

DIAGNOSTICS AND TREATMENT OF HIV-AFFECTED COUPLES WHO WISH TO HAVE CHILDREN

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The following recommendations were adopted by
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the Austrian AIDS Society (OEAG),
as well as the
German AIDS Help Organization (Deutsche AIDS Hilfe),
the German Union of Registered Physicians in HIV and AIDS Patient Care (DAGNAE e.V.),
the German Society for Obstetrics and Gynecology (DGGG),
the German Union for Combating Viral Diseases (DVV)
the Commission for Antiviral Chemotherapy of the Virology Society (GfV)
the German Federal Association of Reproductive Medical Centers e.V. (BRZ)
the German Society for Gynecological Endocrinology and Reproductive Medicine (DGGEF)
the Robert Koch Institute (RKI), and
the Competence Network for HIV/AIDS

I. INTRODUCTION

In Germany, more than 56.000 people are currently infected with HIV, 19% of whom are women [1]¹. Since 1996, the improved therapeutic options have substantially increased life expectancy so that individuals with HIV can now enjoy an almost normal life span [2]. This has also opened up the possibility for people to develop long-term perspectives with regard to their education, career, and family planning. Since 75% of all infected individuals are of childbearing age (between 20 and 40 years old), they often desire to have children. Scientific data has shown worldwide that people with HIV do not differ from the general population on the frequency of the desire and the importance placed on having children [3]. Specifically, this has been proven for Switzerland [4].

In fulfilling the desire of HIV-positive individuals to have children multiple factors have to be considered, such as the course of the HIV-infection, the infection risk for the HIV-negative partner, and the risk of vertical HIV-transmission to the child. In addition, the fertility status and various socio-demographic factors, such as age and marital status, also play a role [5, 6].

For HIV-affected couples who desire to have children the following three variants can be recognized, each of which presents their own particular problems that have to be considered:

- If the man is HIV-positive, protection of the female HIV-negative partner

- If the woman is HIV-positive, in addition to protection of the HIV-negative partner the infection risk for the child, and
- If both partners are HIV-positive, both the infection risk of the child and the avoidance of transfer of resistant viruses between partners.

Each variant requires different strategies for consultation and intervention. Among HIV-affected couples desiring children there is a greater need for support in medical and psychosocial questions and often for reproductive medicine.

This task needs to be addressed in an interdisciplinary setting; therefore, representatives from the above-mentioned organizations have committed themselves to formulating recommendations for medical consultation, diagnostics, and treatment of HIV-affected couples who desire to have children. These are designed to account for the individual life circumstances of people with HIV, to aid in medical and forensic decision-making, and to be used as a guideline for consultation in medical and psychosocial practices.

II. MEDICAL AND PSYCHOSOCIAL CONSULTATION FOR HIV-AFFECTED COUPLES WHO DESIRE TO HAVE CHILDREN

II.1. CONSULTATION GUIDELINES FOR COUPLES WHO DESIRE TO HAVE CHILDREN

Medical and psychosocial care-providers often encounter HIV-affected couples who seek advice and support in their previously unfulfilled desire to have children. However, for many couples it can be assumed that it is difficult to discuss this problem. Therefore, we

¹ Austria: 7.500 HIV-infected, women make up 30% (12. Report by OHIVKO dated 10/09/2007)

recommend actively addressing the question of having children with HIV-patients and their partners.

During a consultation about the desire to have children, it is important to distinguish between the initial counseling and any subsequent counseling that prepares or accompanies a reproductive medical treatment. Counseling must of course involve both partners. Initially, the counselor should inquire about the level of information the couple has already obtained and explore which questions have remained open. These may include life plans, future perspectives as a couple and family, their social and financial situation, the availability of social support/social services, and for each partner, why he/she desires to have children. In the initial consultation, it is important to provide substantial room for expectations and hopes as well as fears and apprehensions. Prior methods of safer sex and contraception should also be discussed. Other major issues that should be addressed during the first consultation include information about methods available to realize the couple's desire to have children, and the specific medical, psychosocial, financial, and legal conditions that need to be considered associated with the various options.

If the woman is HIV-positive, prevention of a vertical transmission, antiretroviral treatment during pregnancy, and any possible adaptations of a therapy before the onset of the reproductive medical treatment must be addressed. The potential risk of antiretroviral medication negatively affecting their children is an important aspect for many couples, which can sometimes lead to a decision not to have children or to forgo reproductive medical treatment [7].

Depending on the disease status and the available treatment options, the future diagnostic procedures must be discussed in the first consultation (as described in chapters III and IV, Tables 1 and 2).

An open and permissive consultation should enable the couple to reach an independent, informed decision [8]. As the process continues (e.g., during reproductive medical treatment), counseling can also support the couple in overcoming conflicts. Such conflicts could arise particularly after a treatment failure or if for some reason a treatment is unfeasible [6]. Disappointment and frustration can sometimes trigger couples to have unprotected sexual intercourse without any further preventive measures, thus accepting the associated infection risk in order to fulfill their desire to have children. In these cases, an open and permissive consultation about other possible options or the development of alternative life perspectives can be helpful. It has often proven to be effective to cooperate with the AIDS-counseling system, self-support groups, translators, and migrant organizations. Ultimately, counseling sessions are vitally important for cooperation between the couple and their health care-provider and for providing medical support.

II.2. LEGAL CONSIDERATIONS

Guidelines of the German Medical Board (Bundesärztekammer, BAEK)

The current guidelines of the BAEK [9] form the basis for all techniques of reproductive assistance and

stipulate the qualification requirements for physicians who provide reproductive medical treatments. These guidelines also emphasize the necessity of counseling.

Contrary to former regulations, treatment is no longer restricted to married couples; treatment of couples living in a stable heterosexual partnership is now allowed. As there has been no statement about HIV-affected couples, it can be concluded that reproductive assistance is acceptable under these guidelines.

Guidelines of the German Joint Federal Committee (Gemeinsamer Bundesausschuss, G-BA)

The G-BA decides which healthcare is considered as useful and adequate. Public health insurance may cover the cost of reproductive medical treatments, if they comply with the guidelines of the G-BA. The reimbursement of costs for all publicly insured couples in fertility treatments is restricted to a maximum of 50% of the treatment costs. The negative HIV status of both partners is a necessary prerequisite for the reimbursement of costs [10]. For HIV-affected couples, this implies that costs are not reimbursable. Various health insurances, however, sometimes reimburse costs out of goodwill.

According to the legal stipulations given in §27a SGB V, reimbursement is only possible for treatments within the so-called "homologous system" (i.e. married couples).

German Embryo Protection Act²

The German Embryo Protection Act defines the requirements regarding the fertilization of ovary cells and the transfer of embryos in detail [11]. It also contains the following restrictions:

- only ova originating from the affected woman may be used
- ova may only be fertilized for the purpose of pregnancy of the donor woman
- a maximum of 3 embryos per menstruation cycle can be transferred (after fertilization, which ends with the fusion of the nuclei, the ovum is considered as an embryo).

A singleton pregnancy should be the goal of every in vitro procedure in HIV-positive women.

Furthermore, donation, procurement, testing, processing, preservation, storage, and distribution of human tissues and cells has to be in accordance with the European Parliament standards of quality and safety [12]. Separate storage containers have to be provided for the treatment of HIV-positive patients. An HIV-

² In Austria, the Reproductive Medicine Law replaces the Embryo Protection Act. This does not take into account the situation of seroconcordant couples. The Austrian IVF funds assume approximately 70% of the treatment costs. An HIV-infection does not justify any exclusion from the coverage of costs (Reproductive Medicine Law, BGBl. No. 275/1992 Reproduction Medicine Law amendment 2004 - FmedGNov 2004, 678 of supplements XXII. GP; IVF fund law, BGB I No. 180/1999, IVF fund law amendment 2004)

test has to be performed before cryo-conservation of gametes and IVF/ICSI-procedure.

II.3. FINANCIAL CONSIDERATIONS

Couples are entitled to have diagnostic costs covered by health insurance, which includes HIV-diagnostics as well as the diagnostics recommended for couples who wish to have children. Beyond this, health insurance coverage differs depending on the procedure. An insemination treatment costs 200 - 800 Euros (not including stimulation medication), while an IVF/ICSI costs 1,500 - 4,000 Euros per cycle³. Thus, costs vary greatly between individuals and can only be precisely determined after diagnostics.

III. DIAGNOSTICS AND THERAPY IN HIV-POSITIVE WOMEN

With the improvement in life expectancy and therapeutic options, an increasing proportion of women with HIV desire to have children. Individual psychosocial counseling should be given in close cooperation with gynecologists, HIV-physicians, and, if necessary, specialists in reproductive medicine. Particularly, the prevention of HIV-transmission from the woman to the HIV-negative partner and the child must be considered.

III.1. MATERNO-FETAL TRANSMISSION RISK

The German-Austrian recommendations for HIV-therapy during pregnancy and for HIV-exposed newborns should be followed to prevent materno-fetal transmission [13]. According to recent studies, these preventive measures can reduce materno-fetal transmission to less than 1% [14, 15, 16], compared to 15 - 20% without intervention [16, 17, 18]. The highest risk of materno-fetal transmission occurs in the last trimester of pregnancy, particularly during birth, and post-partum via breast feeding. Although the individual transmission risk can not be assessed with certainty, conditions that implicate a low materno-fetal transmission risk include: a low viral load [ideally non-detectable or at least below 1000 copies/ml [19], a stable CD4-cell count over the past six months, remaining antiretroviral therapy options, and absence of serious co-morbidity (e.g. chronic hepatitis B and/or C infection, diabetes mellitus, epilepsy)]. In addition, there should not be any serious gynecological/obstetrical risks that represent an absolute contraindication for pregnancy.

III.2. INFLUENCE OF HIV-INFECTION ON PREGNANCY

From the present data on pregnancies in women with HIV, there is no evidence that pregnancy and birth have a negative impact on the course of HIV-infection

[18]. However, it is possible that the infection increases the risk of pregnancy complications [17, 21, 22]. Potential complications include predominantly greater risk of premature birth and increased side effects of the antiretroviral therapy (e.g. hepatotoxicity). These issues should be discussed with the couple during counseling sessions. Furthermore, counseling should address the risks of exposure of children to antiretroviral substances both intrauterine and postpartum, and inform that it has not yet been possible to determine risks of such exposure in long-term studies.

III.3. OPTIONS IF BOTH PARTNERS ARE FERTILE

With no history of fertility disorders [6], self-insemination at the time of ovulation represents the easiest option if the male partner is HIV-negative. Initially, a spermicidal-free condom should be used for sexual intercourse. For self-insemination, the condom can be inserted reversely into the vagina, or the sperm can be applied to the vagina using a cervical cap or syringe. The main advantage is - apart from the fact that the uninfected male partner remains protected - that conception can be left to the privacy of the couple [6].

Should the couple experience problems with self insemination, an intrauterine insemination (IUI) can be considered.

If no pregnancy occurs over a period of 6-12 months, or if there are indicators of reduced fertility of one or both partners, differentiated fertility diagnostics should be carried out (see Table 1). Fertility diagnostics can be offered earlier if the couple desires this.

Table 1. Basic diagnostics in the HIV-positive woman.

Medical and psychosocial case history

Gynecological diagnostics

- Palpation
- Sonography
- Examination of the patency of the fallopian tubes (hystero-contrast sonography, if necessary laparoscopy)
- Endocrinological diagnostics (E2, LH, P, DHEAS, FSH, Testosterone, SHBG, TSH, Prolactin)
- Cervical smear (PAP, chlamydia PCR)
- Serology (rubella, varicella, TPHA, CMV, HBV, HCV)
- Glucose, GOT, GPT, gamma-GT, blood counts

HIV-specific diagnostics

- Ultrasensitive HIV-PCR and - if necessary - resistance testing
 - Lymphocyte differentiation, CD4 / CD8 cell count
 - HIV-antibody test for the seronegative partner
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III.4. OPTIONS IF FERTILITY IS REDUCED

The implementation of reproductive measures for HIV-discordant couples is internationally approved [European Society of Human Reproduction and Embryology (ESHRE) Task Force on Ethics and Law] [23].

In case of a reduced fertility, the following options exist: intrauterine insemination (IUI), in-vitro fertiliza-

³ Austria: An IVF/ICSI cycle costs more than 2,000 Euros plus 350 - 1,500 Euros for medication. If the IVF-fund covers the costs, the contribution made by the couple also reduces correspondingly.

tion (IVF) and intracytoplasmic sperm injection (ICSI). These therapies should be only performed in HIV-experienced centers that perform multiple reproductive treatments of HIV-positive patients per year. The individual liability risk of the treating physician has not yet been definitively made clear. Therefore, a reproductive medical center should clarify and implement the following:

1. Discussion amongst the reproductive team about the proceeding before the start of therapy and written consensus to the implementation of the aforementioned therapeutic measures
2. Written informed consent of the couple about opportunities and risks of fertility treatment if one partner is HIV-positive.
3. Documentation of all diagnostic and treatment procedures.
4. Guarantee a special duty of care for all employees to prevent HIV transmissions.

Since multiple pregnancies bear increased risk of vertical HIV transmission (especially due to the increased risk of premature birth), all efforts must be made to ensure a singleton pregnancy only. With IVF/ICSI treatment, this aim can only be reached if a single embryo transfer is carried out, which reduces the pregnancy rate per cycle. The couple should also be informed about this [24].

III.5. SUCCESS RATES OF MODERN REPRODUCTIVE MEDICAL TREATMENTS

There is evidence that HIV-positive women show a higher incidence of fertility disorders [25], indicating increased demand of reproductive treatments. Data on the success rates of IVF/ICSI in HIV-positive women remain unclear, since current case numbers are too low to estimate exact rates. Only data on 205 cycles among 127 HIV-positive women have been published. The pregnancy rate in HIV-positive women (17% per embryo) was substantially below the rate in the general female population (26 % per embryo) [26]. The couple should also be informed about this.

IV. DIAGNOSTICS AND THERAPY IN HIV-POSITIVE MEN

The improvement in life expectancy and quality of life in people with HIV has also led to an increasing desire to have children among HIV-positive men and their partners [6].

The therapeutic options to be discussed range from sexual intercourse with pre-exposure prophylaxis to intrauterine insemination and IVF/ICSI measures.

Currently no valid data exist on the use of pre-exposure prophylaxis (PrEP) with couples who desire to have children. Various research groups have included counseling on periovulatory sexual intercourse without a condom in their program [28]. The assumption is that transmission risk can be reduced by having the HIV-negative female partner take an antiretroviral prophylaxis twice before periovulatory sexual intercourse [28]. PrEP should only be considered in the HIV-neg-

ative female partner, if the male partner has a viral load below detection limit (ultrasensitive HIV-PCR) and a normozoospermia. In addition, no other sexually transmitted diseases should be present.

Studies have indicated that the sperm quality of HIV-positive men is often impaired compared to that of HIV-negative men [29, 30]. A prospective study of HIV-positive men during the first 48 weeks of antiretroviral therapy revealed a significant impairment of sperm motility, even with therapies that were not regarded as particularly mitochondriotoxic [31]. The effect of these changes on fertility has not yet been examined.

The homologous insemination of cryopreserved sperm subjected to processing before the cryopreservation can be regarded as a standard procedure in men with normozoospermia or mild asthenozoospermia. Native ejaculate consists of spermatozoa, seminal fluid, and other nucleated cells (precursor cells for spermiogenesis and leukocytes). HIV can be found in the seminal fluid, the nucleated cell fraction, and occasionally in immotile sperm. Vital motile sperm is unlikely to carry HIV [25]. The possibility of washing sperm from HIV-positive men was first published in 1987 [30]. In this process, the spermatozoa are first separated from the seminal fluid and the nucleated cell fraction by density gradient centrifugation. After two washing cycles, the pellet is then carefully layered with culture medium and incubated for 30-60 minutes at 37 °C. During this time, the motile sperm accumulates in the upper adjoining layer. An aliquot of the ejaculate prepared in this way is tested for HIV and nucleic acids in order to exclude any contamination with viral particles, while the greater part of the prepared sperm is frozen and inseminated intrauterally 32 hours after the induction of ovulation [16, 18, 28].

The first inseminations of HIV-negative women with processed sperm from their HIV-positive partners were carried out in Italy in 1989 and in Germany in 1991. Since then, reproductive medical support to HIV-affected couples has increased worldwide. Data regarding the safety of such treatment has expanded. CREAThE, a European alliance of reproductive medical centers, recently published the results of a multicenter study on 1,036 couples with an HIV-positive male partner. In 3,390 treatment cycles where processed sperm was used, not a single case of seroconversion in the HIV-negative female partner was observed [33].

The problem with cryopreserving sperm is that the deterioration of motility results in a reduced pregnancy rate. For this reason, other groups have chosen to process the spermatozoa at the moment of the LH-peak of the female partner and test the spermatozoa within 24 hours by PCR. The storage of sperm is then carried out at +4 C, and if the results prove negative, intrauterine insemination [34] is carried out. Using this method, an Italian scientific group achieved a pregnancy rate of 19%. Treatment with IVF/ICSI (n = 160 couples) achieved a pregnancy rate of 22% per cycle. At the follow-up, all female partners were still HIV-negative [34].

Alternative preparation methods such as the double tube/needle tube are currently being tested [28]. Since

any adhesion of the processed spermatozoa to HIV is highly improbable, some groups do not carry out a routine PCR-diagnostics after preparation. However, the gold standard remains to run HIV-PCR testing before and after preparation and the subsequent cryopreservation of the spermatozoa.

If after cryopreservation and preparation the progressively motile spermatozoa content is less than 15 % (WHO A), the option of carrying out an intracytoplasmic sperm injection (ICSI) must be discussed with the couple. In Germany these measures must be carried out according to the guidelines of the respective state medical board.

It is important that both partners are suitably informed (in writing) that even with the most extensive preparation techniques there remains a theoretical risk of a virus transfer to the HIV-negative female partner.

In this respect, there should be no legal objections to a reproductive medical treatment where the male partner is HIV-positive as long as the described procedure is followed and thoroughly documented.

Table 2. Basic diagnostics in the HIV-positive man.

Medical and psychosocial case history

Andrological diagnostics

- 2 spermograms
- Ejaculate culture
- Palpation
- Sonography, if necessary endocrinological diagnostics
- Serology (HBV, HCV, TPHA), Smear for HPV + GO, Chlamydia-PCR in urine

HIV-specific diagnostics

- Ultrasensitive HIV-PCR and-if necessary- resistance testing
 - Lymphocyte differentiation, CD4 / CD8 cells
 - HIV-AB-Test of the seronegative partner
 - HIV-PCR before and after preparation of sperm for IUI/ICSI and, if necessary, cryo-preservation of HIV-free sperm
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V. PROCEDURE WITH HIV-SEROCONCORDANT COUPLES

If both partners are HIV-positive, sexual intercourse without a condom is an option. The low risk of superinfection (possibly with the transfer of medication-resistant viruses) should be discussed. According to current knowledge, the probability of a superinfection during the chronic phase of the infection is low. If both partners are treated successfully with anti-retrovirals, a superinfection is extremely unlikely [35, 36].

Problems emerge, when fertility of one or both partners is impaired. The ESHRE guidelines still discourage reproductive medical support for HIV-seroconcordant couples since the child might become orphaned as a result of the death of both partners [23]. The significantly improved prognosis for HIV-positive individuals has clearly not been taken into account. A reproductive medical treatment for seroconcordant couples is currently a matter of considerable debate in Germany, for ethical as well as for judicial reasons. To date, general recommendations cannot be made because of the

widely varying individual circumstances, but a decision should only be reached after individual counseling and after carefully weighing both risks and benefits. Any absolute exclusion of seroconcordant couples from reproductive medical treatment cannot be justified.

VI. SUMMARY AND OUTLOOK

The counseling and support of HIV-discordant couples who desire to have children represents an interdisciplinary task based on comprehensive diagnostics. When the male partner is HIV-positive there is at most a hypothetical residual risk of infection for the female partner when procedures for assisted reproduction are followed. When the female partner is HIV-positive, the options range from self-insemination and, in case of impaired fertility, to all techniques of assisted reproduction. The couple must be informed comprehensively about the residual risk of a materno-fetal HIV-transmission. The treatment should be carried out in HIV-specialized, highly experienced reproductive medical centers [37].

When both partners are HIV-positive, the decision for reproductive medical support should be made on a case-by case basis after comprehensive counseling. In this case, it is currently not possible to provide any general recommendations.

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