Male reproduction and HIV-1 infection

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General Discussion

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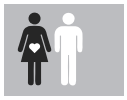
The improved prognosis of patients with HIV-1 infection following the introduction of combination antiretroviral therapy has lead to an increased desire of HIV-1-discordant and HIV-1-concordant couples to mother or father a child. As a consequence, assisted reproductive technologies are now increasingly being offered to these couples. The rationale of assisted reproductive technologies in HIV-1-infected couples can be twofold: to overcome subfertility for the same indications as in non-HIV-1-infected couples, and to minimize the risk of HIV-1 transmission in case of a HIV-1-serodiscordant couple with an HIV-1-infected man. The basic principle underlying assisted reproductive technologies in HIV-1-discordant couples with an HIV-1-infected man is the processing of semen to isolate HIV-1-free, motile spermatozoa with a normal morphology. This is achieved by density gradient centrifugation with swim-up, and testing of the spermatozoal fraction for HIV-1, using PCR-based methods [1]. After negative testing, the remaining spermatozoa can be used for assisted reproductive technologies like intra uterine insemination (IUI), in vitro fertilization (IVF) or intra cytoplasmatic sperm injection (ICSI). Since the lower limit of detection of the PCR tests used is not zero, the risk of HIV-1 transmission by assisted reproductive technologies can never be completely eliminated. These assisted reproductive technologies in HIV-1-discordant couples should therefore be considered risk-reduction and not risk-elimination strategies.

The current state of the art of assisted reproductive technologies for couples with an HIV-1-infected man is summarized below, together with the clinical implications of the findings from the research presented in this thesis. In addition, suggestions for future research are provided.

Intra uterine inseminations

When we started our assisted reproductive technology program for HIV-1-discordant couples in the Academic Medical Centre (AMC), we chose to include both therapy-naive men and men receiving highly active antiretroviral therapy (HAART). From epidemiological studies it was known that each ten-fold increase in blood plasma HIV-1-RNA concentration increases the risk of sexual HIV-1 transmission by a factor 2.5 [2] and that men without HAART generally have higher HIV-1-RNA concentrations in their semen [3]. We therefore reasoned that the exclusion of therapy-naive men would lead to the exclusion of the very patients with the highest risk of sexual transmission.



The assisted reproductive technology program in the AMC for discordant couples with an HIV-1-infected man had, since its inception in 2003, during the first three years a fairly good clinical and ongoing pregnancy rate. Our pregnancy rates for first children were comparable with the 15.1% pregnancies per intrauterine insemination (IUI) which were reported in the largest series of IUI in discordant couples with an HIV-1-infected man [4]. In 2006 and 2007 pregnancy rates for first children were lower than in the first three years, but pregnancy rates for second children were still good. At the moment we have two possible explanations for this. First, in 2006, we lowered the cut-off value for semen quality and thus started to include men with poorer semen quality. Second, we had decided to offer a maximum of nine cycles of IUI per patient at the start of our program, as no data existed on the maximum number of IUI cycles that should be performed for this specific patient group. However, none of the couples that received four or more IUI cycles became pregnant thus gradually reducing overall pregnancy rates.

The assisted reproductive technology of choice: IUI, IVF or ICSI

There is no uniformity in assisted reproductive technologies that are offered by various centres around the world to HIV-1-discordant couples [4]. Most centres perform IUI, as HIV-1-infected couples are not infertile unless proven otherwise. The method is non-invasive and less costly than IVF or ICSI [5]. However, about one-third of HIV-1-infected men are excluded from IUI, because their semen qualities are poor, already prior to the semen processing, or after the intensive semen processing due to its low efficiency (5-10% recovery rate, unpublished data). As a result, only men with good semen quality can opt for IUI. In this light we felt it was important to know whether semen quality might be negatively affected by HIV-1 infection and HAART.

Before our study was carried out, longitudinal data describing the effect of primary- or ongoing HIV-1 infection on semen parameters were lacking.

In the longitudinal cohort study involving men not yet receiving antiretroviral therapy we found that, once these men were chronically infected with HIV-1, semen parameters were not affected by ongoing HIV-1 infection during the observation period of 77 weeks on average [6].

These data are reassuring in the sense that delaying treatment in HIV-1-infected patients until CD4 cells counts reach around 200 cells/mm^3, thus lengthening exposure to untreated infection, has no adverse effect on semen quality. Ongoing HIV-1 infection therefore, probably

does not appear to affect the chance to qualify for IUI. In contrast, we found that HAART did negatively affect the percentage of progressively motile spermatozoa [7], and thus may have a negative effect on the chance to qualify for IUI. However, the consequence on IUI outcome of the observed reduction in the percentage of progressively motile spermatozoa during HAART remains unknown. The only study that described predictors of success in HIV-IUI is flawed by the a priori inclusion of men with good semen qualities only [8,9]. Therefore data on prognostic factors that determine the chance of pregnancy after IUI are urgently needed.

In men with *a priori* lower semen qualities or a low sperm-yield after semen processing, ICSI is now in many countries the preferred treatment [10-15]. Despite the lack of scientific evidence, some authors even advocate the sole use of ICSI to prevent HIV-1 transmission irrespective of semen quality [5]. Arguments used in favour of ICSI are that pregnancy rates are generally higher with ICSI than with IUI, and thus less cycles of ICSI are needed to achieve pregnancy, with less exposure to possibly HIV-1-contaminated spermatozoa [16]. A second argument in favour of ICSI is that, in contrast to IUI, only a single spermatozoon in minute amounts of medium are used, thus decreasing the likelihood of contamination with HIV-1 [11,13].

Although in many programs processed semen is not tested for HIV-1 prior to ICSI, so far not a single case of HIV-1 transmission to the woman or the child has been reported after ICSI [4,10-18].

At present, the joint perspective of the Dutch society of obstetrics and gynaecology, the Dutch society of clinical embryologists and the Dutch working group of clinical virologists is not to perform ICSI in HIV-1-infected men and women, reasoning that the injection of a single spermatozoon, potentially carrying an HIV-1 particle directly into an oocyte may lead to incorporation of the viral genome into the future embryo, with unknown but possible catastrophic consequences; for instance iatrogenically HIV-1-infected children, but again scientific evidence for this statement is lacking.

Natural conception in discordant couples with an HIV-1-infected man

Some infectious diseases specialists and fertility specialists feel that HIV-1-discordant couples should not only be informed about assisted reproductive technologies but also about the possibility of natural conception and its associated risks when they request reproductive advice [19,20].

Arguments in favour of natural conception are twofold. First, the risk of HIV-1 transmission in HIV-1-serodiscordant couples is only 1/1000 to 1/500 unprotected intercourses at blood plasma HIV-1-RNA concentrations between 1,700 and 38, 5000 copies/ml [21], and is estimated to be even lower during successful HAART [22], because the blood plasma HIV-1-RNA concentration, the most important predictor of sexual HIV-1 transmission, decreases to below the limit of detection [23].

Second, even today many HIV-1-discordant couples try to conceive naturally. Such patients include those for whom artificial reproductive technologies are out of reach, patients who cannot pay the costs which in some countries are not covered by health insurance, patients who cannot travel large distances to reach a centre that provides fertility care for HIV-1-infected men and women, or patients who have undergone assisted reproductive treatments without success [19,20,24]. This is illustrated by the fact that half of the couples seen initially in these centres attempted to conceive naturally after unsuccessful inseminations [20], and one woman became HIV-1 infected while she was waiting to undergo assisted reproductive technologies [25].

Infectious diseases specialists and fertility specialists who promote natural conception state that natural conception should only take place after optimization of factors that limit the chance of HIV-1 transmission and improve the chance to conceive.

This would include: (1) a fertility screen, `infertile´ couples should be offered assisted reproductive technologies, (2) the initiation of HAART: an undetectable HIV-1-RNA blood plasma concentration decreases the HIV-1-transmission risk, (3) the exclusion and treatment of genital tract infections, and (4) the avoidance of unprotected intercourse other than around the established time of ovulation and immediate abstinence from unprotected sex as soon as pregnancy is achieved [19,20,26,27].

Nevertheless, most infectious diseases specialists and fertility specialists are reluctant to embrace the concept of unprotected intercourse because of the following reasons.

First, the safety of natural conception will be difficult to prove due to the low seroconversion rate during unprotected intercourse [21]. A 3.8% HIV-1-transmission rate in pregnancy was described in 1997 in previously HIV-negative women who conceived naturally from their HIV-1-infected male partners, but a recent retrospective study did not report HIV-1 transmission in HIV-1-discordant couples achieving pregnancy when the HIV-1-infected man or woman had an

undetectable blood plasma HIV-1-RNA level under HAART [26,28]. Unfortunately, both studies are flawed by the inclusion of successful pregnancies only, couples who were unsuccessfully trying to conceive were not included and both studies do not mention the number of unprotected coital acts needed to achieve pregnancy [26,28]. The actual seroconversion rate during natural conception may thus have been higher.

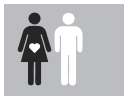
Second, the exact chance of HIV-1 transmission in an individual couple is difficult to predict, as HIV-1 may be intermittently present in the male and female genital tract at variable concentrations, sometimes irrespective of HAART or genital tract infections and is detectable in seminal plasma in 5% of men who are using HAART for at least six months [23,29].

Third, it is very difficult to counsel the couple, taking into account the arguments listed above.

We therefore feel, with the knowledge we have today, that it is unethical to offer natural conception. The ultimate test to compare the safety of assisted reproductive technologies with natural conception would be to perform a randomized controlled trial, but such a study design is for obvious reasons not ethical and not feasible because it requires the inclusion of large numbers of patients. Therefore it is crucial that fertility clinics remain specialized in the treatment of HIV-1-infected patients and extend their knowledge on reproductive issues in order to offer these couples up-to-date assisted reproductive help.

Recommendations and suggestions for future research

The impact of HAART on semen quality becomes more relevant in view of guidelines increasingly recommending to initiate HAART earlier [30]. As a result, more men will use HAART for a longer period during their HIV-1 infection. The impact of this policy on semen quality has not yet been studied, but according to the outcome of our study on HAART and semen quality, it may be associated with a more pronounced negative impact on the percentage of progressively motile spermatozoa. Counselling HIV-1-infected men with a desire to father a child on the benefits versus the possible detrimental effects on semen quality of starting HAART earlier would seem important in this respect. Unfortunately, our research so far does not provide information on which particular HAART regimens have the least toxic effects on semen, and prognostic factors that determine the chance of successful IUI have not been sufficiently evaluated. Therefore, at present HIV-1-infected men with a desire to father a



child may wish to consider completing their family before HAART is initiated, if such delay in starting treatment is acceptable with regard to the prognosis of their own HIV-1 infection.

In our view two issues in the use of assisted reproductive technologies in the setting of HIV deserve priority to be clarified further. First, it is unclear at present which couples benefit from IUI and which couples do not. Also the consequences on IUI outcome of the observed reduction in the percentage of progressively motile spermatozoa during HAART are unknown. We therefore suggest to identify prognostic factors of IUI outcome in HIV-1 infected men, and to adjust assisted reproductive technology protocols accordingly. Second, despite the wide application of ICSI in HIV-1-discordant couples, its safety has not yet been proven. The safety of ICSI is currently being studied in in-vitro studies in the Academic Medical Centre in Amsterdam, the Netherlands. The objectives of this study are to investigate whether human oocytes can be infected via intracytoplasmic injection with HIV-1, and to determine the infection threshold, i.e. how many HIV-1 copies are necessary to accomplish infection of a human oocyte, and to study possible viral replication after injection of a complete virion into an oocyte. If ICSI can be proven safe, semen quality in HIV-1-infected men will become less of an issue.

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