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Deutsche AIDS-Gesellschaft (DAIG e.V.) (*The German AIDS Society*)

Österreichische AIDS-Gesellschaft (ÖAG) (*The Austrian AIDS Society*)

and

Arzneimittelkommission der *Bundesärztekammer* (*The Pharmaceutical Committee of the German Federal Medical Council*)

Deutsche Arbeitsgemeinschaft niedergelassener Ärzte in der Versorgung von HIV- und AIDS-Patienten (DAGNÄ e.V.) (*The German Association of Registered Physicians for the Treatment of HIV and AIDS Patients*)

Deutsche Gesellschaft für Gynäkologie und Geburtshilfe (DGGG) (*The German Society of Obstetrics and Gynaecology*)

Deutsche Vereinigung zur Bekämpfung der Viruskrankheiten (DVV) (*The German Union for the Eradication of Viral Diseases*)

Kommission für Antivirale Chemotherapie der Gesellschaft für Virologie (GfV) (*The Antiviral Chemotherapy Commission of the Society of Virology*)

Bundesverband reproduktionsmedizinischer Zentren Deutschlands e.V. (BRZ) (*The Federal Association of German Reproductive Medical Centers*)

Deutsche AIDS-Hilfe (DAH) (*The German AIDS Help Association*)

KIS - Kuratorium für Immunschwäche e.V. (*The Curatorium for Immune Deficiency*)

Verein All Around AIDS e.V. (*The All Around AIDS Society*)

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## **Diagnosics and treatment of HIV-discordant couples who wish to have children**

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### *Key Words:*

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### *List of abbreviations:*

GOT (glutamate oxaloacetate transaminase), GPT (glutamate pyruvate transaminase)

GGT ( $\gamma$ -glutamyl-transferase), CMV (cytomegalo-virus), HBV (hepatitis B-virus)

HCV (hepatitis C-virus)

### *Abstract*

Over the last years the reality surrounding HIV-infection has undergone a considerable change with regard to the life expectancy of patients, and the plans they can make for their lives. Because the majority of the HIV positive population is of reproductive age, one of these plans might be to have children, often as an expression of a fulfilled partnership. The need for medical support to realize this wish, however, is often confronted with ethical, medical or forensic restraints. For this reason, interdisciplinary recommendations have now been developed – for the first time on a global basis – which aim to provide guidelines for practitioners in this complicated area.

Care and support of HIV-positive individuals who desire children is an interdisciplinary task. If the occasion should arise, non-medical psycho-social measures also have to be integrated. Factors to be considered in couple counseling include disease progression, early and comprehensive infection diagnostics, and fertility screening for both partners. All steps of diagnostics and treatment have to be documented completely, and written documentation must be obtained from the affected individuals stating that they clearly understand the remaining risk of infection for the healthy partner and even the child. If one of the partners is not compliant or has an advanced stage of HIV-disease (CDC B3 or C), active reproductive support should not be provided.

HIV-positive women should be informed about the possibility of self-insemination so that the healthy partner is protected from HIV-infection. Medical measures taken to reestablish fertility or optimize conception are acceptable as long as polyovulations are prevented. However, there are forensic reservations with respect to assisted reproduction techniques due to the remaining risk of materno-fetal transmission which under optimized conditions is low, but still quantifiable.

Wherever the male partner is HIV-infected, infectious viral particles can be separated from motile spermatozoa by density gradient centrifugation and subsequent swim-up. To exclude the possibility of viral contamination to the greatest degree of certainty, one aliquot from each prepared sample should be tested for HIV nucleic acid using highly sensitive detection methods. As a rule, this requires cryo-preservation. Processed, tested sperm samples can then be used for all techniques of assisted reproduction in the healthy female partner.

In Germany more than 50,000 individuals have been diagnosed as HIV positive, of whom more than 20% are women (Robert Koch Institute 2000). Improvements in therapeutic capabilities have significantly increased the life expectancy of HIV infected individuals and provided them with renewed perspectives on life which had previously been considered as lost. Due to the fact that 75% of the HIV positive population is between 20 to 40 years of age, a major intention might be to have children at some point in life. The realization of such an objective is hindered by the risk of infection to the healthy partner and the child. Couples who want to responsibly confront the dilemma between risky conception and being childless need to be provided with medical and psycho-social counseling and treatment measures.

This task can only be solved with an interdisciplinary approach. Therefore, representatives from all the societies mentioned below have worked out the following recommendations for the medical diagnosis and treatment of HIV discordant couples who desire children. These recommendations are designed to take into account the altered reality of HIV infection, and to serve as medical and forensic guidelines for the medical practitioners involved.

#### 1. Preamble

Those who seek our advice are particularly couples who want to handle their HIV infection responsibly and who wish to avoid unprotected sex. Many years of experience in treating HIV discordant couples who desire children have stressed the importance of performing psychosocial counseling on both partners prior to any attempts at reproduction. Here, the life-plan and future prospects (life expectancy) of the couple, the importance of having children and the social and financial situation of the couple are dealt with. After a thorough consultation, up to a third of all couples decide against having a child (even when it is considered as medically feasible) and turn instead towards fulfilling other goals in life. Psycho-social counseling can ultimately help overcome difficult dilemmas resulting from an unsuccessful treatment or the inability to perform such a treatment. From a preventive standpoint it must be taken into account that unresolved disappointment and frustration can push couples into unprotected sexual intercourse (Sonnenberg-Schwan U, Jäger H 1997).

An important precondition for medical support is the couples ability to comply with any advice provided. Wherever compliance might be compromised by psychiatric co-morbidity, substance addiction, an unfavorable social environment, or a lack of understanding for medical or prophylactic measures (e.g. continuous use of condoms!), treatment should be critically reviewed, counseling should be intensified, and if necessary non-medical counseling for self-help should be introduced. The same applies to advanced stages of HIV corresponding to stages B3 or C of the CDC

classification. In principle, HIV discordant couples who desire children present with the following two scenarios:

- If the male partner is HIV positive, one only has to deal with preventing infection of the healthy female partner.
- If the female partner is HIV positive, one is not just concerned with preventing infection of the healthy male partner, but also in preventing infection of the child. In addition, possible interactions between HIV infection and pregnancy also have to be considered.

## 2. Diagnosis and therapy with HIV infection in the female partner

No studies published until now have shown that pregnancy and birth adversely affect the course of a non-advanced HIV infection. However, infection does seem to increase the probability of complications arising during pregnancy (Schäfer A 1999).

The probability of viral transfer from mother to child without medical intervention is about 15-20%. In principle, transmission of the virus from the bloodstream into the trophoblast or placenta can occur at any time during the pregnancy. However, data published until now has indicated that the course of the birth defines the risk of infection to the fetus. The risk is increased by premature labor, premature delivery, premature amniorrhexis, infection of the amnion, and vaginal delivery.

For these reasons, current standard recommendations for reducing the risk of materno-fetal transmission include anti-retroviral therapy during pregnancy, a neonatal anti-retroviral prophylaxis, abstention from breast feeding, and elective caesarian section to spare the amniotic membrane (German-Austrian Guidelines 1999). By performing all of these recommendations, the fetal risk for infection can be reduced to less than 2% (Mandelbrot et al. 1998, The International Perinatal HIV Group 1999).

At present, the individual risk of transmission cannot be defined precisely. Viral production can increase at any time during the course of an HIV infection. Also, the presence of obstetrical risk factors during the course of a pregnancy cannot be foreseen. Important predictors for the transmission risk seem to be viral load in serum and vaginal secretions (Mofenson et al. 1999, Garcia et al. 1999). Conditions favoring a low risk of materno-fetal transmission include:

- A small viral load, if possible less than 1000 copies/ml, and a stable CD4 count during the last 6 months.
- Continuance of anti-retroviral therapeutic measures. No resistance against AZT or NVP.
- No somatic co-morbidity such as chronic Hepatitis B or Hepatitis C infections, diabetes mellitus or epilepsy.
- No pre-existing gynecological or obstetrical risk factors.

The correct recording and weighing up of the abovementioned factors form the basis of recommendations to be made regarding a couple's plans to have children: Can the plans for pregnancy be realized, should they be delayed because of a temporary exacerbation of risk, or should the couple be advised not to have children at all? If the couple decides to pursue their plans after a thorough consultation, an early fertility and infection check on both partners should be performed (see table 1). In this way, the risks of infection from an HIV-infected individual – in case of a pregnancy also for the unborn child – can be decreased, and any existing barriers to fertility can be uncovered. If the latter can be excluded, the couple should be informed about the possibility to perform a self-insemination. At the time-point of ovulation, the spermicide-free condom containing the ejaculate can be introduced into the vaginal cavity after sexual intercourse in inverted form, or the ejaculate can be vaginally injected after masturbation with a syringe or applied with a cup pessary. In doing so, conception can remain within the private sphere of the couple and at the same time be safe for the HIV negative partner (Sonnenberg-Schwan U 1999).

The recommendation and carrying out of reproductive medical interventions needs to be done on a differentiated and individual basis. Counseling and education of the couple regarding medical matters, and measures designed only to reconstruct a normal physiological status (e.g. with anovulation or tubal disorders, or when reversing a previously performed sterilization), can be considered as acceptable. Ovarian stimulation therapy, however, requires highly qualified supervision with the objective of achieving a single ovulation, since the risk of materno-fetal virus transmission increases with multiple gestations. Procedures of assisted reproduction, however, must be evaluated far more critically:

An explicit law forbidding HIV discordant couples against having children does not exist. Any legal decisions cannot be made in a general manner, and instead should be arrived at on a case by case basis by weighing up the various risks mentioned. If the aforementioned techniques are followed, the risk of transmission to the child is low, but still holds an order of magnitude that can not be viewed as merely theoretical. In addition, active medical interventions designed to support the fertilization process should be done with strong reservations, with the well being of the future child being given the highest priority by the guidelines of assisted reproduction. Despite the low risk of infection, it is still a matter of debate whether an infected child should be able to successfully claim any compensation (Eberbach W 1999).

In all cases, documentation has to be obtained that clearly confirms that the couples have been made completely aware that despite all precautions taken, infection of the child is still a possibility. All diagnostic and therapeutic measures taken must also be documented clearly and

comprehensively. In addition, before any such active intervention is undertaken, authorization from the locally responsible ethics committee must be acquired.

### 3. Diagnosis and therapy with HIV infection in the male partner

Native ejaculate consists mainly of three fractions: the spermatozoa, the seminal plasma, and accompanying nucleate cells, i.e. precursors of spermatogenesis and leukocytes. HIV progenomes and viruses can be detected in seminal plasma, the accompanying nucleate cell fraction, and occasionally in immobile spermatozoa. Viable, motile spermatozoa are not considered to be virus carriers (review by Weigel et al. 1999).

Motile spermatozoa can be isolated by standardized preparation techniques (Anderson et al. 1992, Semprini et al. 1992). Firstly, the spermatozoa are separated from the seminal plasma and accompanying cells by density gradient centrifugation (Sil Select®, Ficoll®, Percoll (40/80), for 35 min. at 350 x g). Secondly, the spermatozoa are washed twice with culture medium by resuspension and centrifugation (10 min at 350 x g), and the final pellet is overlaid with culture medium. After incubation for 30 to 60 minutes at 37°C, the motile spermatozoa accumulate in the upper layer of the sample. To exclude the possibility of contamination by viral particles to the greatest possible degree of certainty, one aliquot of the prepared sample should then be tested for HIV nucleic acid using the most sensitive tests available. Any existing viral genome or progenome will be isolated and then amplified and detected by nucleic acid detection technology (PCR, NASBA, or similar). Irrespective of the number of virus particles detected, every contaminated sample should be discarded. As a rule, each prepared spermatozoa sample must then be cryopreserved until all the test results are available.

Prepared, HIV-negative spermatozoa can in principle be used for all assisted reproduction techniques. For HIV discordant couples, assisted reproduction techniques are restricted to intrauterine insemination (IUI), extracorporal fertilization by conventional in-vitro fertilization (IVF), and intracytoplasmic sperm injection (ICSI) followed by embryonic transfer. The choice of method depends on the couple's preference and on the gynecological and andrological diagnostics of both partners (see table 1). These procedures are subject to the guidelines of the German Federal Medical Council, the "Bundesaerztekammer" (Bundesaerztekammer 1998), which currently require that the candidates are married. Any unmarried couple requesting an exception to this requirement requires authorization from the responsible ethical committee of the regional State Medical Council, the "Landesaerztekammer". In some states, however, treatment of unmarried couples in stable relationships is possible without calling for the authorization of an ethics committee (e.g. Berlin).

The couple should be appropriately informed that even the most careful preparation techniques and testing methods cannot exclude the possibility of transmission to the partner (and thereby the child) with absolute certainty. However, this risk is completely hypothetical and is in stark contrast to the risk of infection from unprotected sexual intercourse which is around 0.5-1% (Royce et al. 1997). By adhering to the described procedures and their comprehensive documentation, there should be no legal (liability-based) objections to performing assisted reproduction wherever the male partner is infected with HIV (Eberbach W 1999).

As a matter of principle, all female patients undergoing one of the above procedures, as well as any children born as a result, should be closely monitored for any change in infection status.

#### 4. Summary and outlook

Counseling and treatment of HIV discordant couples who desire children is an interdisciplinary task which is based upon comprehensive medical diagnostics. In the case of an HIV positive male partner, conception can be realized using any of the aforementioned assisted reproductive techniques, where there is at most only a hypothetical risk of transmission to the non-affected female partner. In the case of an HIV positive female partner, the fertile couple should be informed about the possibility of self-insemination. According to our current state of knowledge, especially considering the risk of materno-fetal transmission and the liability issues mentioned, assisted reproduction in HIV positive females can only be decided upon on an individual basis. These recommendations must of course be adapted to future developments as further research continues to break new ground.

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Table 1. Basic diagnostic testing for both partners with HIV discordance

Anamnesis	Comprehensive medical and psycho-social history
Female examination	Palpation, sonography, tubal patency test, (if necessary hysteroscopy) Basal temperature, and if necessary endocrinological diagnostics Cervical smear (cytology, pathogenic spores) Serology (rubella, toxoplasmosis, syphilis, CMV, HBV, HCV)
HIV specific/general medical diagnostics	Associated and accompanying symptoms? Blood-glucose, GOT, GPT, GGT, complete blood count Ultra-sensitive HIV-PCR, CD4/CD8 cell count HIV-antibody test of the serum-negative partner
Male examination	Spermiogram, semen culture Serology (HBV, HCV) Urinary chlamydia-PCR