born to HBsAg-positive mothers should receive immunoprophylaxis within 12 hours after birth. Immunoprophylaxis consists of both HBV vaccine and immunoglobulin, followed by two more injections of HBV vaccine in the first 6 months of life.

Breastfeeding is not contraindicated in women chronically infected with HBV (39). For mothers on antiviral therapy, the antivirals are minimally excreted in breast milk and are unlikely to pose a risk to the infant.

Hepatitis C

Hepatitis C virus is a blood-borne RNA virus that is transmitted primarily through parenteral exposure (blood products, shared needles, needle-stick injuries). Hepatitis C virus has been detected also in saliva, urine, semen, vaginal secretions, and breast milk, and sexual and vertical transmission are probable secondary modes of transmission (40). Hepatitis C virus infects 71 million individuals worldwide, for a prevalence of >1%. In the United States, the prevalence is 0.8%–1.3%, but it is as high as 4.2%, for example, in the country of Georgia and 6.3% in Egypt (41). Most currently infected individuals in the United States are Baby Boomers born between 1945 and 1965, and most newly infected individuals are people who inject drugs from 20 to 29 years of age. Currently, a large burden of chronic HCV infection in the United States is among people who inject drugs, individuals in jails and prisons, and men who have sex with men. Hepatitis C virus is a highly pathogenic virus: 80% of patients infected with HCV develop chronic liver disease, 35% develop cirrhosis, and 5% progress to hepatocellular carcinoma (42). Unlike HBV, there is no vaccine for HCV. Therefore, it is essential to use risk reduction measures during assisted reproduction.

Current recommendations are to test all pregnant women at the onset of prenatal care. This recommendation is extended to include the testing of all male and female patients before IVF. There is a small but measurable risk of HCV transmission via semen. All patients with hepatitis C should be counseled about the risks of transmission to their partner, which is rare through sexual transmission, and to their children through vertical transmission (occurring in 4%–6%). Patients who are hepatitis C positive should be referred to a hepatitis specialist for discussion of potential treatment and cure. Current treatment of hepatitis C with direct-acting antiviral therapy is 98% effective in achieving a sustained virologic response (SVR; i.e., a cure) with 8–12 weeks of treatment. An SVR is defined as a negative HCV RNA 12 weeks after treatment. With the ease and accessibility of insurance coverage and the short duration of therapy, it is recommended to treat all couples before natural conception and all patients before IUI or IVF (43).

Although only a few women have been studied, there does not appear to be an increase in adverse pregnancy outcomes in HCV-infected pregnant women. The risk of vertical transmission is increased with coinfection with HIV (19.4% risk), in patients with a high viral load (i.e., R2.5 106 IU/mL), and with invasive procedures (44). A cesarean section for delivery is not recommended to prevent vertical transmission; there is no vaccine available to treat infants born to HCV-infected women; and breastfeeding is considered safe in women who are chronic carriers of HCV (43).

Human T-Cell Lymphotropic Virus (HTLV) Types 1 and 2

Human T-cell lymphotropic virus types 1 and 2 appear to be ancient retroviruses of humans that establish permanent infections but have low potential to cause human disease (45). Human T-cell lymphotropic virus type 1 infects CD4 T cells primarily and is the cause of adult T-cell leukemia and HTLV-1-associated myelopathy, also known as spastic paraparesis. Only 1%–4% of infected individuals develop either adult T-cell leukemia or HTLV-1-associated myelopathy. Human T-cell lymphotropic virus type 2 infects CD8 T cells. Although HTLV-2 has no proven connection to human disease, links to neurologic disorders are suspected. The distributions of HTLV-1 and HTLV-2 in the United States differ from elsewhere in the world and are quite low. Semen donors are screened for HTLV-1 and HTLV-2 because of the potential for transmission through ART procedures. Because HTLV-1 and HTLV-2 have several properties in common with HIV, risk reduction protocols devised for HIV-discordant couples that separate infected white blood cells and free virus from sperm (i.e., sperm wash before insemination) could be applied in cases where semen from directed donors infected with HTLV-1 or HTLV-2 is used to inseminate an uninfected partner.

Management of Cryopreserved Tissue

Contamination with HIV, HBV, and HCV has been documented in ART clinics (46) and blood banks (47). Although there is no documentation of cross-contamination of cryopreserved stored human tissue, it is highly recommended that the processing and culturing of gametes from viral carriers be completed in a designated space (e.g., a separate incubator) or at a designated time (e.g., the last case of the day) within the laboratory to allow for the separation of these samples and minimize cross-contamination risk. Human immunodeficiency virus, HCV, HBV, and possibly other viruses can survive in liquid nitrogen, making it possible to cross-contaminate samples in liquid nitrogen storage tanks, although this risk is very low. To protect cryopreserved specimens from the potential cross-contamination risk, it is advised that HIV-, HBV-, and HCV-infected specimens be stored in separate canisters within the same tank. The following measures have been proposed to further reduce the risks of cross-contamination of samples in liquid nitrogen storage:
Use of cryopreservation devices guaranteed by the manufacturer to withstand freezing temperatures and thawing cycles.

Use of a closed-system vitrification device or sealing techniques to prevent the direct contact of cryopreservation devices with liquid nitrogen.

Storage of samples in liquid nitrogen vapor instead of in the liquid phase of nitrogen itself. Recent studies have demonstrated that the use of liquid nitrogen vapor storage of both oocytes and sperm may be a viable alternative to the storage of gametes and/or embryos in the liquid phase alone, which has the theoretical potential of becoming contaminated (48, 49), but may pose more risk to the integrity of the sample if storage conditions are compromised.

Use of sperm wash techniques to decrease the viral load before freezing semen samples (50).

**CONCLUSIONS**

- People with HIV who take antiretroviral therapy as prescribed and achieve and maintain an undetectable viral load have effectively no risk of transmitting HIV through sex.

- Viral screening of intimate partners undergoing fertility treatment is not required, but it can help to ensure that appropriate precautions are taken to greatly minimize risk of transmission to uninfected partners and offspring.

- Infertile couples should be advised that transmission of viral hepatitis and HIV in assisted reproduction is possible, but the magnitude of the risk is likely low for a low-risk population.

- Good clinical practice dictates that fertility services should not be withheld from individuals with chronic viral infections, including HIV.

- There is good evidence to support the recommendation that, whether the male partner is infected with HIV and ART is needed for an infertility diagnosis, antiretroviral drugs should be used in the HIV-infected partner to reduce HIV viremia. Sperm wash methods could be used to further reduce the levels of HIV-infected white blood cells and free virus in the insemination fraction of IUI or IVF specimens. In addition, strategies to avoid infection for the uninfected partner should include condom use as well as PREP.

- There is good evidence to support the recommendation that when one partner is infected with HBV, the seronegative partner should be vaccinated against HBV. Once the female partner has been immunized against HBV, modified sperm washes solely to reduce the HBV viral load in the male partner are unnecessary. There is good evidence to support the recommendation that infants born to mothers who are HBV positive should receive both hepatitis B immunoglobulin and the hepatitis B vaccine within 12 hours after birth. Breastfeeding of newborns is not contraindicated.

- There is good evidence to support the recommendation that all men and women undergoing IVF should be screened for HCV and that infected individuals be treated with direct-acting antiviral therapy. Infertility treatments should be delayed until SVR is achieved. There is good evidence to support the recommendation that women who are HCV-infected should be counseled about the risk of transmission of HCV to their fetus with increasing viral loads and positive HIV status. Breastfeeding is not contraindicated.

- Although there is insufficient evidence to endorse the recommendation, best-practice guidelines recommend that semen and embryos from patients infected with HIV, HCV, or HBV be stored in a separate canister for each HIV, HCV, or HBV in the same cryostorage tank owing to the theoretical risk of transmission.

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**REFERENCES**


Recomendaciones para reducir el riesgo de transmisión viral durante el tratamiento de fertilidad con el uso de gametas autólogas: opinión de comité

Las infecciones de transmisión sexual son una de las mayores preocupaciones de los especialistas de la reproducción. Encabezando la lista están virus de inmunodeficiencia tipos 1 y 2 y virus de hepatitis B y C. Estos patógenos, los cuales pueden causar infecciones crónicas incurables, pueden transmitirse a través de las tecnologías de reproducción asistida y desde madres infectadas a fetos o recién nacidos. Este documento reemplaza al documento con el mismo nombre, último publicado en 2020.