Comparison of in vitro fertilization cycles in couples with human immunodeficiency virus type 1 infection versus noninfected couples through a retrospective matched case-control study

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Objective: To compare in vitro fertilization (IVF) outcomes in couples in which at least one partner is human immunodeficiency virus (HIV) positive with that of couples in which neither partner is HIV-positive.
Design: Retrospective matched case-control study.
Setting: Fertility center at Tenon Hospital, Paris, France.
Patient(s): A total of 179 IVF cycles in couples infected with HIV-1 and 179 IVF cycles in control couples.
Intervention(s): Ovarian stimulation, oocytes retrieval, IVF (standard and microinjection), embryo transfer, pregnancy, and live birth follow-up.
Main Outcome Measure(s): Live birth rate and IVF outcomes
Result(s): The first comparison between HIV and non-HIV couples showed poorer outcomes in the HIV group (higher administered gonadotropin doses and longer stimulation periods, lower cumulative pregnancy and live birth rates, among other things). A subgroup analysis was performed in addition. No differences were found in the "men HIV" group compared with the controls. In contrast, poorer outcomes in the "women HIV" and "women and men HIV" groups were shown in terms of administered doses, duration of stimulation, and number of oocytes retrieved. For the "women HIV" group, lower cumulative clinical pregnancy and live birth rates were found.
Conclusion: The data suggested that couples with HIV-positive women have poorer medically assisted procreation outcomes than couples with non-HIV-infected women. Therefore, physicians should pay particular attention to couples with HIV-positive women. (Fertil Steril Rep® 2021;2:376–85. ©2021 by American Society for Reproductive Medicine.)
Key Words: Assisted reproductive technology, human immunodeficiency virus, in vitro fertilization outcomes

In 2017, the number of people living with human immunodeficiency virus (HIV) reached 36.9×10^6 people (49.3% women) worldwide. Despite global actions to prevent it, and notwithstanding a decrease in the number of new cases in 2017 (1.8×10^6 compared with 3.4×10^6 in 1996), the number is still growing (1). A decrease in deaths related to opportunistic pathologies of acquired immunodeficiency syndrome (1.9×10^6 in 2004 compared with 940,000 in 2017) has been accomplished in recent years thanks, in particular, to the use of antiretroviral therapy (1). In France, the number of new infections discovered has been stable since 2011 (6,200 new cases in 2018, 35% women).

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Surveillance of HIV testing activity is conducted throughout the country; this screening has notably increased in recent years (3% between 2013 and 2015). Heterosexual intercourse was the predominant mode of infection (56%), followed by sex between men (40%), and intravenous drug use (2, 3). In 2013 in France, 153,400 people were living with HIV. Eighty-four percent knew that they were infected, and 75% received antiretroviral therapy. Ninety percent of those treated had a negative viral load (2, 3).

Advances in diagnosis and treatment have resulted in improved quality of life and increased life expectancy for these infected individuals. The desire for a child occupies a completely legitimate place in the care of HIV-positive couples. This point needs to be addressed as early as possible in this care. The aim is to inform couples about the possibilities of conceiving through natural procreation or medically assisted procreation (assisted reproductive technology [ART]), about antiretroviral treatments and their undesirable and/or teratogenic effects, and the need to adapt therapies and implement strategies to avoid the risks of sexual and/or mother-child transmission.

The risk of transmission has been assessed in many studies (4, 5), including a meta-analysis (6) of 2,848 people infected with HIV. The investigators showed the absence of viral transmission in serodiscordant couples under optimal antiretroviral treatment conditions (undetectable plasma load for >6 months). In 2008, Sauer et al. (7) studied 10 years of in vitro fertilization (IVF) care to HIV-positive men and seronegative women in the United States. They observed no maternal or neonatal HIV infections.

Thanks to diverse measures undertaken during pregnancy, labor, delivery, and the postnatal period, including antiretroviral therapy, cesarean delivery when indicated, and no breastfeeding, the vertical transmission rate of HIV remains low. Indeed, in 2018, the Centers for Disease Control and Prevention surveillance showed that of 1,042,270 cases of diagnosed HIV at the end of 2018, <1% were among children with diagnosed perinatal HIV (8).

The effectiveness of antiretroviral treatments and the very low rate of maternal-fetal transmission (9) have made natural procreation the first choice for certain serodiscordant couples wishing to conceive. The virologic conditions required, according to the latest Morlat report (2018), are as follows (2):

- Long-term antiretroviral therapy with good compliance
- Undetectable viral load for 6 months
- Absence of genital infection, inflammation, or genital wounds in both partners
- Fertility conditions that will not delay support with ART in case of proven infertility factors

When ART is needed, the reproductive technique is based on the fertility criteria used in the general population. Intrauterine insemination is used in the case of normal sperm parameters and absence of tubal abnormalities. Otherwise, IVF or intracytoplasmic sperm injection is used according to the sperm parameters. HIV-positive patients must meet the management criteria for ART, and serodiscordant partners must have negative HIV serology.

The prevalence of infertility among those with HIV was studied from 1994 to 2002 in a prospective cohort in the United States, and the results showed that HIV-positive women were less likely to conceive than seronegative women (pregnancy rates 7.4% vs. 15.2% per 100 person-years) (10). On the other hand, HIV-1-infected male patients showed altered semen parameters compared with controls. This was related to the infection and to antiretroviral treatments (11, 12).

There are only a few studies of IVF results in couples living with HIV. Observational studies (7, 13–16) evaluated the pregnancy rate per cycle in this population, which ranged from 9.2% to 45%. Other retrospective case-control studies compared IVF outcomes in HIV-infected and noninfected patients. Some studies (17–20) found lower rates of clinical pregnancy and/or implantation and live birth rates in the HIV group (women HIV-positive or men and women HIV-positive). Other studies (21–24) found no significant difference or even better results in couples in which the man was HIV-positive (25). Because of the discordant results, different biases, and low numbers in these studies, it is difficult to draw any conclusions with certainty.

In 2016, 209 cycles of IVF for couples living with HIV were made in France, which resulted in 21 active pregnancies, 21 deliveries, and 24 live births (26). Our reproductive health care center has been treating HIV-positive couples since 2012. Our interest in this topic is to increase the literature data, to better understand the influence of HIV infection on the fertility of seropositive patients, and to improve the management of these couples by orienting them as well as possible.

MATERIALS AND METHODS

Study Design

This was a single-center case-control retrospective study with standardization of the control population on different adjustment criteria. The study period included the ovarian stimulations that resulted in oocyte retrieval from January 1, 2013, to March 4, 2018, in the fertility center of Tenon Hospital (APHP-Paris).

Ethics

This study was approved by the local ethics committee within the Avicenne health care establishment on April 21, 2020, under the protocol number: CLEA-2020-108 and had no source of funding.

Inclusion/Exclusion Criteria

All IVF cycles performed during the study period at Tenon Hospital were included in our study. Couples supported in our center meet the criteria for access to ART in France (27). The “case” group was composed of couples with HIV infection: the woman, the man, or both members of the couple were infected. Couples could be coinfected with hepatitis B virus (HBV) or hepatitis C virus (HCV). The HIV-positive patients must meet the management criteria defined by the decrees relating to the best-practice methods in ART (27):

- Couples must be followed by a multidisciplinary team throughout their care.
- Couples must have a CD4 T-cell count >200/μL and an undetectable HIV viral load on two successive assessments at 3-month intervals in the 6 months preceding the treatment, then an undetectable HIV viral load every 3 months during the medical care.
- Serodiscordant couples must have negative HIV serology in the HIV-negative partner 15 days preceding oocyte retrieval.

The "control" group was composed of couples who were not infected with HIV, HBV, or HCV and were patients of our center. In vitro fertilization cycles with gamete donation were excluded from our study.

Matched Criteria and Studied Groups

To overcome the main confounding factor, each IVF cycle in the HIV group was matched with an IVF cycle in the control group according to the following criteria: woman's age; IVF technique (conventional or with microinjection); etiology of infertility (tubal, ovulatory, or decreased ovarian reserve, masculine, endometriosis, idiopathic, or mixed female and male factors); rank of the IVF cycle; type of infertility (primary or secondary); and body mass index of the woman.

The HIV group was composed of opposite-sex couples with at least one HIV-positive member. The control group consisted of opposite-sex couples in which neither member was HIV-positive.

The first comparison carried out was between HIV couples and non-HIV couples. Then analysis in subgroups was made (women HIV vs. Women non-HIV, Men HIV vs. Men non-HIV, and Women and Men HIV vs. Couples non-HIV).

In Vitro Fertilization Cycle Procedure

Before the IVF cycle, a complete physical checkup was carried out on the two members of the couple. None of our non-HIV patients used pre-exposure prophylaxis (PrEP) during the IVF cycle.

The stimulation protocol was chosen according to the woman's ovarian reserve, her age, and any previous stimulation to achieve the best ovarian response and to avoid ovarian hyperstimulation. The long agonist protocol was usually chosen for women with normal ovarian reserve. This protocol combines pituitary desensitization with pituitary gonadotropin-releasing hormone (GnRH) agonist, in the mid-luteal phase of the previous cycle, prior to ovarian gonadotropin stimulation. For poor-responders, the protocol chosen was the short agonist, which combines gonadotropins in high doses and GnRH agonists to take advantage of the "flair-up" effect of the latter. The antagonist protocol was chosen for hyper-responders at risk for ovarian hyperstimulation. This protocol combines the use of gonadotropins and the introduction of GnRH antagonists in the mid-follicular phase.

Stimulation monitoring was performed on the seventh day by endovaginal ultrasound with counting and measurement of growing follicles, coupled with estradiol, luteinizing hormone, and progesterone blood levels. This ultrasound and biological surveillance were repeated as many times as necessary.

The onset of ovulation was triggered when there were at least three follicles >17 mm and an estradiol level >150–200 pg/mL per mature follicle. This was performed by recombinant human chorionic gonadotropin (Ovitrelle; Merck Serono S.p.A., Modugno, Italy) or GnRH analog in antagonist protocols only (Decapeptyl; Ferring Pharmaceuticals, Italy). Oocyte retrieval was performed in the operating room and under general anesthesia 36 hours after the triggering of ovulation.

The sperm samples were taken at the laboratory after a period of sexual abstinence of 2–7 days. The fresh sperm was treated on a density gradient (PureSperm; Nidacon International, Gothenburg, Sweden), followed by a pellet wash in 2 mL of IVF medium (Universal IVF Medium; Origio, Malov, Denmark).

When the man was infected with HIV, a sperm freeze was performed prior to the IVF cycle associated with a detection test of the virus in seminal plasma and/or sperm preparation for virological validation. In case of positive viral load in seminal plasma but <100,000 copies/mL, a straw was thawed to perform HIV ribonucleic acid testing by the virology laboratory. If HIV ribonucleic acid was found in the final fraction, the initially frozen flakes for ART could not be used and were destroyed.

Conventional IVF or microinjection of spermatozoa was performed according to sperm parameters and based on previous IVF cycles. In our fertility center, the embryo transfer was performed on day 2 or 3 after oocyte retrieval. Supernumerary embryos of good quality (good development kinetics and fragmentation <30%) were frozen on day 2 or 3. Embryos that could not be transferred or frozen on day 2 or 3 were left in culture and could then be frozen on day 5 or 6 if they reached the blastocyst stage. The number of embryos to be transferred was chosen according to the characteristics of the couple (age of the woman, duration of infertility, rank of IVF cycle, type of infertility) and the embryo quality. Luteal phase support was provided by the daily administration of vaginal progesterone (200 mg three times a day) from the evening of oocyte retrieval.

Data Collection and Statistical Analysis

The main outcome was the live birth rate. The secondary end points were the following: stimulation data, including total doses of gonadotropins, duration of stimulation, and hormonal assays at triggering; and data from IVF cycles, including the number of oocytes collected, the fertilization rate, the number of embryos obtained (transferred, frozen), the implantation rate, the clinical pregnancy rate, the multiple pregnancy rate, and cumulative rates of clinical pregnancy and live birth, among others.

Data were extracted from "Medifirst" software in an Excel file. The quantitative variables were expressed as mean $\pm$ SD and the statistical comparison was performed using a Student's t-test. The X^2 test (+/- Yates' correction) or Fisher's exact test were used for the comparison of nominal qualitative data when appropriate. All tests were performed bilaterally and $P<.05$ was considered significant.

TABLE 1

Characteristics of HIV population and controls.

Criteria	HIV	Controls	*P* value
Number of IVF cycles	179	179	
Women Age (years)[a]	(179) 37 ± 3.57	(179) 36.9 ± 3.43	.71[c]
Women BMI (kg/m^2)[a]	(172) 25.7 ± 4.88	(179) 25.3 ± 4.47	.36[c]
Technique[b]			.84[d]
ICSI	86 (48%)	85 (47%)	
IVF	93 (52%)	94 (53%)	
Rank of IVF cycle[b]			1[d]
1st	114 (63%)	114 (63%)	
2nd	43 (24%)	43 (24%)	
≥3rd	22 (13%)	22 (13%)	
Infertility[b]			1[d]
Primary	107 (60%)	107 (60%)	
Secondary	72 (40%)	72 (40%)	
Infertility etiology[b]			.12[e]
Tubal	56 (31%)	47 (26%)	
Anovulation	7 (4%)	4 (3%)	
DOR	28 (16%)	25 (14%)	
Male	18 (10%)	33 (18%)	
Male and female factors	13 (7%)	22 (12%)	
Endometriosis	8 (5%)	10 (6%)	
Idiopathic	49 (27%)	38 (21%)	
AMH (ng/mL)[a]	(163) 2.71 ± 10.36	(169) 2.86 ± 3.77	.61[c]
FSH (mUI/mL)[a]	(165) 8.24 ± 2.89	(165) 7.3 ± 11.24	.08[c]
E2 (pg/mL)[a]	(163) 50.7 ± 33.76	(153) 57 ± 66.36	.27[c]
LH (mUI/mL)[a]	(163) 6.2 ± 7.21	(145) 5.42 ± 9.90	.14[c]
PRL (ng/mL)[a]	(108) 22.1 ± 19.29	(98) 18.7 ± 11.53	.12[c]

Note: AMH = antimüllerian hormone; BMI = body mass index; DOR = decreased ovarian reserve; E2 = estradiol; FSH = follicle stimulating hormone; HIV = human immunodeficiency virus type 1; ICSI = intracytoplasmic sperm injection; IVF = in vitro fertilization; LH = lutenizing hormone; PRL = prolactin.

[a] Values are (number of IVF cycles) average ± SD.

[b] Values are number of IVF cycles (percentage).

[c] Student's *t*-test.

[d] X^2 test.

[e] Yates' corrected X^2.

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RESULTS

During the inclusion period, 179 IVF cycles of couples living with HIV met our criteria and were able to be included. Among these IVF cycles, 97 were in serodiscordant couples in which the woman was HIV-positive, 60 in serodiscordant couples in which the man was HIV-positive, and 22 in couples in which both were HIV-positive. Some couples have benefited from several IVF cycles. That represents 64 couples in which the women were HIV-positive (subgroup "women HIV"), 38 couples in which the men were HIV-positive (subgroup "men HIV"), and 15 couples in which both partners were HIV-positive (subgroup "women and men HIV"). Within the "women HIV" subgroup, there were four couples with coinfections: one woman with HBV (1.56% of the subgroup), two men with HBV (3.13% of the subgroup), and one man with HCV (1.56% of the subgroup). Within the "men HIV" subgroup, six couples had coinfections: three men with HCV (7.89% of the subgroup) and three women with HBV (7.89% of the subgroup). Within the subgroup "women and men HIV," three couples were coinfected: two women with HBV (13.33% of the subgroup) and one man with HCV (6.6% of the subgroup).

The control group consisted of 179 IVF cycles in 179 couples with no infection, selected according to the matched criteria mentioned previously. During our study period, 73 frozen embryo transfers were performed in HIV couples and 99 in non-HIV couples.

Population characteristics of patients living with HIV and control patients are presented in Table 1. No statistical difference was found between the two groups. The characteristics of the subgroups ("women HIV", "men HIV", or "women and men HIV") and their controls are presented in Supplemental Table 1 (available online). Women in the "men HIV" subgroup had a baseline estradiol level significantly lower than that in the control women. Women in the "women and men HIV" group had significantly higher estradiol levels than women controls. The other parameters were comparable for the three groups.

Concerning the antiretroviral therapy, 128 patients (97 %) were under treatment at the beginning of the procedure: 66 patients (51.56 %) were treated with the association of 2 nucleoside reverse transcriptase inhibitors (NRTIs) and 1 protease inhibitor, 30 patients (23.44%) with the association of 2 NRTIs and 1 non-nucleoside reverse transcriptase inhibitor, 12 patients (9.38 %) with 2 NRTIs and 1 integrase inhibitor, 6 patients (4.68 %) had a monotherapy of protease inhibitors, and 14 patients (10.94 %) with different "other" associations.

TABLE 2

In vitro fertilization outcomes in HIV population vs. controls.

Outcome	HIV	Controls	*P* value
Number of IVF cycles	179	179	
Total dose of gonadotropins used (IU)[a]	(179) 3263 ± 1511	(179) 2830 ± 1255	.003[c]
Duration of stimulation (days)[a]	(179) 11.2 ± 2.2	(179) 10.6 ± 1.7	.001[c]
Initial dose of gonadotropins (IU)[a]	(179) 285 ± 113	(179) 259 ± 96	.02[c]
Estradiol at trigger (pg/mL)[a]	(162) 1796 ± 979	(179) 2020 ± 1245	.07[c]
Progesterone at trigger (ng/mL)[a]	(162) 0.78 ± 0.36	(179) 0.87 ± 0.7	.35[c]
LH at trigger (IU/mL)[a]	(162) 1.6 ± 1.7	(179) 1.7 ± 0.14	.6[c]
Number of follicles expected at trigger[a]	(161) 8.5 ± 5.8	(178) 9.5 ± 7	.3[c]
Endometrium thickness at trigger (mm)[a]	(140) 9.5 ± 2.2	(178) 10.2 ± 2.6	.03[c]
Number of oocytes retrieved[a]	(179) 9 ± 6.7	10.3	.07[c]
Number of oocyte in MII[a]	(179) 6.3 ± 4.5	7.1	.22 [c]
% 3PN/number of oocytes in MII	5.8	3.7	.09[c]
Fertilization rate (%)	56.4	64.8	.009[c]
Cleavage rate (%)	57	67	.002[c]
Number of transferred embryos[a]	(179) 1.2 ± 0.9	(179) 1.3 ± 0.8	.12[c]
Number of frozen embryos[a]	(179) 0.96 ± 1.7	(179) 1.3 ± 2.0	.06[c]
Number of good quality embryos[a]	(179) 2.1 ± 1.9	(179) 2.6± 2.1	.02[c]
Biochimical pregnancy rate/fresh transfer[b]	(26) 21%	(33) 24.3%	.53[d]
Implantation rate[b]	(26) 12.6%	(31) 13.4%	.8[d]
Clinical pregnancy rate/fresh transfer[b]	(20) 16.1%	(28) 23.8%	.35[d]
Live birth rate/fresh transfer[b]	(14) 11.3%	(23) 16.9%	.19[d]
Fresh transfer cancellation rate[b]	(43)24.3%	(25)14 .1%	.045[d]
Live birth rate/ oocyte retrieval (without the freeze-all)[b]	(15) 9.3%	(23) 14.3%	.16[d]
Twin pregnancy rate[b]	(6) 30%	(3) 10.7%	.19[e]
Twin live birth rate[b]	(5) 35.7%	(3) 13%	.22[e]
Clinical pregnancy rate/(fresh and frozen tansfers)[b]	(34) 17.3%	(56) 23.8%	.09[d]
Live birth rate/(fresh and frozen transfers)[b]	(23) 11.7%	(40) 17%	.11[d]
Remaining frozen embryos (%)	29	26.6	.18[d]
Cumulative live birth rate[b]	(23) 12.8%	(40) 22.3%	.02[d]
Cumulative pregnancy rate[b]	(34) 19.6%	(56) 29.6	.03[d]

Note: HIV = human immunodeficiency virus type 1; IVF = in vitro fertilization; LH = lutenizing hormone; MII = metaphase II; PN = pronuclei.
[a] Values are (number of IVF cycles) average ± SD.
[b] Values are (number of IVF cycles) percentage.
[c] Student's *t*-test.
[d] X^2 test.
[e] Yates' corrected X^2.

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Table 2 presents the comparison between the HIV group and the non-HIV control group. The cumulative rates of clinical pregnancy and live birth were lower among couples living with HIV ($P = .03$ and $P = .02$, respectively). In couples with HIV, we noticed more fresh transfer cancellations than in the non-HIV group ($P = .045$). No IVF cycle cancellation occurred in either groups.

The initial and total doses of gonadotropins used were higher in the HIV group than those in the control group ($P = .02$ and $P = .03$, respectively). In addition, the duration of stimulation was longer ($P = .001$) and the thickness of the endometrium was significantly lower in the HIV group ($P = .03$).

The fertilization rate, the cleavage rate, and the average number of good quality embryos were significantly lower in the HIV group compared with those in the controls ($P = .009$, $P = .002$, and $P = .02$, respectively). Other parameters were comparable ($P \geq .05$).

In a second step, a subgroup study was conducted to clarify the influence of HIV on fertility according to the infected partner. In the "women HIV" subgroup, regarding the IVF outcomes, we found the following: the clinical pregnancy rate per fresh embryo transfer, the live birth rate per oocyte retrieval (all cycles excluding freeze-all: fresh transfer, retrieval without oocyte, cancelled transfer), the live birth rate per transfer (fresh and frozen transfers), the cumulative clinical pregnancy rate, and live birth rate were all significantly lower in HIV-infected women compared with results for controls ($P = .04$, $P = .02$, $P = .03$, $P = .03$, and $P = .005$, respectively) (Table 3). The fresh transfer cancellation rate was higher in HIV-positive women compared with that in controls (19.6% vs. 10.3%, $P = .07$) because of an absence of available embryos to transfer. The number of oocytes collected and the cleavage rate were significantly lower in HIV-positive women compared with those in controls ($P = .04$). The rate of multinucleated zygotes was significantly higher ($P = .04$).

In the "women and men HIV" subgroup, the number of oocytes collected, the number of mature oocytes, the cleavage rate, the fertilization rate, and the average number of embryos of acceptable quality were all significantly lower compared with those of controls ($P = .004$, $P = .03$, $P < .001$, $P = .009$, $P = .005$, respectively). The fresh transfer cancellation rate was higher in the subgroup "women and men HIV"

TABLE 3

In vitro fertilization outcomes in subgroup "women HIV" vs. controls.

Outcome	Women HIV	Controls	*P* value
Number of IVF cycles	97	97	
Total dose of gonadotropins used (IU)[a]	(97) 3245 ± 1443	(97) 2726 ± 1165	.007[c]
Duration of stimulation (days)[a]	(97) 11.1 ± 2.4	(97) 10.5 ± 1.7	.03[c]
Initial dose of gonadotropins[a]	(97) 286 ± 111	(97) 252 ± 90	.02[c]
Estradiol at trigger (pg/mL)[a]	(87) 1871 ± 1040	(97) 2219 ± 1260	.15[c]
Progesterone at trigger (ng/mL)[a]	(87) 0.78 ± 0.44	(97) 0.88 ± 0.63	.38[c]
LH at trigger (IU/mL)[a]	(87) 1.6 ± 2.08	(97) 1.72 ± 1.61	.59[c]
Number of follicles expected at trigger [a]	(86) 9 ± 6.4	(96) 9.6 ± 6.7	.63[c]
Endometrium thickness at trigger (mm)[a]	(87) 9.7 ± 1.9	(96)10.2 ± 2.51	.16[c]
Number of oocytes retrieved[a]	(97) 8.6 ± 5.6	(97) 10.5 ± 6.9	.04[c]
Number of oocytes in MII[a]	(97) 6.2 ± 4.2	(97) 8.6 ± 5.8	.002[c]
% 3PN/nombre of oocytes in MII	7.9	3.8	.04[c]
Fertilization rate (%)	61.6	68.5	.11[c]
Cleavage rate (%)	62	71	.04[c]
Number of transferred embryos[a]	(97) 1.2 ± 0.9	(97) 1.3 ± 0.8	.44[c]
Number of frozen embryos[a]	(97) 1.05 ± 1.8	(97) 1.47 ± 2.1	.13[c]
Number of good quality embryos[a]	(97) 2.25 ± 2.0	(97) 2.8 ± 2.1	.09[c]
Biochimichal pregnancy rate/fresh transfer[b]	(12) 17.6%	(16) 21.1%	.6[d]
Implantation rate[b]	(9) 7.7%	(17) 13.5%	.14[d]
Clincal pregnancy rate/fresh transfer[b]	(6) 8.8%	(16) 21.1%	.04[d]
Live birth rate/fresh transfer[b]	(3) 4.4%	(12) 15.8%	.05[e]
Fresh transfer cancellation rate[b]	(19) 19.6%	(10) 10.3%	.007[d]
Live birth rate/oocyte retrieval (without the freeze-all)[b]	(3) 3.6%	(12) 15.1%	.02[e]
Twin pregnancy rate[b]	(2) 33.3%	(1) 6.6%	.18[f]
Twin live birth rate[b]	(2) 66.7%	(1) 8.3%	.08 [f]
Clinical pregnancy rate/(fresh and frozen transfer)[b]	(18) 15.7%	(34) 24.8%	.07[d]
Live birth rate/(fresh and frozen transfer)[b]	(10) 8.7%	(25) 18.2%	.03[d]
Remaining frozen embryos (%)	24.5	25.2	.9d
Cumulative live birth rate[b]	(10) 10.3%	(25) 25.8%	.005[d]
Cumulative clinical pregnancy rate[b]	(18) 18.6%	(34) 35.1%	.03[d]

Note: "Women HIV" were couples in which the women were HIV-positive. HIV = human immunodeficiency virus type 1; IVF = in vitro fertilization; LH = lutenizing hormone; MII = metaphase II; PN = pronuclei.
[a] Values are (number of IVF cycles) average ± SD.
[b] Values are (number of IVF cycles) percentage.
[c] Student's *t*-test.
[d] X^2 test.
[e] Yates' corrected X^2.
[f] Fisher's exact test.

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compared with that in controls ($P = .002$). However, no significant difference was noted in pregnancy outcomes (Table 4).

The same significant differences were found in the "women HIV" and "women and men HIV" subgroups compared with their control population; for the two subgroups, the total dose of gonadotropins was greater ($P = .007$ and $P = .003$, respectively), the duration of stimulation was longer ($P = .03$ for both), and the initial dose of gonadotropins was higher ($P = .02$ and $P = .003$, respectively) than those in the control group. In contrast, the hormonal assay results (estradiol, progesterone, luteinizing hormone), the number of expected follicles, and the thickness of the endometrium at triggering of ovulation were comparable in the subgroup analysis ($P \geq .05$). The data of these two subgroups are shown in Tables 3 and 4. In the "men HIV" subgroup, no significant differences from the control group results were found ($P \geq .05$) for the studied parameters (Supplemental Table 2, available online).

DISCUSSION

In our study, we were able to show several significant differences in the outcomes of IVF cycles in our population of couples with HIV infection compared with control couples without HIV, with a decrease in fertility in the groups of HIV-positive women. The choice of controls in our study was made based on six matched criteria: woman's age and body mass index, the type of infertility of the couple (primary or secondary), the rank of the IVF cycle, the type of technique used (conventional IVF or IVF with microinjection), as well as the etiology of the infertility. These criteria are factors that may affect the outcomes of ART. The selected controls allowed us to overcome certain biases and obtain comparable populations to study the influence of HIV infection on the outcomes of IVF cycles.

Previous studies have already approached this subject. Descriptive studies (7, 13–16, 28) found lower pregnancy rates per cycle in the population with HIV, but those studies did not have a control group. Other case-control studies

TABLE 4

In vitro fertilization outcomes in subgroup "women and men HIV" vs. controls.

Outcome	Women and Men HIV	Controls	*P* value
Number of IVF cycles	22	22	
Total dose of gonadotropins used (IU)[a]	(21) 4013 ± 1690	(22) 2603 ± 1233	.003[c]
Duration of stimulation (days)[a]	(22) 11.1 ± 2	(22) 10.5 ± 1.7	.03[c]
Initial dose of gonadotropins[a]	(21) 334 ± 129	(22) 234 ± 79	.003[c]
Estradiol at trigger (pg/mL)[a]	(20) 1556 ± 746	(22) 2241 ± 1506	.07[c]
Progesterone at trigger (ng/mL)[a]	(20) 1.26 ± 0.32	(22) 0.79 ± 0.31	.15[c]
LH at trigger (IU/mL)[a]	(20) 1.71 ± 0.56	(22) 0.79 ± 1.18	.004[c]
Number of follicles expected at trigger[a]	(20) 6.9 ± 4	(22) 11.2 ± 7.9	.18[c]
Endometrium thickness at trigger (mm)[a]	(15) 9.2 ± 3.7	(22) 10.5 ± 1.4	.11[c]
Number of oocytes retrieved[a]	(22) 6.7 ± 4.4	(22) 11 ± 4.9	.004[c]
Number of oocytes in MII[a]	(22) 5.2 ± 3.4	(22) 8.5 ± 3.7	.004[c]
% 3PN/nombre de oocytes in MII	4.7	6.3	.53[c]
Fertilization rate (%)	39.6	62.9	.009[c]
Cleavage rate (%)	35	66	<.001[c]
Number of transferred embryos[a]	(22) 0.8 ± 0.9	(22) 1.6 ± 0.7	.002[c]
Number of frozen embryos[a]	(22) 0.54 ± 1.1	(22) 1 ± 1.2	.2[c]
Number of good quality embryos[a]	(22) 1.4 ± 1.3	(22) 2.6 ± 1.5	.005[c]
Biochimichal pregnancy rate/fresh transfer[b]	(2) 16.7%	(5) 25%	.68[f]
Implantation rate[b]	(2) 11.1%	(5) 14.3%	1[f]
Clincal pregnancy rate/fresh transfer[b]	(2) 16.7%	(4) 20%	1[f]
Live birth rate/fresh transfer[b]	(1) 8.3%	(4) 20%	.62[f]
Fresh transfer cancellation rate[b]	(8) 40%	(1) 5%	.02[d]
Live birth rate/oocyte retrieval (without the freeze-all)[b]	(1) 5.6%	(4) 19%	.35[f]
Twin pregnancy rate[b]	(0) 0%	(1) 25%	1[f]
Twin live birth rate[b]	(0) 0%	(1) 25%	1[f]
Clinical pregnancy rate/(fresh and frozen transfer)[b]	(2) 11.1%	(6) 20%	.69[f]
Live birth rate/(fresh and frozen transfer)[b]	(1) 5.6%	(5) 16.7%	.38[f]
Remaining frozen embryos (%)	16.7	22.7	1[f]
Cumulative live birth rate[b]	(1) 4.5%	(5) 22.7%	.18[f]
Cumulative clinical pregnancy rate[b]	(2) 9.1%	(6) 27.2%	.24[e]

Note: "Women and men HIV" were couples in which both partners were HIV-positive. HIV = human immunodeficiency virus type 1; IVF = in vitro fertilization; LH = lutenizing hormone; MII = metaphase II; PN = pronuclei.
[a] Values are (number of IVF cycles) average ± SD.
[b] Values are (number of IVF cycles) percentage.
[c] Student's *t*-test.
[d] X^2 test.
[e] Yates' corrected X^2.
[f] Fisher's exact test.

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were conducted by standardizing their control population according to the age of the woman (18, 20, 21, 24, 25); the results of these studies were sometimes discordant. In 2016, Stora (19) conducted a study of the influence of HIV infection on the IVF cycle outcomes in 82 couples by standardizing the control population on more criteria than in previous studies (woman's age, type and etiology of infertility, date of the oocyte retrieval, rank of the cycle). The investigators found lower rates of clinical pregnancy, implantation, and live birth in the women with HIV infection. This standardization on different criteria would undoubtedly make it possible to obtain more comparable populations and to highlight differences.

In our study, in the couples in which the woman was seropositive, significant differences compared with controls were found in terms of stimulation data (initial and total doses and duration), number of oocytes collected at the oocyte retrieval, clinical pregnancy rate by fresh transfer, live birth rate by oocyte retrieval and by transfer, as well as cumulative rates of clinical pregnancy and live birth. These results were all at the expense of couples with HIV-positive women. In the literature, these results were discordant: some studies found no significant difference between the IVF results of the two groups (21–24). Other studies found differences to the detriment of the "women HIV" group. In a prospective 72-pair case-control study in 2006, Coll et al. (17) found a significantly lower clinical pregnancy rate in HIV-infected women compared with that in controls (6% vs. 30% $P = .02$). In a women's age-adjusted study in 2005, Terriou et al. (22) showed that the total gonadotropin dose, the duration of stimulation, and the cancellation rate were significantly higher, and the clinical pregnancy rate was much lower in the "women HIV" group compared with controls. In 2016, in a retrospective case-control study, Stora et al. (19) compared 82 couples who were HIV-positive with 82 seronegative couples standardized on several criteria (age of the woman, etiology and type of infertility, the rank and technique of the IVF cycle). In the "women HIV" group, implantation rate, clinical pregnancy rate (by transfer and by oocyte retrieval), and live birth rate (by transfer) were significantly lower compared with those of controls. In 2017, Vankerkem et al. (20) found similar results in a case-control study (higher

cancellation rate, lower number of oocytes, and lower clinical transfer rate and oocyte retrieval rate in the "women HIV" group).

In our study, results found in couples composed of two HIV-positive partners were similar to those found in the group of couples in which only the woman was HIV-positive. Thus, the total dose of gonadotropins and the duration of stimulation were higher in HIV-positive couples compared with seronegative controls. The number of oocytes at the oocyte retrieval and the rate of fertilization were lower in HIV-positive couples. Despite a trend to the detriment of HIV-positive couples for the other parameters, no significant difference could be found in pregnancy outcomes, probably because of the small size of this subgroup. Few studies in the literature have investigated the outcomes of IVF cycles in these couples. However, despite this limited data, the results seemed to be pejorative for these couples. In their 2011 study, Santulli et al. (18) had higher cancellation rates and significantly lower clinical pregnancy rates by oocyte retrieval in HIV-infected female and male couples vs. controls. In 2017, Vankerkem et al. (20) did not show any significant difference in the outcome of HIV couples compared with HIV-negative controls. However, a negative trend was found for HIV couples with a live birth rate of 3% vs. 12% in the control group ($P = .3$) and an evolutionary clinical pregnancy rate per transfer of 5% vs. 15% in the control group ($P = .28$). These nonsignificant results may be because of the reduced numbers of studied couples. Nevertheless, it can be hypothesized that in these couples, the most negative factor regarding ART outcomes was the seropositivity of the woman.

In our study, no significant difference was found in the "men HIV" group compared with the controls. In the literature, other studies reported no significant difference between IVF results between HIV men versus controls (18, 24). In 2009, a case-control study found higher rates of pregnancy and implantation in the "men HIV" group compared with controls (25). Another study, in 2017 (20), found clinical pregnancy rates comparable to controls despite a lower fertility rate in the "men HIV" group. Overall, the literature seems reassuring concerning IVF results when HIV-positive men are compared with a population of uninfected controls. Thus, HIV infection or the use of antiretroviral treatment would not affect the sperm fertility capacity of HIV-positive men (when infection is controlled, a necessary condition for access to ART).

One of the first hypotheses that we can put forward is the toxicity of antiretroviral treatments, and in particular, the undesirable effects of nucleoside inhibitors on the mitochondria (29, 30), which would thus alter the oocyte quality. NRTIs inhibit HIV replication with their high affinity for viral DNA polymerase. However, they might also inhibit similar human structures such as the mitochondrial DNA polymerase, leading to a dysfunctional mitochondrial protein. Key metabolic functions are therefore no longer provided by the mitochondria, notably the oxidative phosphorylation, leading to an accumulation of reactive oxygen species. In 2008, Lopez et al. (31) found objective mitochondrial DNA depletion in oocytes of seropositive patients treated with nucleoside inhibitors. In addition, results to the detriment of HIV-positive women were found in a study conducted by Mataró et al. (32) on cycles with oocyte donation in HIV vs. non-HIV patients, suggesting that infection or antiretroviral therapy may also affect endometrial receptivity. One possible hypothesis to advance would be that this is a consequence of the inflammatory process associated with HIV (33) (alteration of coagulation, monocytic activation, and elevation of interleukins), which would disturb the exchanges between the endometrium and the embryo (34). This alteration in the implantation and the continuous inflammatory process might cause other complications during pregnancy such as miscarriage and intrauterine growth retardation (35). On the other hand, with identical ovarian reserve, the ovarian response was worse in HIV-positive women. Some investigators suggested possible indirect effects of antiretroviral therapy and HIV infection on the process of folliculogenesis (36, 37). Indeed, antiretroviral therapy, and especially PIs, have been associated with the modification of lipid metabolism and insulin resistance, which may impact the regulation of ovulation and folliculogenesis. The infection of the gland itself, or systemic effects of HIV, can cause endocrine abnormalities as well, such as hormonal deficiencies (36). Antiretroviral therapy is known to have negative consequences on the metabolism of individuals (37). However, we know that these metabolic disorders also have an impact on the fertility of women (38). Protease inhibitors can have other deleterious effects, notably on decidualization and embryo implantation. In 2020, Kala et al. (39) found that lopinavir impaired uterine decidualization and spiral artery remodeling in human ex vivo and mouse in vivo experimental models, which caused defective maturation of the endometrium and thus poorer birth outcomes.

Another hypothesis that we can put forward is that comorbidities resulting from HIV infection can affect fertility as well. Immunosuppression resulting from HIV infection promotes the development of sexually transmitted infections, which tend to be more severe and more complicated to treat. Other opportunistic infections such as vaginitis, balanitis, and orchiepididymitis may affect fertility as well.

By taking into account the side-effects of antiretroviral therapy with regard to IVF outcomes, we wonder what consequences PrEP could have on pregnancy chances. A randomized trial published in 2016 was rather reassuring on this subject and showed that there was no increase in pregnancy loss or congenital anomalies in HIV seronegative women using PrEP during the peri-conception period (40). The duration of the treatment could be an important factor to take into account. In our study, we were unable to assess the effects of PrEP on IVF outcomes because none of our HIV-negative patients used this treatment. In light of our results and the literature, randomized controlled trials would be necessary to clarify the repercussions of HIV infection on IVF outcomes.

CONCLUSION

Since 2013 and following the latest updates of 2015 and 2018, French experts in the Morlat report (2, 41) and international experts (42, 43) recommend the use of natural conception when HIV infection is controlled. The orientation of couples toward ART is more motivated by the problem of infertility.

Given our results, as well as data from the literature, it seems important to consider HIV infection as a factor aggravating infertility, especially among women. The desire for children should be addressed early in the care of couples living with HIV to provide comprehensive information on the chances of pregnancy, fertility assessment, and the possibilities of care, if necessary. For men infected with HIV, the infection does not seem to compromise fertility. Thus, reassuring information should be given as to the chances of pregnancy for these couples. Further studies will be needed to understand the mechanisms involved in this phenomenon.

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