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### Male reproduction and HIV-1 infection

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**Publication date**

2009

**Document Version**

Final published version

[Link to publication](#)

**Citation for published version (APA):**

van Leeuwen, E. (2009). *Male reproduction and HIV-1 infection*. [Thesis, fully internal, Universiteit van Amsterdam].

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# Reproduction and fertility in human immunodeficiency virus type-1 infection

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*Human Reproduction Update 2007;13:197-206*

## Abstract



Human immunodeficiency virus type-1 (HIV-1) affects mostly men and women in their reproductive years. For those who have access to highly active antiretroviral therapy (HAART), the course of HIV-1 infection has shifted from a lethal to a chronic disease. As a result of this, many patients with HIV-1 consider having offspring, as do other patients of reproductive age with chronic illnesses. This article summarizes the current knowledge on the presence of HIV in the male and female genital tract, the effects of HIV-1 infection and HAART on male and female fertility and the results of various assisted reproduction techniques (ART) in HIV-1-infected men and women who wish to have offspring.

## Introduction

At present, over 40 million people are infected with the human immunodeficiency virus type-1 (HIV-1). Most HIV-1 infected men and women are of reproductive age [Joint United Nations Programme on HIV/AIDS (UNAIDS), 2005]. For those who have access to highly active antiretroviral therapy (HAART), the course of HIV-1 has shifted from a lethal to a chronic disease<sup>1,2</sup>. As a result of this, many patients with HIV-1 infection consider having offspring, as do other patients of reproductive age with chronic illnesses<sup>3</sup>.



In couples with one HIV-1-infected partner, that is serodiscordant couples, the uninfected partner is at risk of becoming HIV-1 infected, if trying to conceive naturally. Sexual HIV-1 transmission from men to women seems more likely than vice versa<sup>4</sup>, although some studies claim similar transmission rates<sup>5</sup>. It is therefore generally accepted to advise serodiscordant couples to avoid unprotected intercourse at all times. This artificial sterility implies that serodiscordant couples with an HIV-1-infected man have to rely on assisted reproduction techniques (ART), and serodiscordant couples with an HIV-1-infected woman have to practise self-insemination, if they wish to achieve parenthood.

The purpose of this article is to summarize the current knowledge on HIV in the male and female genital tract, to review the effects of HIV-1 and HAART on male and female fertility and to outline the results of various ART in HIV-infected men and women who wish to have offspring.

## HIV in the male genital tract

The exact origin of HIV-1 in the male genital tract is at present unclear. Histological studies show a loss of testicular germ cells and maturation arrest of spermatozoa during spermatogenesis<sup>6,7</sup>. However, because these studies were performed in men who died of acquired immune deficiency syndrome (AIDS), these data may not be representative for asymptomatic HIV-1 infection.

HIV-1 is present in the semen of asymptomatic HIV-1-infected men as free HIV-1 RNA particles in seminal plasma and as cell-associated virus in non-spermatozoal cells (NSC) such as lymphocytes and macrophages<sup>8</sup>. Most HIV-1 RNA seems to originate from the seminal vesicles and prostate, given that a vasectomy did not influence the concentration of HIV-1

RNA in semen<sup>9,10</sup>. The detection of distinct HIV-1 populations in the epididymis and prostate suggests that HIV-1 particles can be produced locally in the male genital tract<sup>11-13</sup>.



Early studies claimed that HIV-1 DNA was present in spermatozoa and spermatogonial stem cells<sup>14-17</sup>, but later studies have contradicted these findings<sup>18-20</sup>. In addition, the presence of HIV-1 (co)-receptors CD4, CXCR4, and CCR5, necessary for cellular entry of HIV-1, has not been demonstrated on the spermatozoal surface<sup>21</sup>. Therefore, it seems unlikely that spermatozoa are directly infected with HIV-1<sup>18-20</sup>.

Intermittent shedding of HIV-1 RNA is the most common pattern of HIV-1 presence in semen. There are two explanations for this phenomenon. First, the composition of the ejaculate varies between men as well as over time within the same individual. Second, local inflammation may increase HIV-1 RNA levels in semen, independent of HIV-1 RNA concentrations in blood<sup>22,23</sup>.

In untreated HIV-1 infection, the concentration of HIV-1 RNA in semen is on average ~10-fold lower than that in blood plasma. Nevertheless, in some individuals, the HIV-1-RNA concentration in seminal plasma is higher than that in blood plasma<sup>8</sup>. Most antiretrovirals penetrate well into the male genital tract, except for some protease inhibitors<sup>8,24</sup>, and in general, HIV-1 RNA concentrations in blood and seminal plasma show a parallel decrease in response to HAART<sup>25-27</sup>.

However, intermittent shedding leads to occasional discrepancies between HIV-1 RNA in blood and seminal plasma. HIV-1 RNA can be detected in seminal plasma despite adequate suppression of HIV-1 RNA in blood, and HIV-1 RNA can be detected on and off in semen despite stable levels or even undetectable levels of HIV-1 RNA in blood<sup>21,28-33</sup>.

Thus, although of undefined origin, HIV-1 is clearly present in the male genital tract albeit at variable concentration and frequency.

## **HIV and male fertility**

From cross-sectional and case control studies, it appears that, in general, semen parameters are not impaired by asymptomatic HIV-infection<sup>34-36</sup>, although occasionally a reduction in sperm motility and a decrease in the percentage of spermatozoa with normal morphology has been observed<sup>37,38</sup>. The fact that men with and without antiretroviral therapy were analysed

as one group in these studies limits these conclusions. It is therefore unclear whether the observed changes are caused by the HIV-1 infection itself or by the antiretroviral therapy.

A decrease in semen volume and sperm motility was observed in a single semen donor, of whom multiple semen samples were available before and after seroconversion for HIV-1<sup>39</sup>. Obviously, such observations are not available for larger patient numbers.



We have recently completed a longitudinal study describing semen parameters during natural HIV-1 infection, with a follow-up period of 2 years [Pre-congress course on ART and HIV, annual meeting of the European Society of Human Reproduction and Embryology, Prague, Czech Republic, 2006]. The longitudinal study design allowed us to evaluate the effect of ongoing HIV-1 infection on semen parameters. None of the semen parameters changed significantly during a follow-up period of 96 weeks. However, progressive motility was low at all time points, and semen volume was in the lower normal range according to World Health Organization criteria<sup>40</sup>, in agreement with the above-mentioned semen donor. Above 200 cells/mm<sup>3</sup> CD4 counts were not associated with any of the semen parameters studied. Because concern for long-term side effects of antiretroviral therapy has led to postponing start of antiretroviral therapy until CD4 counts drop to 200-350 cells/mm<sup>3</sup><sup>41</sup>, the data of this longitudinal study are reassuring in so far that postponing treatment does not appear to negatively affect semen parameters.

## HAART and male fertility

Data on semen parameters before and after antiretroviral therapy are limited to two studies: semen parameters were normal according to WHO criteria and remained stable after administration of zidovudine (AZT) monotherapy in 5 HIV-1-infected men<sup>35</sup> but improved in 20 men after 4 or 12 weeks of HAART<sup>42</sup>. The observed improvement in the latter study may be because of an improved general health resulting from HAART. The follow-up in this study was too short to evaluate any potential detrimental impact of HAART on spermatogenesis, because a full round of spermatogenesis takes ~ 70 days.

Mitochondria are abundant in spermatozoa and necessary for progressive motility. Deletions in mitochondrial DNA of spermatozoa have been described as a result of antiretroviral therapy<sup>43</sup>. Unfortunately, semen quality parameters were not analysed in this study. Theoretically, penetration of nucleoside reverse transcriptase inhibitors into spermatozoa

or their precursors could result in mitochondrial toxicity and thereby may lead to impaired progressive motility. This hypothesis however remains to be proved.



## HIV in the female genital tract

HIV-1 can be detected in both vaginal and cervical secretions as cell-free virus and also as cell-associated virus<sup>44,45</sup>. Most HIV-1 in the female genital tract arises from the cervix<sup>13</sup>. Blood plasma HIV-1 RNA concentration is the most important predictor for HIV-1 genital shedding<sup>46</sup>, but the use of oral contraceptives, vitamin A deficiency, *Candida albicans* infection and gonorrhoea cervicitis are associated with increased vaginal or cervical shedding of HIV-1<sup>47,48</sup>. Analogous to the male genital tract, HAART results in decreased shedding of HIV-1 in the female genital tract. Despite HAART, HIV-1 RNA was still detected in the genital secretions of 33% of women in whom the blood plasma HIV-1 RNA concentration was <500 copies/ml<sup>46</sup> and in 25% of women with <50 copies/ml. This may explain why the risk of sexual and vertical transmission can be reduced by HAART but never completely eliminated. As a consequence, even during successful HAART, unprotected intercourse should be discouraged at all times.

## HIV and female fertility

Polymenorrhoea and oligomenorrhoea, that is very short menstrual cycles or long menstrual cycles, which are associated with subfertility, are equally prevalent in asymptomatic HIV-1-infected women and in HIV-1-negative controls<sup>49,50</sup>, although more advanced immunodeficiency is associated with menstrual dysfunction<sup>50</sup>. Cohort studies have demonstrated a high prevalence of sexually transmitted diseases (STD) in HIV-1-infected women. These women may therefore also be at risk for tubal infertility<sup>51,52</sup>. Results on the ovarian reserve of HIV-1-infected women are conflicting. Some describe a normal ovarian reserve<sup>53,54</sup>, whereas others claim a higher incidence of severe ovarian dysfunction, that is premature ovarian failure<sup>55,56</sup>.

Case control studies have suggested lower pregnancy rates in HIV-1-infected women when compared with women without HIV-1 infection, irrespective of past or current additional STD<sup>57,58</sup>. Progression of HIV-1 disease resulted in a dramatic decline in pregnancy and live birth rates<sup>59</sup>.

One should realize that most data were generated by studies carried out in Africa, and these data may not reflect the situation elsewhere<sup>54</sup>.

## HAART and female fertility

Data on HAART and fertility in women are limited to one case report <sup>60</sup>. No conclusions are possible at present.



## ART

The purpose of ART in case of HIV-1 infection varies from merely an HIV-1-transmission reduction strategy to a treatment for co-existing subfertility or a combination of both (Table I). Which type of ART to use depends on whether the man is HIV-1 infected or the woman or both.

In serodiscordant couples in which the male partner is HIV-1 infected, high- technology ART is necessary to prevent sexual transmission. This type of ART involves semen processing in such a way that an HIV-1-free spermatozoal fraction is obtained. This HIV-1-free spermatozoal fraction can then be used for intrauterine insemination (IUI), in vitro fertilisation (IVF) or intra cytoplasmatic sperm injection (ICSI).

HIV-1-infected women with an HIV-1 seronegative male partner can practise self-insemination around the time of ovulation at home to conceive without any risk of sexual transmission. If conception does not occur, IUI, IVF or ICSI can be effective to overcome their subfertility, again without any risk of sexual transmission.

When both partners are HIV-1 infected, the reason for ART could be either preventing transmission of discordant HIV-1 strains or subfertility treatment after unsuccessful attempts to conceive normally.

Since the first report on ART and HIV in 1992 <sup>61</sup>, it is increasingly accepted that it is unethical to deny such treatment to HIV-1-infected patients <sup>62-65</sup>. A survey in the United Kingdom revealed that the demand for fertility care in HIV-1-infected couples is high and set to increase <sup>3</sup>.

Recently, a non-profit organization (CREAThE) was founded by European centres providing reproductive assistance to couples with HIV, to obtain a network of hospitals that guarantee the careful evaluation and treatment of couples with HIV-1. Such initiatives will help to formulate guidelines for ART in HIV-1 serodiscordant and seroconcordant couples.



## Serodiscordant couples with an HIV-1-infected male partner



There is no agreement on the optimal method of semen processing in case of an HIV-1-infected man. The goal of semen processing is to separate the spermatozoa from all other semen components and thereby to obtain an HIV-1-free spermatozoal fraction that contains a sufficient amount of morphologically normal spermatozoa with progressive motility. After semen processing, the spermatozoal fraction is tested for the presence of HIV-1 by PCR-based methods. This is a crucial step, because the spermatozoal fraction could still be contaminated with seminal plasma, NSC containing HIV-1 or free virus.

Successful semen processing is defined as a spermatozoal fraction that contains sufficient spermatozoa with a negative (undetectable), valid HIV-1 test. The semen quality, the HIV-1 RNA concentration in semen before processing and the applied laboratory technique determine the success of semen processing<sup>31,32,66</sup>.

HIV-1 could not be detected by PCR in the spermatozoal fraction in 98% of samples of men using HAART and in 82% of men without antiretroviral therapy after semen processing<sup>32</sup>. Therefore, semen processing seems more effective in men using HAART than in men without HAART, but even in men with full suppression of HIV-1 RNA in blood, HIV-1 RNA has been measured in the spermatozoal fraction after semen processing<sup>32</sup>. Double gradient centrifugation followed by swim up is more effective in removing HIV-1 RNA than double gradient centrifugation alone (Table II). Double tube gradient centrifugation seems to be a promising innovation, especially effective in removing high HIV-1 RNA concentrations in semen, but these tubes are not commercially available yet<sup>67</sup>. Most centres use PCR tests that are adapted from commercial PCR kits designed to test for HIV-1 DNA and HIV-1 RNA in blood. Because none of the DNA and RNA tests have been developed solely to test for the presence of HIV in purified spermatozoa, results may differ from one centre to another<sup>68</sup>.

**Table I.** High technology assisted reproduction techniques (ART) in human immunodeficiency virus type-1 (HIV-1) serodiscordant and seroconcordant couples

Man	Woman	Risk for (super)infection partner	HIV semen processing	Primary goal treatment
HIV+	HIV-	Yes	Yes	Prevent HIV-1 transmission
HIV-	HIV+	No	No	Overcome subfertility
HIV+	HIV+	No	No	Overcome subfertility
HIV+	HIV+	Yes	Yes	Prevent HIV-1 transmission

There are several important issues to be considered in PCR testing. First, some test for HIV-1 DNA and HIV-1 RNA, whereas others test only for HIV-1 RNA. An argument against testing for HIV-1 DNA may be that HIV-1 DNA does not necessarily represent infectious virus. HIV-1 DNA may be integrated in the host DNA of a lymphocyte, without the capacity of HIV-1 replication. Second, some groups only test once for the presence of HIV-1 RNA, presuming the presence or absence of HIV-1 RNA in semen is constant over time. Knowing that intermittent shedding of HIV-1 RNA in semen is the most common pattern, this strategy should be advised against. Third, the sensitivity of HIV testing varies from 1 copy HIV-1 RNA to 400 copies and is expressed as either copies per millilitre or copies per  $1 \times 10^6$  spermatozoa (Table II). HIV-1-



**Table II.** Detection of human immunodeficiency virus type-1 (HIV-1) RNA and HIV-1 DNA in processed semen

Publication	Swim up	HIV-1 RNA lower detection limit	HIV-1 DNA lower detection limit	HIV-1 RNA present	HIV-1 DNA present
Marina <i>et al.</i> (1998) <sup>85</sup>	No	200 copies/ml	10 cells	NM	6/107 (6%)
Leruez-Ville <i>et al.</i> (2002) <sup>32</sup>	No	5 copies/ $1 \times 10^6$ spermatozoa	5 copies/ $1 \times 10^6$ spermatozoa	8/125 (6%)	2/125 (2%)
Semprini <i>et al.</i> (1992) <sup>61</sup>	Yes	NM	ND	NM	ND
Lasheeb <i>et al.</i> (1997) <sup>86</sup>	Yes	1 copy/NM	1 copy/NM	0/6	0/6
Chrystie <i>et al.</i> (1998) <sup>87</sup>	Yes	400 copies/ml	ND	4/10 (40%)	ND
Marina <i>et al.</i> (1998) <sup>88</sup>	Yes	200 copies/ml	10 cells	0/1	0/1
Kim <i>et al.</i> (1999) <sup>21</sup>	Yes	40 copies/ $1 \times 10^6$ spermatozoa	1-10 copies	0/11	0/11
Hanabusa <i>et al.</i> (2000) <sup>89</sup>	Yes	50 copies/ml	50 copies/ml	0/12	0/12
Pasquier <i>et al.</i> (2000) <sup>90</sup>	Yes	NM	NM	0/51	0/51
Gilmour <i>et al.</i> (2001) <sup>98</sup>	Yes	400 copies/ $1 \times 10^6$ spermatozoa	1-10 cells	1/60 (2%)	ND
Weigel <i>et al.</i> (2001) <sup>82</sup>	Yes	NM	10 copies/ml	3/80 (4%)	0/80
Bujan <i>et al.</i> (2002) <sup>31</sup>	Yes	NM	NM	0/6	0/6
Meseguer <i>et al.</i> (2002) <sup>91</sup>	Yes	1 copy/NM	1 copy/NM	2/41 (5%)	5/41 (12%)
Kato <i>et al.</i> (2006) <sup>92</sup>	Yes	1 copy/ $8 \times 10^6$ spermatozoa	1 copy/ $8 \times 10^6$ spermatozoa	0/73	0/73

ND, not done; NM, not mentioned.

spiking experiments, that is adding a known amount of HIV-1 virus to spermatozoal fractions containing a variable amount of spermatozoa, revealed that the sensitivity of the HIV-1 PCR depends on the number of spermatozoa in the fraction (unpublished data). Therefore, the test result should preferably be expressed as HIV-1 copies per constant number of spermatozoa instead of per millilitre. Fourth, it is unclear what should be done in the presence of a severe oligozoospermia or azoospermia, when a testicular biopsy is needed. In this case, the number of tested cells may be too limited to guarantee a reliable test result.

Initially, IUI was the favoured ART after semen processing. No seroconversions have been reported since the start of using these techniques (Table III). However, as the natural risk

**Table III.** Results of assisted reproduction techniques (ART) in human immunodeficiency virus type-1 (HIV-1) serodiscordant couples with an HIV-1-infected male partner

Reference	No couples	IUI cycles	IVF cycles	ICSI cycles	Pregnancies	Babies born
Semprini <i>et al.</i> (1992) <sup>61</sup>	29*	59*	-	-	17*	10*
Semprini <i>et al.</i> (1997) <sup>93</sup>	350*	1000*	-	-	200*	NM
Marina <i>et al.</i> (1998) <sup>85</sup>	63	101	-	-	31	37
Marina <i>et al.</i> (1998) <sup>88</sup>	1	-	-	1	1	NM
Tur <i>et al.</i> (1999) <sup>94</sup>	97	155	-	-	32	34
Semprini <i>et al.</i> (1999) <sup>95</sup>	43	-	48	-	13	7
Semprini (2000) <sup>96</sup>	623	1954	-	-	272	242
Loutradis <i>et al.</i> (2001) <sup>97</sup>	2	-	-	2	2	2
Gilmour <i>et al.</i> (2001) <sup>98</sup>	23	56	-	1	11	3
Weigel <i>et al.</i> (2001) <sup>82</sup>	54	101	10	21	30	24
Sauer en Chang (2002) <sup>70</sup>	34*	-	-	55*	25*	25*
Pena <i>et al.</i> (2002) <sup>99</sup>	1	-	-	2	2	2
Ohl <i>et al.</i> (2003) <sup>74</sup>	47	5	-	49	20	14
Pena <i>et al.</i> (2003) <sup>100</sup>	61	-	-	100	35	39
Bujan <i>et al.</i> (2004) <sup>101</sup>	56	213	-	-	37	33
Nicopoulos <i>et al.</i> (2004) <sup>38</sup>	105	133	-	-	25	NM
van Leeuwen <i>et al.</i> (2005) <sup>73</sup>	20	76	-	-	8	10
Kato <i>et al.</i> (2006) <sup>92</sup>	43	-	31	12	20	27
<b>Total</b>	<b>1239</b>	<b>2794</b>	<b>89</b>	<b>188</b>	<b>539</b>	<b>474</b>

IUI, intrauterine insemination; NM, not mentioned.

\*Not considered for the total numbers, because Semprini (2000)<sup>96</sup> and Pena *et al.* (2003)<sup>100</sup> are cumulative reports.

of seroconversion is low, very large numbers are necessary to prove the ultimate safety of these techniques. In fact, the Centers for Disease Control is now running a program to locate women who have undergone any kind of ART with HIV-1 processed semen in the past [Symposium on assisted reproduction of HIV-discordant couples, Annual meeting of the American Society of Reproductive Medicine (ASRM) 2005, no abstract available].



Although IUI with processed and PCR-tested semen is currently still the preferred method in many countries <sup>69</sup>, several groups advocate the use of ICSI instead of IUI <sup>70,71</sup>. Physicians in favour of ICSI argue that by using ICSI one in fact limits the risk of infection, because the amount of semen exposed to the oocyte is extremely low, that is one spermatozoon. However, it is unknown what will happen if one accidentally injects a viral particle directly into a human oocyte. Theoretically, this could result in a new endogenous retrovirus, and/or active production of HIV from the embryo. Scientific data supporting this hypothesis are currently lacking. It is because of this uncertainty that in some countries ICSI is forbidden in HIV-1-infected couples. As a result of the prohibition to use ICSI in case of HIV-1 infection in the Netherlands, more than one-third of the HIV-1-infected men who report to our clinic for ART cannot be treated, because their semen quality is so low that they would require ICSI to achieve pregnancy.

All couples should practise safe sex while being treated with ART, and clinicians should actively enquire about condom accidents. After a reported condom accident, ART should be delayed for 6 months to cover the window of seroconversion for HIV-1 <sup>72</sup>.

Women should have HIV-1 testing after unsuccessful ART and at 4, 12 and 24 weeks amenorrhea, to detect an iatrogenic infection. It is a wise precaution to advise women to have HIV-1 testing throughout the whole pregnancy and post-partum period to detect possible sexual transmission of HIV-1. Although an HIV-1-infected man cannot infect a child directly, in some programs, the child is also tested for HIV-1 after birth <sup>73</sup>.

### **Serodiscordant couples with an HIV-1-infected female partner**

In these couples, pregnancy can be achieved without the risk of sexual transmission by self-insemination. IUI, IVF or ICSI are indicated to overcome subfertility in such a couple. The important question arises whether the ICSI procedure itself increases vertical transmission rates. IUI and IVF seem safe procedures to perform in these women. Although receptors for HIV-1 have not been demonstrated on the surface of the oocyte itself, HIV-1 has been

detected in ovarian follicles. Theoretically, a viral particle could be injected into a human oocyte during an ICSI biopsy, analogous to the situation in an HIV-1-infected man.



There are few data on success rates of IVF/ICSI in HIV-1-infected women. Initially, reduced pregnancy rates were observed after IVF/ICSI in HIV-1-infected women when compared with non-HIV-1-infected women. However, the HIV-1-infected women in these studies were significantly older and had higher FSH levels, indicative of decreased ovarian reserve<sup>74</sup>. The most recent studies report clinical pregnancy rates per initiated cycle varying from 11% to 21% in HIV-1 infected women after IVF or ICSI, compared with 26% clinical pregnancies in matched controls (Table IV).

A lower CD4 count and a high amount of gonadotrophins during ovarian hyperstimulation were negatively associated with reproductive outcome in one of these studies<sup>75</sup>. Because the number of reported IVF and ICSI cycles in HIV-1-infected women is very small, no ultimate conclusion can be drawn from these data (Table IV).

The highest risk of vertical transmission from mother to child is during the third trimester of pregnancy, during delivery and lactation. The vertical transmission risk can be reduced to <1%, with the right precautions and interventions<sup>76</sup>. There is consensus on some measures that have to be taken during pregnancy and post-partum. First, all HIV-1-positive pregnant women are treated with HAART, with the goal to reach undetectable blood plasma HIV-1 RNA levels at the time of delivery. Second, breastfeeding is prohibited, because the HIV-1 transmission risk during lactation is 7-22%<sup>77</sup>. Third, all newborns receive antiretroviral

**Table IV.** IVF/ICSI in human immunodeficiency virus type I (HIV-1)-infected women

Reference	IVF/ICSI	HIV+ women (n)	HIV- women (n)	Cycles HIV+ (n)	Cycles HIV-(n)	HIV+ clinical pregnancies [n(%)]	HIV- clinical pregnancies [n(%)]
Ohl <i>et al.</i> (2005) <sup>102</sup>	IVF/ICSI	36	ND	62	ND	13 (21)	ND
Terriou <i>et al.</i> (2005) <sup>103</sup>	ICSI	29	NM	66	NM	9 (14)	(20)*
Coll <i>et al.</i> (2006) <sup>75</sup>	IVF	35	82	50	100	6 (12)	30 (30) <sup>†</sup>
Martinet <i>et al.</i> (2006) <sup>54</sup>	IVF/ICSI	27	77	27	77	3 (11)	16 (21)
Total		127	159	205	ND	13 (21)	ND

ND, not done; NM, not mentioned.

\*Pregnancy rate per embryo transfer.

<sup>†</sup>Significant result.

treatment for several weeks as a post-exposure prophylaxis. However, some other interventions are still under debate. Most countries have the policy to avoid interventions like an amniocentesis or an instrumental delivery, although others feel that the use of early invasive techniques may be safe <sup>78,79</sup>. In addition, a Caesarean section is advised irrespective of the blood plasma HIV-1 RNA concentration in most industrialized countries <sup>80</sup>, but there is a tendency to accept a vaginal delivery under successful HAART <sup>81</sup>.



There is no consensus on the inclusion criteria for ART in HIV-1-infected women. The inclusion criteria used in the Academic Medical Centre in Amsterdam are summarized in Table V.

Women who are offered ART should be in good clinical condition and need careful evaluation in a centre specialized in HIV, preferably in a team consisting of a gynaecologist, an embryologist, a virologist, an HIV specialist and a social worker. A singleton pregnancy is preferred, because prematurity and other obstetric complications in twins enhance the risk of vertical transmission <sup>82</sup>. HIV testing of the HIV-1 seronegative man is performed during the ART treatment, to confirm his negative HIV-1 sero-status. HIV-1 testing of the man during follow-up is not necessary, because HIV-1 infection can never be the result of ART.

**Table V.** Inclusion criteria for assisted reproduction techniques (ART) in human immunodeficiency virus type 1 (HIV-1)-infected women in the Academic Medical Centre in Amsterdam

Age <43 years
An irregular menstruation cycle or unsuccessful self-insemination after 1 year in a regular menstruation cycle
Health care insurance
HAART
At least 6 months CD4 >300 cells/mm <sup>3</sup> and blood plasma HIV-1 RNA <50 copies/ml
At least 12 months no CDC-C events
No teratogenic medication
No HAART (because of sufficient clinical condition)
At least 6 months CD4 counts >350 cells/mm <sup>3</sup> irrespective of blood plasma HIV-1 RNA concentration

HAART, highly active antiretroviral therapy.

## Seroconcordant HIV-positive couples



Seroconcordant couples are treated in some centres, but these data have not been evaluated separately from those of the serodiscordant couples with an HIV-1-infected woman. The ESHRE advises against ART in case of HIV-1 infection of both partners, because of the possibility of an untimely death from HIV disease of both future parents, leaving an orphaned child<sup>83</sup>. Not everyone agrees with this viewpoint, but at least these issues should be discussed with the couple.

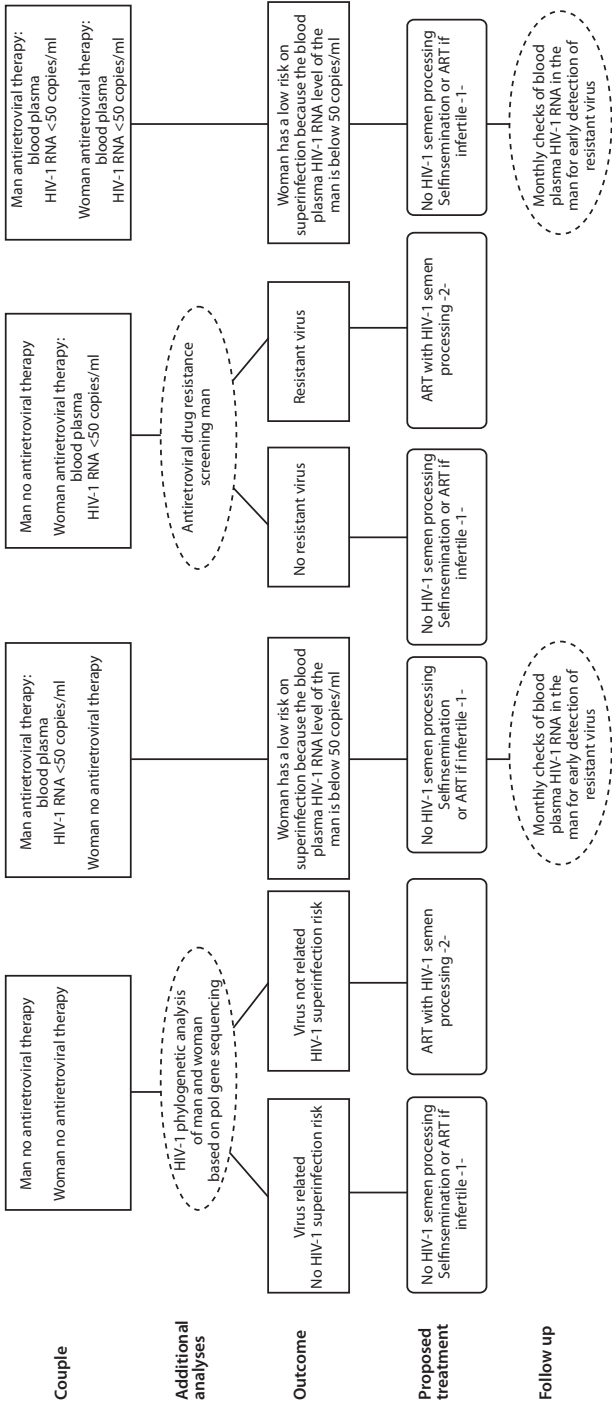
Therefore, it is important to realize that most seroconcordant couples can practice self-insemination, but HIV-1 superinfection of the woman might occur and can possibly enhance disease progression, although data are scarce<sup>84</sup>. For this reason, some clinics, including ours, do offer ART to these couples regardless of the ESHRE guidelines<sup>54</sup>. An algorithm was designed in our clinic to warrant the careful evaluation of seroconcordant couples (Figure I). In this algorithm, three assumptions were made: possible health loss in case of superinfection with a discordant HIV-1 strain is less harmful than a seronegative woman becoming HIV-1 infected, no precautions are necessary when both partners are infected with the same viral strain and both do not receive treatment, and the risk of HIV-1 superinfection is low at blood plasma HIV-1 RNA levels in the male partner below 50 copies/ml. Regular determination of blood plasma HIV-1 RNA concentration in a male treated partner is necessary to ensure that no resistant strains develop that will make semen processing necessary. Semen processing is always advised when resistant virus is present, because HAART options could be limited if this virus is transmitted. Formally, self-insemination will be the advice instead of unprotected intercourse, because this eliminates the risk of superinfection of the man.

The female partner on HAART also undergoes regular determination of the blood plasma HIV-1 RNA concentration, to ensure that antiretroviral resistance does not develop during conception or early pregnancy.

## Conclusion

In infected individuals, HIV-1 is intermittently present in the male and female genital tract at variable concentrations.

Semen parameters are stable in asymptomatic HIV-1-infected men without antiretroviral therapy, but spontaneous pregnancy rates seem to be reduced in HIV-1-infected women



-1- For all couples the formal advice is selfinsemination instead of unprotected intercourse to prevent HIV-1 superinfection of male partner.  
 -2- HIV semen processing is desired in case of discordant HIV-1 strains, in the presence of proven resistant virus in the male partner or when blood plasma HIV-1 RNA levels are detectable under antiretroviral therapy in the male partner.

**Figure i:** Flow chart clinical decision in ART in seroconcordant couples in the Academical Medical Centre in Amsterdam



when compared with HIV-1-negative women. The long-term effects of antiretroviral therapy on male and female fertility are unknown.



HIV-1-infected patients desiring offspring can opt for several modes of reproduction, including various ART. Although ART with semen processing is effective by means of generating pregnancies and has been performed in HIV-1-infected couples since the early 1990s without any reported seroconversion, more data are needed to prove its ultimate safety. Data on ART in HIV-infected women are scarce. More data should be generated on ART in HIV-infected women and prognostic factors on ART outcome of both HIV-1-infected men and women need to be identified.

## Acknowledgements

This research has been funded by grant number 7003 from AIDS Fonds Netherlands, which is a non-profit charity organization. The funding source had no influence on the analysis of the data or on the content of the manuscript.

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