

# Lower endometrial receptivity in HIV-infected women receiving oocyte donation: a comorbidity of HIV infection?

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**STUDY QUESTION:** Are the reproductive outcomes of HIV-infected donor oocyte recipient women comparable to those of non-infected women?

**SUMMARY ANSWER:** HIV-infected women have lower clinical pregnancy and live birth rates than non-infected women.

**WHAT IS ALREADY KNOWN:** The literature on the effect of HIV infection on reproductive outcome is scarce at best; the only report to date comparing oocyte donation cycles in HIV-infected women versus non-infected controls found no differences in pregnancy rates between the two groups. However, this study was performed nearly a decade ago and did not evaluate the effect of immuno-virological characteristics of oocyte recipients or the HIV antiretroviral therapy effect.

**STUDY DESIGN SIZE, AND DURATION:** This is a matched-cohort study including 514 oocyte donation cycles, 257 from HIV-infected women and 257 non-infected controls, performed between April 2004 and November 2014.

**PARTICIPANTS/MATERIALS, SETTING, AND METHOD:** Each cycle of an HIV-infected woman ( $n = 257$ ) was matched with a cycle of a non-infected woman (1:1). Biochemical pregnancy, clinical pregnancy, ongoing pregnancy and live birth in the two groups were compared using a multivariate logistic regression analysis. The effect of antiretroviral treatment options on pregnancy outcomes of HIV-infected women was analyzed using a logistic regression model adjusted for time elapsed from diagnosis, and CD4 levels and viral load prior to embryo transfer.

**MAIN RESULTS AND THE ROLE OF CHANCE:** Cycles of HIV-infected patients receiving oocyte donation presented lower pregnancy and live birth rates than matched non-infected controls. Treatment options and infection parameters analyzed do not seem to affect the reproductive results in HIV-infected women. The variable most influencing pregnancy outcomes was the number of transferred embryos; lower pregnancy rates were obtained after single embryo transfer.

**LIMITATIONS REASONS FOR CAUTION:** Patients with HIV infection have specific health issues, such as infection/treatment side effects, which makes it impossible to find a matching control group of non-infected patients for these variables.

**WIDER IMPLICATIONS OF THE FINDINGS:** HIV-infected women receiving donated oocytes present lower pregnancy rates when compared to non-infected controls, regardless of the antiretroviral treatment followed. The complexity of the treatments (both in medication types and combinations) makes it difficult to define whether any one treatment option is better than the others in terms of pregnancy outcomes in oocyte recipients.

**STUDY FUNDING/COMPETING INTERESTS:** None.

**TRIAL REGISTRATION NUMBER:** Not applicable.

**Key words:** HIV / IVF / oocyte donation / antiretroviral treatment / AIDS

## WHAT DOES THIS MEAN FOR PATIENTS?

This article investigates whether women who are HIV positive are less likely to get pregnant and have a baby after egg donation. Studies in the past have found that fertility treatment is not as successful in women who are HIV positive, and it was thought that HIV might have an impact on egg quality. Focusing on women using donated eggs would rule this out as a possible cause.

The researchers compared the treatment outcomes for a group of HIV positive women going through egg donation with a group of others who were not infected. They found that both pregnancy rates and live birth rates were lower in the group of HIV positive women after egg donation. There were no differences relating to the type of HIV treatment the women were having, how long they'd been diagnosed or the level of the HIV virus in their bodies. The team noted that having a single embryo transferred during treatment had more of a negative impact on outcomes in women who were HIV positive than in the group who were not infected.

The researchers suggest that the womb lining may be less receptive in women who are HIV positive, but say that more research is needed.

## Introduction

According to United Nations & Acquired Immune Deficiency Syndrome (UNAIDS), the AIDS epidemic has infected more than 78 million people with HIV, leaving 39 million dead (UNAIDS, 2014). The infection affects people of all ages although it is especially frequent (86%) in individuals of reproductive age (Ethics Committee of the American Society for Reproductive Medicine. Electronic address, 2015). Owing to the introduction of antiretroviral treatment the prognosis of HIV-infected people has improved, and currently the infection often leads to a chronic disease. Furthermore, improved obstetric management has diminished significantly mother-to-child transmissions (Townsend et al., 2008). Improved prognosis, together with very low toxicity of antiretroviral treatment on the offspring (Sperling et al., 1998; Culnane et al., 1999; Hanson et al., 1999; Registry, 2013), has enabled HIV-infected women to pursue motherhood.

Women infected with HIV have lower birth rates (Massad et al., 2004; Ross et al., 2004; Hunter et al., 2003; Lewis et al., 2004; Thackway et al., 1997; Gray et al., 1998). This could be due to the effect of the infection itself, the decrease of intercourse frequency after an HIV diagnosis, or the use of contraception in order to protect the partner from infection. As a consequence, changes in sexual behavior after diagnosis hinder the reliable study of natural fertility in this group (Wekesa and Coast, 2013).

ART could offer insights into the effect of HIV infection and antiretroviral treatment on female fertility. Several groups reported lower pregnancy rates after ART in HIV-infected women (Ohl et al., 2003; Terriou et al., 2005; Coll et al., 2006), however, others reported lower pregnancy rates in women older than 35 years but not in younger ones (Nurudeen et al., 2013). More recent studies found similar implantation and pregnancy rates compared to uninfected controls (Douglas et al., 2009; Prisant et al., 2010; Santulli et al., 2011; Nurudeen et al., 2013).

The cause of the lower pregnancy rates in HIV-infected women is not clear: HIV infection and/or the use of antiretroviral drugs have been related to disturbances of menstrual cycle length (Hinz et al., 2002), while antiretroviral treatments of the nucleotide reverse transcriptase inhibitors (NRTIs) family are toxic to mitochondria (Dalakas

et al., 1990; Arnaudo et al., 1991; Kohler and Lewis, 2007). Mitochondrial DNA content has been reported to be altered in HIV patients and this depletion was higher in those HIV-infected women who did not get pregnant (Lopez et al., 2008; Reynier et al., 2001). Finally, it is unclear whether the infection and antiretroviral treatments have an effect on the endometrial receptivity as it is impossible in patients to separate the quality of the oocytes from the endometrial state when analyzing pregnancy outcomes.

The oocyte donation model, where HIV-infected women receive oocytes from uninfected donors, allows dissociating the HIV infection/treatment effects on the female gamete from those on the endometrial milieu. We present here an evaluation of endometrial fitness in HIV-infected women, by comparing the reproductive outcomes between HIV-infected women who received oocyte donation and non-infected controls; in addition, we assess the potential impact of the immuno-virological characteristics and antiretroviral treatment on reproductive results.

## Materials and Methods

### Study design and ethical considerations

This is a retrospective matched-cohort study including all oocyte donation cycles of HIV-infected recipients performed between April 2004 and November 2014. Each cycle of an HIV-infected woman ( $n = 257$ ) was matched 1:1 with the cycle of a non-infected woman by: age of recipient ( $\pm 0.5$  years), ethnicity (1:1, since African women have lower pregnancy rates after IVF) (Bodri et al., 2010; McQueen et al., 2015), and embryo transfer day (closest date). All transfers included were fresh embryo transfers. In total, 514 cycles of 450 women (197 HIV-infected and 253 not infected) were analyzed. Permission to conduct the study was sought and obtained from the local Institutional Review Board.

### Oocyte donors

All oocyte donors were healthy women aged between 18 and 35 years. Controlled ovarian stimulation was performed using recombinant FSH or highly purified hMG (Gonal-F, Serono, Madrid, Spain; Menopur Ferring Pharmaceuticals, Madrid, Spain, respectively) and GnRH antagonist

(Cetrotide, Merck Serono, Madrid, Spain; Orgalutran, Merck Sharp & Dohme, Madrid, Spain) for hypophysary suppression. Oocyte retrieval was performed 36 h after the administration of 0.2 or 0.3 mg of GnRH agonist (Triptoreline, Decapeptyl; Ipsen Pharma, Madrid, Spain).

## Oocyte recipients

HIV-infected women had to be under active care of an infectious disease specialist, and a report from the specialist describing time from diagnosis, historical and current antiretroviral therapy demonstrating stable and preferably undetectable viral load was requested. CD4 counts of >200 cells/mm<sup>3</sup> were required. Before initiating the reproductive cycle, the infectious disease specialist had to approve assisted reproduction treatment. The majority of patients followed an antiretroviral treatment regime, which could include protease inhibitors (PI), NRTI and a non-nucleoside reverse transcriptase inhibitors (NNRTI), either individually or in combination. Some patients accepted for oocyte reception did not require antiretroviral treatment. Indication for an oocyte donation cycle was independent from the woman's HIV serological state. Before treatment, all recipients underwent a routine gynecological examination, Pap smear and blood tests. In addition, the uterine cavity was evaluated by pelvic ultrasound, hysteroscopy or hysterosalpingography. The recipient endometrium was prepared for embryo transfer with estradiol valerate, either orally (6 mg/24 h) or transdermally (150 µg every 3 days) in either a constant or progressively increasing dose. Furthermore, progesterone (800 mg daily, vaginally) was administered from the day of ICSI combined with estradiol valerate supplementation for 70 days if the patient was pregnant.

## Insemination and embryo development

As per the clinic standard protocol, all oocytes were inseminated by ICSI. Fresh or frozen sperm samples have been used depending on sperm quality and/or based on international patient's ability to be at the clinic on the day of donor oocytes fertilization. Sperm from either the male partner or an anonymous donor have been used in the reported cycles. In the cases where the male partner was HIV-infected, an extended sperm wash with triple gradient was performed, coupled with extensive centrifugations. Finally, one to three embryos were transferred at either cleavage or blastocyst stage.

## Reproductive outcomes

Reproductive outcomes recorded were: biochemical pregnancy (a positive β-HCG level in serum 14 days after embryo transfer), clinical pregnancy (the presence of one or more intrauterine sacs 5 weeks after embryo transfer), ongoing pregnancy 12th week of gestation and live birth.

## Statistical analysis

Differences in reproductive outcomes between HIV-infected and non-infected women were tested by Pearson's  $\chi^2$  test. The effect of antiretroviral treatment options (therapies with and without PIs, versus antiretroviral-naïve) on reproductive outcomes was analyzed by multivariable logistic regression, where immuno-virological characteristics (time elapsed from diagnosis, CD4 levels, and viral load prior to embryo transfer), day of embryo transfer (4 or 5 versus 2 or 3), semen status (fresh/frozen) and number of transferred embryos (1 versus 2 or 3) were covariates.

A multilevel (level 1: women; level 2: cycle) logistic regression was additionally constructed (Serban *et al.*, 2013). To overcome the potential biases of including non-independent observations, such as in repeated cycles in the same woman, a multilevel analysis decomposing total variance was performed. The significance of the regression coefficients were tested by Student's *t*-tests (with the *n*-2 as degrees of freedom). The Statistical Package for the Social Sciences (SPSS version 22.0, IBM, USA) was used

for the statistical analysis. Multilevel modeling was performed with MLWin 2.3.1 (University of Bristol, UK) (Rasbash *et al.*, 2012). A *P* value of < 0.05 was set as statistically significant for all analyses.

## Results

### Cohort characteristics

Demographic characteristics of the 514 cycles of infected and non-infected patients are presented in Table I. The distribution of cases with sperm from donor, testicular biopsy, number of embryos and day of embryo transfer between the HIV-infected and control group were similar between the two study groups. Only frequency of frozen sperm and HIV-infected partner were statistically different between groups. In the group of HIV-infected women, 47 male partners were HIV-infected (18.3%); of these, 46 couples (97.9%) underwent the ICSI cycle with partner sperm.

### Reproductive outcomes

Biochemical pregnancy rate was lower among HIV-infected women than in controls (37.0 versus 46.3%; *P* = 0.032). The same decline was observed in clinical (30.6 versus 40.2%; *P* = 0.023), ongoing (24.4

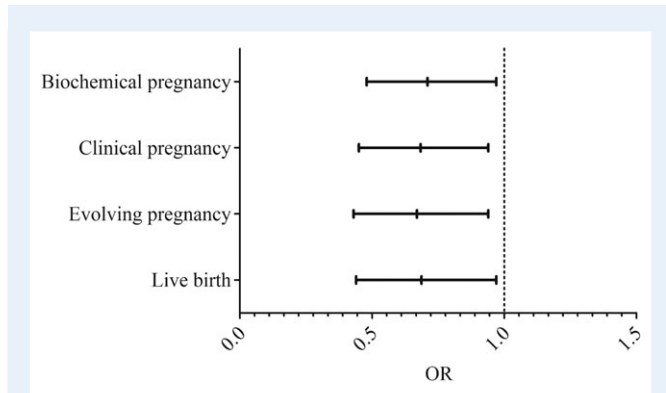
**Table I** Demographic characteristics of participants by study group.

	HIV-infected <i>n</i> = 257	HIV non infect <i>n</i> = 257	<i>P</i> -value*
Ethnicity, <i>n</i> (%)			
African or Caribbean	120 (46.7)	119 (46.3)	0.996
Caucasian	134 (52.1)	135 (52.5)	
Other	3 (1.2)	3 (1.2)	
Woman age (years), mean (SD)	42.3 (4.2)	42.6 (4.1)	0.330
Partner age (years), mean (SD)	45.4 (7.8)	45.4 (7.8)	0.052
BMI (kg/m <sup>2</sup> ), mean (SD)	24.2 (4.1)	24.1 (4.5)	0.954
Sperm origin, <i>n</i> (%)			
Partner	219 (88.3)	231 (89.9)	0.848
Donor	28 (11.3)	25 (9.7)	
Testicular biopsy	1 (0.4)	1 (0.4)	
Sperm status, <i>n</i> (%)			
Fresh	80 (31.1)	58 (22.6)	0.014
Frozen	167 (65.0)	198 (77)	
Transferred embryos, mean (SD)			
1	24 (9.3)	14 (5.4)	0.053
2	226 (87.9)	241 (93.8)	
3	7 (2.7)	2 (0.8)	
Day of embryo transfer, <i>n</i> (%)			
2	122 (47.5)	132 (51.4)	0.660
3	121 (47.1)	116 (45.1)	
4	5 (1.9)	3 (1.2)	
5	9 (3.5)	6 (2.3)	
Positive HIV men, <i>n</i> (%)	47 (18.3)	0 (0.0)	<0.001

\*Student's *t*-test or  $\chi^2$  test as appropriate.

versus 33.6%;  $P = 0.022$ ), and live birth rate (23.4 versus 31.9%;  $P = 0.034$ ). The odds ratios (ORs) for each pregnancy outcome are represented in Figure 1. The implantation rate was also lower in the study group (21 versus 27%;  $P = 0.027$ ). When comparing the reproductive

results of HIV-infected women by the HIV status of the male partner, we observed higher pregnancy rates when both partners were HIV-infected as opposed to the woman only being infected (biochemical pregnancy rate: 46.8 versus 34.6%,  $P = 0.12$ ; clinical pregnancy rate: 43.5 versus 27.5%,  $P = 0.034$ ; ongoing pregnancy rate: 39.1 versus 21.4%,  $P = 0.011$ ; live birth 37.0 versus 20.6%,  $P = 0.018$ ).



**Figure 1** Odds ratio for pregnancy outcomes in HIV-infected women. OR: odds ratio; biochemical pregnancy: a positive  $\beta$ -HCG level in serum 14 days after embryo transfer; clinical pregnancy: the presence of one or more intrauterine sacs 5 weeks after embryo transfer; evolving pregnancy: 12th week of gestation, and live birth.

## Immuno-virological characteristics and treatment of HIV-infected women

In 205 out of 257 (79.8%) HIV-infected women, HIV viral load was undetectable at the time of treatment; in the 52 women with detectable viral load, the median was 1297 copies/ml (interquartile range: 10 626; Table II). Mean CD4 count was 626 cells/mm<sup>3</sup> (SD: 277.2). Detailed data by reproductive outcome are presented in Table II. Antiretroviral treatment combining NRTI with PI was the most commonly used treatment both during the course of infection (35.8%) and during the ART (49.8%; Table II).

## Relationship between HIV infection, treatment and reproductive outcomes

Time from diagnosis, CD4 levels, viral load and type of antiretroviral treatment just before embryo transfer were not related to reproductive

**Table II** Immuno-virological characteristics and treatment of HIV-infected women, overall and by reproductive outcome (biochemical pregnancy).

	Total <i>n</i> = 257	Pregnant ( <i>n</i> = 95)	Not pregnant ( <i>n</i> = 162)
Time elapsed from diagnosis (months), mean (SD)	146.5 (71.4)	151.2 (69.5)	143.8 (72.6)
Undetectable VL prior to ET, <i>n</i> (%)	205 (79.8)	77 (81.1)	128 (79.0)
VL among women with Detectable VL, median (IQR)	1297 (10626)	1240 (10098)	1297 (11786)
CD4 T cell count prior to ET, mean (SD)	626.1 (277.2)	636.4 (307.7)	620.1 (258.8)
Past treatment			
Naïve, <i>n</i> (%)	28 (10.9)	10 (10.5)	18 (11.1)
NRTI, <i>n</i> (%)	3 (1.2)	1 (1.1)	2 (1.2)
NRTI + PI, <i>n</i> (%)	92 (35.8)	34 (35.8)	58 (35.8)
NNRTI + PI, <i>n</i> (%)	6 (2.3)	2 (2.1)	4 (2.5)
NRTI + NNRTI, <i>n</i> (%)	33 (12.8)	13 (13.7)	20 (12.3)
NRTI + NNRTI + PI, <i>n</i> (%)	62 (24.1)	20 (21.1)	42 (25.9)
PI, <i>n</i> (%)	1 (0.4)	1 (1.1)	0 (0)
Current treatment			
Naïve, <i>n</i> (%)	31 (12.1)	11 (11.6)	20 (12.3)
NRTI, <i>n</i> (%)	9 (3.5)	3 (3.2)	6 (3.7)
NRTI + PI, <i>n</i> (%)	128 (49.8)	43 (45.3)	85 (52.5)
NNRTI + PI, <i>n</i> (%)	6 (2.3)	2 (2.1)	4 (2.5)
NRTI + NNRTI, <i>n</i> (%)	52 (20.2)	22 (23.2)	30 (18.5)
NRTI + NNRTI + PI, <i>n</i> (%)	8 (3.1)	3 (3.2)	5 (3.1)
PI, <i>n</i> (%)	5 (1.9)	3 (3.2)	2 (1.2)

VL: viral load.

NRTI: nucleotide reverse transcriptase inhibitors.

NNRTI: non-nucleoside reverse transcriptase inhibitors.

PI: protease inhibitors.

**Table III** Effect of immuno-virological characteristics and treatment on pregnancy outcomes.

	OR	95% CI inferior	95% CI superior	P <sup>a</sup>
Biochemical pregnancy				
Treatment without PI versus naïve	1.06	0.33	3.37	0.92
Treatment with PI versus naïve	0.90	0.30	3.37	0.85
Infection duration from diagnosis (log)	0.89	0.27	2.78	0.84
CD4 prior to ET (log)	0.95	0.19	1.86	0.95
Positive viral load prior to ET	0.74	0.29	1.86	0.52
Frozen sperm	1.17	0.63	2.18	0.61
ET of 1 embryo versus 2 or 3	0.51	0.27	0.95	0.035
ET Day 4 or 5 versus 2 or 3	4.31	0.78	23.93	0.10
Clinical pregnancy				
Treatment without PI versus naïve	1.07	0.33	3.50	0.91
Treatment with PI versus naïve	1.07	0.35	3.26	0.91
Infection duration from diagnosis (log)	0.90	0.28	2.89	0.85
CD4 prior to ET (log)	0.94	0.18	4.88	0.94
Positive viral load prior to ET	1.12	0.44	2.83	0.85
Frozen sperm	1.03	0.54	1.97	0.92
ET of 1 embryo versus 2 or 3	0.45	0.21	0.95	0.036
ET Day 4 or 5 versus 2 or 3	2.73	0.57	13.17	0.21
Ongoing pregnancy				
Treatment without PI versus naïve	0.86	0.24	3.07	0.81
Treatment with PI versus naïve	0.86	0.26	2.87	0.81
Infection duration from diagnosis (log)	0.79	0.23	2.76	0.72
CD4 prior to ET (log)	0.74	0.12	4.47	0.75
Positive viral load prior to ET	0.85	0.30	2.40	0.76
Frozen sperm	0.81	0.40	1.65	0.56
ET of 1 embryo versus 2 or 3	0.37	0.13	1.03	0.06
ET Day 4 or 5 versus 2 or 3	2.23	0.45	10.89	0.32
Live birth				
Treatment without PI versus naïve	1.05	0.28	3.91	0.95
Treatment with PI versus naïve	1.00	0.29	3.50	1.00
Infection duration from diagnosis (log)	0.65	0.18	2.30	0.50
CD4 prior to ET (log)	0.68	0.11	4.25	0.68
Positive viral load prior to ET	0.80	0.28	2.32	0.68
Frozen sperm	0.91	0.44	1.87	0.80
ET of 1 embryo versus 2 or 3	0.39	0.14	1.07	0.07
ET Day 4 or 5 versus 2 or 3	2.60	0.53	12.80	0.24

<sup>a</sup>Multivariate logistic regression.

outcome (Table III). When antiretroviral treatment was analyzed, we found no difference in reproductive outcomes when the treatment included a PI: biochemical pregnancy (OR = 0.9; 95% CI: 0.3, 0.37;  $P = 0.85$ ), clinical pregnancy (OR = 1.1; 95% CI: 0.4, 3.3;  $P = 0.91$ ), ongoing pregnancy (OR = 0.9; 95% CI: 0.3, 3.2;  $P = 0.81$ ) or live birth (OR = 1.1; 95% CI: 0.3, 3.5;  $P = 1$ ), or when the treatment did not: biochemical pregnancy (OR = 1.1; 95% CI: 0.33, 3.4;  $P = 0.92$ ), clinical pregnancy (OR = 1.07; 95% CI: 0.3, 3.5;  $P = 0.91$ ) ongoing pregnancy (OR = 0.9; 95% CI: 0.2, 3.1;  $P = 0.81$ ) or live birth (OR = 1.1; 95% CI: 0.3, 4.0;  $P = 0.95$ ), versus antiretroviral-naïve individuals.

The multivariable analysis of the embryo transfer day did not show significant differences in reproductive outcomes. However, the number of embryos transferred did affect reproductive results; biochemical (OR = 0.5; 95% CI: 0.3, 0.9;  $P = 0.025$ ) and clinical pregnancy (OR = 0.4; 95% CI: 0.2, 0.9;  $P = 0.032$ ), were statistically significant higher when 2 or 3 embryos were transferred versus 1. However, possibly owing to a small sample size, the effect of single embryo transfer only reached a borderline significant effect for ongoing pregnancy (OR = 0.4; 95% CI: 0.1, 1.0;  $P = 0.05$ ) and a marginally significant effect for live birth (OR = 0.4; 95% CI: 0.1, 1.0;  $P = 0.06$ ) (Table III).

The multilevel analysis accounting for the inclusion of more than one cycle of the same woman indicated that treatment options and infection parameters did not affect the reproductive results in HIV-infected women. Again, the variable most influencing pregnancy outcomes was the number of transferred embryos. In this analysis single embryo transfer significantly lowered pregnancy and live birth rates. Embryo transfer day showed a borderline significant effect ( $P = 0.05$ ) on biochemical pregnancy and a marginal significant effect on live birth ( $P = 0.07$ ) (Table IV).

## Discussion

We found that reproductive outcomes of HIV-infected women using oocytes from a healthy, uninfected donor remain lower than those of matched uninfected women also using donor oocytes for assisted reproduction. ART in HIV-infected women using their own oocytes yield lower pregnancy rates; this has been related to a likely lower developmental competence of the oocyte itself (Ohl et al., 2003; Coll et al., 2006). In oocyte donation cycles, oocyte quality is homogeneously high, and since oocyte quality is a major determinant of pregnancy success, we expected to see a full recovery of pregnancy rates in these patients. Interestingly, we found lower pregnancy rates in HIV-infected women using this technique too. Among the possible explanations for these outcomes, we can hypothesize an HIV infection/treatment effect on the embryo that has been transferred, and on endometrial receptivity.

After transfer, the embryo must develop precise biochemical signals with the endometrium in order to implant, however, it is difficult to imagine a strong effect of the HIV infection and/or antiretroviral treatment on early pregnancy given the protective effect of the zona pellucida, and the self organizing nature of early embryonic development (Shahbazi et al., 2016). We initially hypothesized that the longer the patient has been in contact with the HIV virus, the higher the impact on the uterine environment, and therefore the lower the pregnancy or implantation rate. However, we did not find any relationship between duration of infection and reproductive outcomes. Lower pregnancy rates in HIV-infected women who undergo ART with their own oocytes have been linked to lower CD4 levels (Coll et al., 2006), however, in our study we have not found an effect of CD4 levels on HIV-infected recipients and pregnancy rate. Moreover, antiretroviral treatment and levels of viral load prior to embryo transfer did not affect the results either. One possible reason for this lack of effect could be that physicians are wary to prescribe newer drugs to women trying to become pregnant, given the comparatively limited experience with regard to teratogenesis and obstetrical complications. A possible explanation for our results could be that there is an effect of HIV infection/treatment on both oocyte quality and endometrial health. The effect on oocyte quality is more pronounced and more readily seen, so much so that the endometrial effect only becomes apparent when the oocyte factor is eliminated, such as in oocyte donation cycles. The most important predictor of pregnancy and live birth was the number of embryos transferred.

We have found that one of the factors more highly predictive of pregnancy and live birth was the number of embryos transferred; this is an important finding that should be taken into account when discussing the number of embryos to transfer, together with the fact that implantation rate was lower among HIV-infected women overall.

**Table IV** Reproductive results in HIV-infected women. Multilevel analysis.

	Biochemical pregnancy				Clinical pregnancy				Ongoing pregnancy				Live birth			
	OR	Lower 95% CI	Upper 95% CI	P	OR	Lower 95% CI	Upper 95% CI	P	OR	Lower 95% CI	Upper 95% CI	P	OR	Lower 95% CI	Upper 95% CI	P
Frozen sperm	1.46	0.77	2.77	0.25	1.22	0.64	2.33	0.55	0.87	0.42	1.82	0.71	0.99	0.47	2.09	0.97
ET of 2 or 3 embryo versus 1	6.85	1.51	31.16	0.014	5.14	1.15	22.93	0.033	7.39	0.95	57.75	0.06	6.99	0.89	54.71	0.07
ET Day 4 or 5 versus 2 or 3	3.94	0.98	15.86	0.05	2.97	0.80	11.08	0.11	2.98	0.78	11.37	0.11	3.51	0.91	13.56	0.07
Infection duration from diagnosis (log)	0.96	0.58	1.59	0.88	0.98	0.59	1.63	0.94	0.94	0.54	1.62	0.81	0.86	0.49	1.50	0.60
CD4 prior to ET (log)	0.91	0.44	1.87	0.80	0.90	0.44	1.86	0.78	0.81	0.37	1.81	0.61	0.78	0.34	1.75	0.54
Positive viral load prior to ET	0.75	0.29	1.92	0.54	1.11	0.44	2.81	0.82	0.85	0.30	2.43	0.76	0.79	0.27	2.34	0.67
Treatment without PI versus naïve	1.10	0.34	3.64	0.87	1.07	0.32	3.56	0.91	0.87	0.23	3.25	0.84	1.09	0.28	4.26	0.90
Treatment with PI versus naïve	0.89	0.29	2.73	0.83	1.07	0.35	3.27	0.91	0.86	0.25	2.97	0.82	1.02	0.28	3.69	0.98
Units: women	161				162				163				164			
Units: cycles	208				210				211				212			



HIV-infected women present a higher rate of prematurity (Lopez *et al.*, 2012), and an increase of materno-fetal transmission with extended labors after membrane rupture (Garcia-Tejedor *et al.*, 2003), therefore, it would be recommended to decrease the risk of prematurity in HIV-infected women by limiting the probability of carrying twins, and ideally only one embryo should be transferred (Sunderam *et al.*, 2013). However, given the lower reproductive outcomes and lower implantation rate in this population, the number of embryos recommended for transfer in HIV-infected women remains under discussion.

Contemporary care of HIV-infected patients has changed and the knowledge and management of co-morbidities is important in this population. There is increasing attention on diseases that affect cardiovascular, mental and reproductive health. HIV infection is associated with inflammation, altered coagulation, monocyte activation (Sandler *et al.*, 2011; Neuhaus *et al.*, 2010) and elevated interleukin-6 and D-dimer. HIV infection leads to a chronic systemic inflammatory process, which is increasingly accepted as having an important role in the pathogenesis of arteriosclerosis and acute cardiovascular events. HIV patients present unique histological features of coronary artery disease, including a rapid progression of smooth muscle cells, elastic fibers and endoluminal protrusions (Neto *et al.*, 2013). Although data are lacking in this regard, we hypothesize that the inflammatory process could affect endometrial vascularization, modifying endometrial receptivity and decreasing reproductive outcomes. We posit that the lower endometrial receptivity found in our study could be a new comorbidity not described in the literature, and further studies should assess potential direct or indirect factors that may impact endometrial health.

Implantation is the key to human reproduction. As implantation rates are lower in HIV-infected women, even after the transfer of embryos unexposed to HIV, we might hypothesize that an alteration in the implantation process, even though it might lead to a viable pregnancy, could also be linked to complications at later stages of pregnancy, in agreement with the observation that HIV-infected women also present a higher rate of growth retardation, pre-eclampsia and fetal death (European Collaborative *et al.*, 2000; Suy *et al.*, 2006).

According to our results, this comorbidity could be related to the infection itself because we have found no relation between treatment and lower reproductive outcomes, indicating that modifying the treatment might not solve the problem.

A more thorough comparative analysis of our results remains difficult owing to the very scarce literature available on the topic, with just one reported study analyzing a matched and controlled population, albeit with a smaller sample size ( $n = 116$  oocyte donation cycles) (Coll *et al.*, 2006), while other reports are mostly isolated cases (Manigart *et al.*, 2006; Douglas *et al.*, 2009; Nurudeen *et al.*, 2013). Further studies should be aimed at understanding the effect of chronic systemic inflammation and antiretroviral treatment on pregnancy rates and implantation, and how it impacts obstetrical management. Given the lower reproductive results presented by HIV-infected women overall, fertility preservation (such as oocyte vitrification) in these women early on in the infection might be a tool to preserve as much as possible the competence of their oocytes, thus increasing the probability of pregnancy in an already compromised endometrial environment.

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## Authors' roles

D.M.: study design, data analysis and article preparation. D.G.: study design, statistical analysis and article preparation. O.C.: expert knowledge article revision and final approval. R.V.: study design and supervision, expert knowledge, article revision and final approval. A.R.: article revision and final approval.

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## Conflict of interest

None to report.

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