

## REPRODUCTIVE ENDOCRINOLOGY AND INFERTILITY

# Safe conception for HIV-discordant couples: insemination with processed semen from the HIV-infected partner

Augusto Enrico Semprini, MD; Maurizio Macaluso, MD, DPH; Lital Hollander, MSc; Alessandra Vucetich, MD; Ann Duerr, MD, PhD; Gil Mor, MD, PhD; Marina Ravizza, MD; Denise J. Jamieson, MD, MPH

**OBJECTIVE:** The objective of the study was to evaluate the safety of semen washing with intrauterine insemination (SW-IUI) for achieving pregnancy when the man is human immunodeficiency virus (HIV) infected and the woman is HIV negative.

**STUDY DESIGN:** We conducted a retrospective analysis of 635 HIV-discordant couples enrolled in a SW-IUI program and followed up 367 Italian women. We computed pregnancy, live birth, and multiple delivery rates and assessed the women's postinsemination HIV status.

**RESULTS:** The retrospective analysis included 635 couples (2113 SW-IUI cycles): 41% of the women (95% confidence interval [CI], 37–45%) had a live birth (per-cycle live birth rate 13%; 95% CI, 11–14%). HIV status after SW-IUI was negative when available but unknown for 26% of the women: missing HIV status was not associated with correlates of

HIV risk. The follow-up study included 367 couples (1365 cycles): 47% of the women (95% CI, 42–52%) had a live birth (per-cycle rate 14%; 95% CI, 12–16%). Ascertainment of postinsemination HIV status was complete and confirmed no HIV transmission attributable to SW-IUI. The upper 95% confidence limit of the HIV transmission rate was 1.8 per 1000 cycles in the retrospective analysis and 2.7 per 1000 cycles in the follow-up study.

**CONCLUSION:** SW-IUI appears to be a safe and effective method for achieving pregnancy in HIV-discordant couples in which the man is HIV infected.

**Key words:** assisted reproduction, effectiveness, follow-up studies, human immunodeficiency virus transmission, safety

Cite this article as: Semprini AE, Macaluso M, Hollander L, et al. Safe conception for HIV-discordant couples: insemination with processed semen from the HIV-infected partner. *Am J Obstet Gynecol* 2013;208:402.e1-9.

Human immunodeficiency virus (HIV)-affected couples may need assisted reproduction to avoid sexual transmission of the virus or to overcome infertility.<sup>1-3</sup> The American Society for Reproductive Medicine (ASRM)<sup>4</sup> and the American College of Obstetricians and Gynecologists (ACOG)<sup>5</sup> support fertility services for HIV-discordant

couples. The Centers for Disease Control and Prevention (CDC) recommends that reproductive counseling be noncoercive and supportive of patient decisions.<sup>6</sup> The ASRM recently issued recommendations that fertility clinics make fertility treatments aimed at reducing the risk of transmission more easily accessible to couples who live with HIV.<sup>7</sup>

Risk avoidance through conception with donor sperm or adoption may not be acceptable or accessible to many couples. Risk-reduction strategies that may enable couples to conceive their biological children include semen washing (SW) followed by intrauterine insemination (IUI) and in vitro fertilization (IVF) followed by embryo transfer. Early semen-processing techniques did not yield virus-free spermatozoa and 1 documented case of seroconversion led the CDC to recommend against exposing an HIV-negative woman to her HIV-infected partner's semen.<sup>8</sup> Today assisted conception offered to HIV-discordant couples in the United States primarily is based on IVF with intracytoplasmic sperm injection (IVF-ICSI).<sup>9</sup>

A 3-step SW technique was developed in Italy in 1987<sup>10</sup> and evaluated in combination with IUI.<sup>11</sup> Reproductive health clinics in Europe have since offered SW-IUI to patients, reporting no HIV transmission attributable to the procedure.<sup>12,13</sup> Incomplete follow-up, however, has been a source of uncertainty in previous studies. We conducted this

From Esman Medical Consulting (Drs Semprini, Vucetich, and Mor and Ms Hollander) and Department of Obstetrics and Gynecology, San Paolo Hospital (Dr Ravizza), Milan, Italy, and the Division of Reproductive Health, Centers for Disease Control and Prevention, Atlanta, GA (Drs Macaluso, Duerr, and Jamieson).

Received Nov. 21, 2012; revised Jan. 15, 2013; accepted Feb. 4, 2013.

This study was supported by Contraceptive Research and Development, Eastern Virginia Medical School, subproject (CSA-01-388) under a Cooperative Agreement with the United States Agency for International Development (grant HRN-A-00-98-00020-00), which in turn receives funds for AIDS research from an interagency agreement with the Division of Reproductive Health, Centers for Disease Control and Prevention.

The views expressed herein are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention, United States Agency for International Development, or Contraceptive Research and Development.

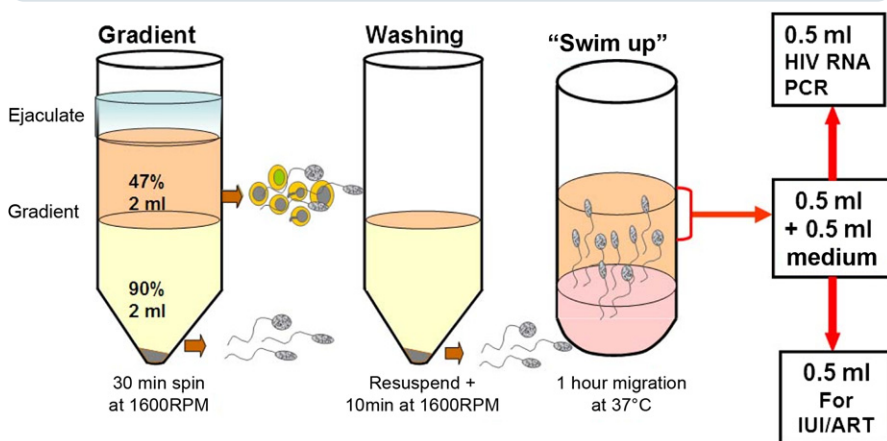
Dr Macaluso is currently Director, Division of Biostatistics and Epidemiology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH. Dr Duerr is currently Director of Scientific Affairs, HIV Vaccine Network, Fred Hutchinson Cancer Research Center, Seattle, WA.

The authors report no conflict of interest.

Reprints not available from the authors.

0002-9378/\$36.00 • © 2013 Mosby, Inc. All rights reserved. • <http://dx.doi.org/10.1016/j.ajog.2013.02.009>

**FIGURE 1**  
Semen washing for HIV-positive men



HIV, human immunodeficiency virus.

Semprini. Conception for HIV-discordant couples. *Am J Obstet Gynecol* 2013.

study to improve follow-up of a cohort of couples treated in Milan, Italy, between 1989 and 2005.

## MATERIALS AND METHODS

The study comprised a retrospective review of patient records from a program based at the San Paolo University Hospital and the Studio Semprini clinic and a follow-up study of couples in Italy who attended the program. The protocol was approved by the Ethics Committee of the Local Health Agency of the City of Milan and by the CDC Institutional Review Board.

Semen washing includes centrifugation with silica-based discontinuous density gradient, double washing and centrifugation, and sperm swim-up (Figure 1).<sup>11</sup> In laboratory conditions, the technique reduces the HIV titer by 1000-fold so that washed motile sperm is not infectious to peripheral blood lymphocytes.<sup>14</sup> Since 1997, washed sperm in this program has been routinely tested using polymerase chain reaction and discarded if HIV positive.<sup>15</sup> HIV is infrequently detected in washed sperm.<sup>16-18</sup>

At enrollment in the program, women were required to provide documentation of a negative HIV test within the previous 30 days. Women and their partners were evaluated for genital tract infections and infertility and treated as indicated. Women in fertile couples were offered SW-IUI, whereas IVF was used if indicated by infertility or if the motile

sperm count after SW was below  $1.5 \times 10^6/\text{mL}$ . All women were asked to undergo HIV serologic testing quarterly for a year after the last SW-IUI cycle.

As part of routine care, clinic staff inquired about missing HIV test results by telephone, probing as much as possible the veracity of the report by asking specific questions about the clinic or laboratory at which the test was performed, the reasons for not sending the test result in, and broadly inquiring into the health of the woman and her male partner.

From the clinic roster, 811 couples who were not currently undergoing treatment at the time of the research participated in the program between July 1, 1989, and April 30, 2005. For the retrospective analysis, we excluded couples in which the man was not HIV infected, who had never completed an SW-IUI cycle, or whose charts were missing. Deidentified data obtained from these couples included demographic characteristics, an HIV-related medical history, a fertility profile of the couple, assisted conception treatment and its outcome, and the postinsemination HIV status of the woman.

Evidence of HIV status consisted of an HIV-antibody test dating 90 or more days after the last SW-IUI cycle; a written note from a follow-up call made by clinic staff; or a new assisted conception cycle (eg, IVF-ICSI) 90 or more days after the last SW-IUI cycle. Women with missing

HIV status after the last SW-IUI were compared with those with known status with respect to demographics, medical history, HIV risk behaviors, history of participation in the program, and immune compromise and history of HIV treatment of the man.

For the follow-up study, the same 811 couples were potentially considered for inclusion. However, in addition to the exclusion criteria for the retrospective analysis, the follow-up study also excluded women whose charts contained inadequate tracing information or whose current address or telephone number could not be identified after following up 50 possible leads, whose residence address was not in Italy, who could not speak Italian or English, or whose partner objected to the woman's participation.

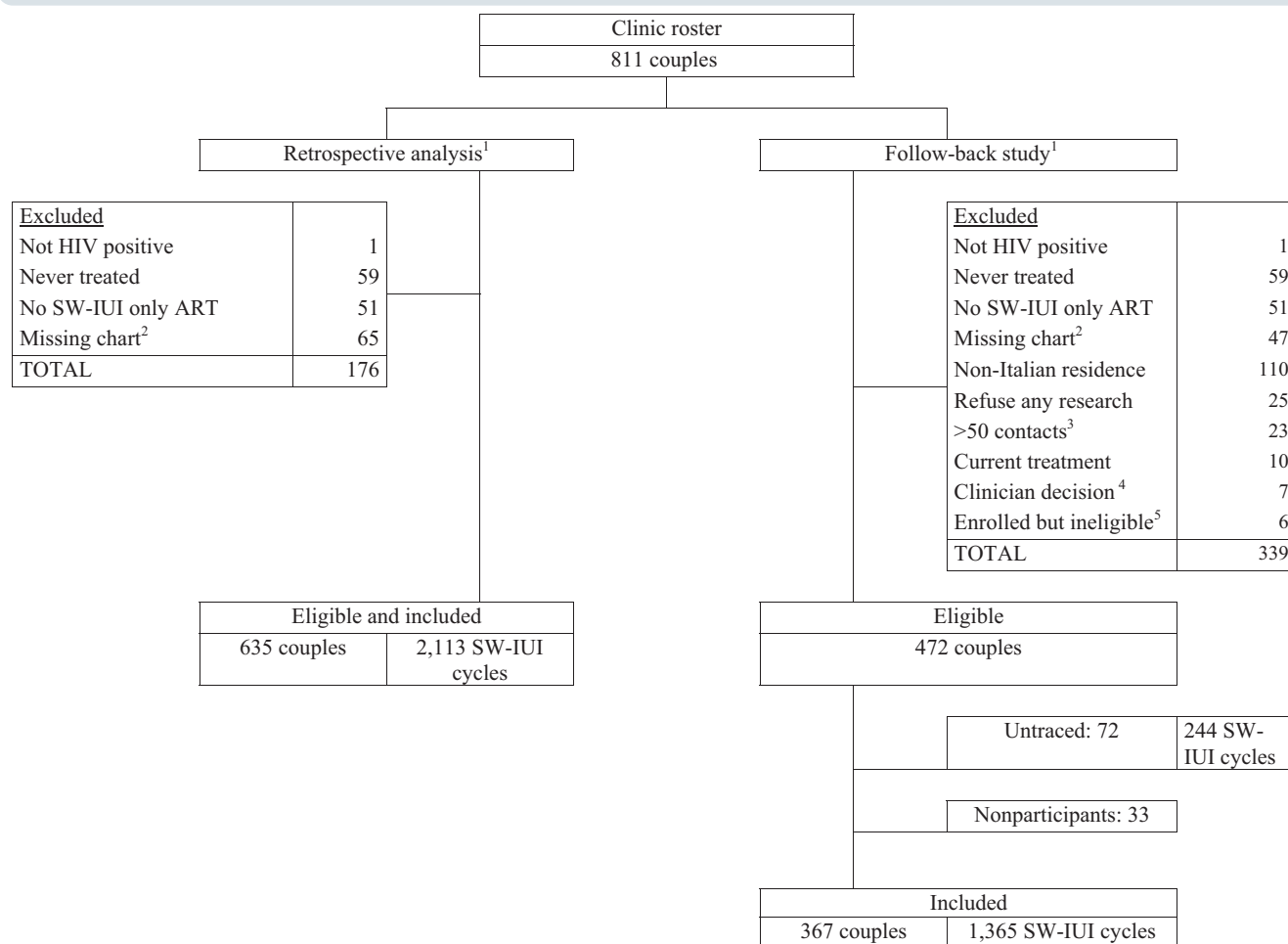
The physician who administered treatment initiated recruitment by telephone, and study staff made a second call to explain study procedures and obtain informed consent. Both partners were asked to consent to medical record review and to a telephone interview. Women were asked to provide evidence of, or at least tell about, their postinsemination and current HIV status. Women who refused to participate (nonparticipants) were probed to ascertain whether their refusal was due to HIV transmission. The institutional review board allowed analysis of limited data from women who could not be reached for recruitment (untraced) and from nonparticipants to assess whether these groups were at a higher risk of HIV acquisition than were follow-up participants.

The objectives of data analysis were to describe the characteristics of couples included in the retrospective analysis or in the follow-up study by computing univariate statistics and frequency distributions; to assess the effectiveness of SW-IUI by computing pregnancy, live birth rates, and multiple delivery rates; to assess the safety of SW-IUI by summarizing the available evidence on the postinsemination HIV status of the women; and to evaluate the correlates of the missing HIV status.

A Student *t* test and  $\chi^2$  statistics evaluated the significance of differences in means and frequency distributions. Ninety-five percent

FIGURE 2

## Disposition of patients attending SW-IUI program in Milan, Italy, 1989-2005



<sup>1</sup> Both study populations were drawn from the clinic roster of 811 couples who were not currently undergoing treatment at the time of the research and participated in the program between July 1, 1989 and April 30, 2005.

<sup>2</sup> A woman whose chart could not be located but whose name, address and other locating information was available was excluded from the retrospective analysis, but considered eligible for the follow-back study.

<sup>3</sup> In these cases, the address on record was no longer valid, and the woman was excluded from the study only after 50 failed attempts to locate the current address through the telephone directories and the postal service.

<sup>4</sup> In these cases, the clinician decided not to pursue enrollment because of the recent death of the HIV+ man (N=3), mental illness or drug addiction of either partner (N=2), and one or both partners' hostility toward the program, also unrelated to HIV status (N=2).

<sup>5</sup> In these cases, the interview contradicted the patient record and the couple was excluded because SW-IUI was never performed (N=3) or the couple had recently resumed treatment (N=3).

SW-IUI, semen washing with intrauterine insemination.

Semprini. Conception for HIV-discordant couples. *Am J Obstet Gynecol* 2013.

confidence intervals (CIs) for rates and proportions were computed using exact binomial or Poisson distribution tests, as appropriate. Logistic regression was used to evaluate multiple potential determinants of missing HIV status in the retrospective analysis and to compare follow-up participants with untraced women. Odds ratios (ORs)

and their CI were computed from the estimates of the logistic regression coefficients and their variances.

## RESULTS

Among the 811 couples who participated in the program during 1989-2005 and

were not undergoing treatment at the time of this research project, 635 eligible couples who underwent 2113 SW-IUI cycles contributed data for the retrospective analysis (Figure 2). Of 472 eligible couples, 367 couples who underwent 1365 SW-IUI cycles participated in the follow-up study.

**TABLE 1**  
**Characteristics of study participants**

Characteristic	Women in retrospective analysis (n = 635) Mean (median)	Follow-up participants (n = 367) Mean (median)	Untraced women (n = 72) Mean (median)	P value <sup>a</sup>
<b>Age, y</b>				
Woman	34 (33)	34 (33)	33 (33)	.21
Male partner	31 (31)	31 (31)	29 (29)	
<b>Italian resident</b>				
Yes	525 (83%)	367 (100%)	72 (100%)	
No	110 (17%)	N/A	N/A	
<b>Mode of HIV acquisition by male partner</b>				
Injection drug use	440 (70%)	236 (64%)	52 (72%)	.01
Sexual	116 (18%)	46 (13%)	15 (21%)	
Other	34 (5%)	10 (3%)	1 (1%)	
Missing/not specified	45 (7%)	75 (20%)	4 (6%)	
<b>Year of entry to program</b> < .001				
Prior to 1995	198 (31%)	115 (31%)	37 (51%)	
1995-1999	329 (52%)	182 (50%)	32 (44%)	
After 1999	108 (17%)	70 (19%)	3 (4%)	
<b>Year of last SW-IUI</b> < .001				
Prior to 1995	96 (15%)	55 (15%)	16 (22%)	
1995-1999	329 (52%)	172 (47%)	44 (61%)	
After 1999	210 (33%)	140 (38%)	12 (17%)	
<b>SW-IUI cycles</b> .05				
1	3.3 (range, 1–17)	3.8 (range, 1–14)	3.4 (range, 1–17)	
2	176 (28%)	80 (22%)	23 (32%)	
3-4	120 (19%)	64 (17%)	10 (14%)	
≥5	167 (26%)	91 (25%)	22 (31%)	
Missing	172 (27%)	128 (35%)	17 (24%)	
<b>Treatment regimen</b> .36				
SW-IUI only	544 (86%)	311 (85%)	64 (89%)	
SW-IUI plus ART	91 (14%)	56 (15%)	8 (11%)	
<b>Unprotected intercourse before program entry</b> .76				
Never	255 (40%)	147 (40%)	30 (42%)	
Never after HIV diagnosis	180 (28%)	89 (24%)	20 (28%)	
Some after HIV diagnosis	159 (25%)	94 (26%)	21 (29%)	
Always	4 (0.2%)	11 (3%)	0 (0%)	
Unknown	40 (6%)	26 (7%)	1 (1%)	

Semprini. Conception for HIV-discordant couples. *Am J Obstet Gynecol* 2013.

(continued)

**TABLE 1**  
**Characteristics of study participants** (continued)

Characteristic	Women in retrospective analysis (n = 635) Mean (median)	Follow-up participants (n = 367) Mean (median)	Untraced women (n = 72) Mean (median)	P value <sup>a</sup>
<b>Pregnancy before program entry</b>				
0	367 (58%)	209 (57%)	N/A	
≥1 with HIV-positive partner	97 (15%)	47 (13%)		
Only with other partner(s)	130 (20%)	71 (19%)		
Unknown	41 (6%)	40 (11%)		
<b>Children born before program entry</b>				
0	537 (85%)	300 (82%)	N/A	
≥1 with HIV-positive partner	40 (6%)	19 (5%)		
Only with other partner(s)	17 (3%)	8 (2%)		
Missing	41 (6%)	40 (11%)		
<b>Male partner's CD4 count at entry</b>				
				.56
<200 cell/mm <sup>3</sup>	92 (14%)	45 (12%)	10 (14%)	
200-500 cell/mm <sup>3</sup>	229 (36%)	115 (31%)	25 (35%)	
>500 cell/mm <sup>3</sup>	144 (23%)	69 (19%)	19 (26%)	
Missing	170 (27%)	138 (38%)	18 (25%)	
<b>Male partner on HAART at last SW-IUI cycle</b>				
				.01
Yes	144 (23%)	84 (23%)	9 (13%)	
No	368 (58%)	181 (49%)	49 (68%)	
Missing	123 (19%)	102 (28%)	14 (19%)	

ART, assisted reproductive technology; HAART, highly active antiretroviral treatment; HIV, human immunodeficiency virus; N/A, not applicable; SW-IUI, semen washing with intrauterine insemination.

<sup>a</sup> Untraced women versus follow-up participants.

Semprini. Conception for HIV-discordant couples. *Am J Obstet Gynecol* 2013.

In the retrospective analysis, the average age was 31 and 34 years for the men and women, respectively (Table 1). Of 635 couples, 525 (83%) resided in Italy. Male partners had acquired HIV mainly through injection drug use (70%) or unprotected intercourse (18%). The average number of SW-IUI cycles was 3.3 (range, 1–17). Many couples (53%) reported unsafe sex before entering the program, even after the partner was diagnosed with HIV (25%); 15% had pregnancies and 6% had children with their HIV-positive partner. Low CD4 counts at program entry (<200 cell/mm<sup>3</sup>) were reported in 14% of the male partners, and only 23% were on highly active antiretroviral treatment (HAART) at the time of the last SW-IUI cycle (Table 1).

Follow-up participants were similar to the subjects in the retrospective analysis but were only Italian residents (by de-

sign); had more SW-IUIs (mean, 3.8; range, 1–14); and were more often lacking information on the man's HIV acquisition, baseline CD4 count, and HAART at the last SW-IUI cycle (Table 1). As compared with follow-up participants, untraced women joined the program in earlier years ( $P < .001$ ), left it earlier ( $P \leq .001$ ), were more likely to have male partners who acquired HIV mainly through injection drug use ( $P = .01$ ), had fewer SW-IUI cycles (average 3.4 vs 3.8) ( $P = .05$ ), and were less likely to have had a male partner on HAART at last SW-IUI cycle ( $P = .01$ ) (Table 1).

In the retrospective analysis, 16% of the SW-IUI cycles resulted in pregnancy (95% CI, 15–18%), and 13% resulted in a live birth (95% CI, 11–14%) (Table 2). The cumulative per-woman pregnancy and live-birth rates were 48% (95% CI, 44–52%) and 41% (95% CI, 37–45%),

respectively. The multiple delivery rate was 8% (95% CI, 5–12%). In the follow-up study, the pregnancy and live birth rates among SW-IUI cycles were 17% (95% CI, 15–19%) and 14% (95% CI, 12–16%); the cumulative per-woman pregnancy and live-birth rates were 53% (95% CI, 48–59%) and 47% (95% CI, 42–52%), respectively; and the multiple delivery rate was 5% (95% CI, 3–9%).

No cases of HIV seroconversion were recorded among women included in the retrospective analysis. Evidence of negative HIV status was available for 1899 (90%) SW-IUI cycles (test result on file: 68%; clinician's notation in chart: 18%, other: 4%) (HIV status was unknown 90 days after 214 SW-IUI cycles [10%] performed in 162 women [26%]). On the basis of the cycles with known postinsemination HIV status, the estimate of

**TABLE 2**  
**Pregnancies and live birth deliveries following SW-IUI**

Variable Outcome	Retrospective analysis				Follow-up study			
	SW-IUI cycles (n = 2113)		Women (n = 635)		SW-IUI cycles (n = 1365)		Women (n = 367)	
	n	(%)	n	(%)	n	(%)	n	(%)
No pregnancy	1676	(84) <sup>a</sup>	308	(52) <sup>a</sup>	1134	(83) <sup>a</sup>	168	(47) <sup>a</sup>
Early pregnancy loss	62	(3) <sup>a</sup>	41	(7) <sup>a</sup>	41	(3) <sup>a</sup>	22	(6) <sup>a</sup>
Live birth delivery	255	(13) <sup>a</sup>	238	(41) <sup>a</sup>	185	(14) <sup>a</sup>	172	(47) <sup>a</sup>
Multiple delivery	20	(8) <sup>b</sup>	20	(8) <sup>c</sup>	9	(5) <sup>b</sup>	9	(5) <sup>c</sup>
Live infants	285	<sup>d</sup>	285	<sup>d</sup>	196	<sup>d</sup>	196	<sup>d</sup>
Missing data	120	(6)	48	(8)	5	(0)	1	(0)

SW-IUI, semen washing with intrauterine insemination.

<sup>a</sup> As a percent of cycles/women with known outcomes; <sup>b</sup> As a percent of all deliveries; <sup>c</sup> As a percent of women who had at least 1 delivery; <sup>d</sup> Not applicable as a percent because it includes multiple deliveries.

Semprini. Conception for HIV-discordant couples. *Am J Obstet Gynecol* 2013.

the HIV transmission rate was zero, and its upper 95% confidence limit was 1.8 per 1000 cycles.

The strongest predictor of missing HIV status in the retrospective analysis was the country of residence: the evidence was missing in 71% of non-Italian residents and 16% of Italian residents ( $P < .001$ ; OR, 9.2; 95% CI, 5.2–16.3) (Table 3). HIV status was missing more often among couples who had less than 5 SW-IUI cycles than among couples who had 5 or more cycles ( $P \leq .01$ ; OR, 2.3; 95% CI, 1.2–4.2). HIV status was missing for 90% of women whose pregnancy status was unknown after the last SW-IUI cycle, 23–32% of women who did not achieve a pregnancy or had a biochemical pregnancy/early pregnancy loss, and 15% of women who had 1 live birth or more ( $P = .004$ ).

These differences were also significant among Italian residents (data not shown). Correlates of the risk of HIV transmission (viral load, CD4 cell count at entry into the program, on HAART at time of last SW-IUI, years of abstinence from drug use in the man, history of drug use in the woman, history and length of unprotected sex behavior prior to program entry, and year of enrollment in the program) were not associated with missing HIV status in multiple regression analyses.

Evidence of negative HIV status was available for all of the 367 follow-up participants and for the corresponding 1365 SW-IUI cycles. The HIV transmission rate was zero (upper 95% confidence limit 2.7 per 1000 cycles).

We investigated the concern that untraced women and nonparticipants could conceal events of HIV transmission after SW-IUI. A negative HIV test result was on file for 22 of 72 eligible, untraced women (31%). As reported above, they were not different from participants with respect to correlates of risk of HIV transmission in multiple regression analyses. The male partners of untraced women were less frequently on HAART at the time of the last SW-IUI, but this association reflected the large proportion of couples in this group whose participation in the program occurred before HAART became available and was no longer significant after adjusting by year of entry into the program and year of last SW-IUI. All nonparticipants ( $n = 33$ ) declared that their refusal was not due to HIV acquisition after SW-IUI.

Although no seroconversions related to program participation were documented, additional data were collected during the follow-up study on behaviors and events that occurred outside participation in the program. These follow-up

data indicated that 73 participants (19.6%) attempted conception through unprotected intercourse with their HIV positive partner, either before joining or after leaving the program, and 59 (15.9%) reported that they had children following unprotected intercourse. One woman reported seroconversion following such a conception attempt, 4 years after leaving the program (she was HIV negative 1 year after the last SW-IUI).

## COMMENT

People with HIV can lead healthy lives and raise children<sup>19</sup>: it is important that they have options for conceiving safely. SW-IUI is simple and is likely to be much less expensive than IVF. The 1990 CDC recommendation against semen washing was based on the seroconversion of a woman whose partner's semen was processed by a method that did not reliably separate spermatozoa from seminal plasma and leukocytes.<sup>8</sup> The present study evaluates methods that were developed during this same period of time in Italy to yield HIV-free motile spermatozoa.

The practice of assisted reproduction for HIV-discordant couples in Europe and the United States has since diverged. In Europe, SW-IUI became routine because reports repeatedly confirmed no seroconversion events.<sup>12</sup> Thus, SW-IUI was incorporated into a French law<sup>20</sup> and into a protocol by the European region of the World Health Organization.<sup>21</sup> In the United States, SW-IUI never became part of mainstream patient care. One group in New York obtained ethics board approval for IVF-ICSI followed by embryo transfer.<sup>22</sup>

Compared with no intervention, IVF-ICSI should greatly reduce the risk of HIV transmission, and no seroconversion has occurred in 181 couples who underwent 420 IVF-ICSI cycles.<sup>9</sup> The method, however, is expensive and carries the risks of assisted reproductive technology (ART): in the New York cohort, 41% of the deliveries were associated with multifetal gestation and 74% were preterm. Our findings suggest that SW-IUI may provide a safer and less expensive alternative for fertile couples who are seeking protection from the sex-

ual transmission of HIV. Recently ASRM and ACOG have expressed their support for the provision of fertility services for HIV-discordant couples, and in 2008, the State of California enacted legislation enabling the provision of such services.<sup>23</sup> Infertility specialists are willing to assist people who live with HIV.<sup>24</sup>

The CDC funded this study to provide evidence for a possible review of the 1990 recommendation. Neither the retrospective review of the cohort of 635 women who participated in the program nor the follow-up study of 367 Italian couples identified any seroconversions attributable to SW-IUI. This finding is statistically compatible with a transmission rate as low as 1.8 or 2.7 per 1000 cycles (the upper limits of our estimates), depending on the analysis, and strengthens the published evidence.<sup>11,25-27</sup> SW-IUI was effective, with a per-cycle pregnancy rate of 16% and a cumulative per-woman live birth rate of up to 47%. These rates are comparable with those achieved using IUI with infertile couples<sup>28</sup> and single fertile women treated with donor sperm.<sup>29</sup> Of 255 live birth deliveries, only 20 (8%) were multiple, and SW-IUI seems safer than IVF with respect to the risk of adverse pregnancy outcomes.

The most important limitation of this study is that we did not have complete ascertainment of HIV status for all SW-IUI cycles, and therefore, we cannot exclude the possibility that HIV transmission occurred. The postinsemination HIV status was available for 90% of SW-IUI cycles and 74% of women in the retrospective analysis (100% of follow-up study participants). These ascertainment rates are high but cannot definitely exclude a rare outcome. The strongest predictor of missing HIV status was residence in a country other than Italy; distance may have interfered with patient follow-up.

Other strong predictors were fewer SW-IUIs, a shorter time in the program, and failure to achieve a pregnancy. Correlates of HIV risk were not associated with missing HIV status. Untraced women tended to have been enrolled in the treatment program in early years when effective antiretroviral treatment was not available but were otherwise

TABLE 3

### Correlates of missing HIV status after the last SW-IUI procedure, retrospective analysis

Variable	Missing HIV status		Documented HIV status <sup>a</sup>		P value <sup>b</sup>
	n	(%)	n	(%)	
Number of cycles					
1–4	142	(31)	321	(69)	.01
≥5	20	(12)	152	(88)	
Italian resident					
Yes	84	(16)	441	(84)	< .001
No	78	(71)	32	(29)	
Outcome for last SW-IUI cycle					
No pregnancy	70	(23)	238	(77)	
Biochemical/pregnancy loss	13	(32)	28	(68)	.004
Live birth	36	(15)	202	(85)	
Unknown	43	(90)	5	(10)	
Mode of HIV acquisition by male partner					
Injection drug use	85	(19)	355	(81)	.08
Other	77	(39)	118	(61)	

HAART, highly active antiretroviral treatment; HIV, human immunodeficiency virus; SW-IUI, semen washing with intrauterine insemination.

<sup>a</sup> When evidence about HIV status after the last SW-IUI was available, it always indicated no transmission of HIV infection to the woman; <sup>b</sup> Test of the null hypothesis of no association with lack of missing HIV status, from a logistic regression model including all independent variables displayed as well as the following nonsignificant independent variables: risk of HIV transmission by the man (on the basis of low CD4 count or high viral load and no HAART at entry), man infected through injection drug use, years of abstinence from injection drug use prior to program entry, sperm count after SW at last SW-IUI cycle, year of first visit, and year of last SW-IUI.

Semprini. Conception for HIV-discordant couples. *Am J Obstet Gynecol* 2013.

similar to study participants with respect to HIV risk. Nonparticipants clarified that their refusal to participate was not because they had acquired HIV after SW-IUI. Thus, it seems unlikely that HIV transmission occurred in women with unknown postinsemination HIV status.

An additional limitation was that this study had limited power. Because the risk of HIV transmission is low (1-2 per 1000 acts of unprotected intercourse),<sup>30</sup> a large study size was required<sup>31</sup> to demonstrate protection. Thus, taken in isolation, the present report may not be sufficient to document the protective effect of SW-IUI. However, collectively, the published reports on the safety of SW-IUI<sup>11,25-27</sup> cover more than 5400 cycles with no HIV transmission, reducing the upper 95% confidence limit of the HIV transmission rate to 0.67 per 1000 cycles.

The results pertain to the largest and earliest cohort of HIV-discordant couples who have conceived through SW-IUI and include many couples who participated before the advent of HAART and viral load assessment, when the risk of transmission in the absence of intervention may have been higher. This strengthens the evidence about SW-IUI safety. It is reassuring that intense follow-up achieved complete ascertainment of HIV status without uncovering seroconversions.

Follow-up data also highlighted the importance of safe conception for HIV-discordant couples by documenting HIV transmission to a woman who attempted conception by unprotected intercourse after leaving the program without HIV infection. Reproductive desire can overcome the fear of transmission.<sup>9</sup> Although risk may be reduced through the

use of antiretroviral therapy,<sup>32</sup> there still may be some risk of HIV transmission. In a recent randomized clinical trial, which demonstrated that early initiation of antiretroviral therapy reduces the risk of sexual transmission of HIV compared with delayed initiation, the 1 transmission in the early-therapy group was from a man to his uninfected female partner.<sup>32</sup>

The risk of HIV transmission varies as a function of time-dependent characteristics of both partners. HAART reduces HIV secretion in semen.<sup>33</sup> Genital tract infections increase the concentration of infected leukocytes in semen and enhance the susceptibility of the female genital tract.<sup>34</sup> Thus, viral transmission is more likely to occur when the seminal viral load is high and the woman's genital tract is receptive. SW-IUI can reduce the viral load to undetectable levels every time that the woman needs to be exposed, thus eliminating variation in risk associated with changes in semen.

Finally, SW-IUI should be part of a comprehensive reproductive care strategy for the HIV-discordant couple, in which the risk of transmission is synergistically reduced by managing the HIV-positive man and his response to antiviral treatment,<sup>32</sup> by detecting and treating genital tract infections in both partners, by increasing awareness of fertility, by detecting and managing infertility, and by providing treatment options ranging from SW-IUI to ART.

In conclusion, this study provides reassuring evidence about the safety and effectiveness of SW-IUI for HIV-discordant couples who wish to conceive. If this method is adopted in the United States, it would be prudent to establish a surveillance program to ensure that the laboratories adhere to performance standards and to monitor patient outcomes. ■

#### ACKNOWLEDGMENTS

The study staff expresses its gratitude to Dr Maria Gallo (CDC) for her valuable scientific input, to Ms Jennifer Legardy-Williams (CDC) for her methodological and administrative support, to Ms Elena Parisi for the administrative and logistic support, to Mr Claudio Innocenti for his important contribution to the study datasets development and management, to Professor Ferruccio Osimo for his supervision of the for-

mative phase and development of study tools, and to the counselors Alessia Bajoni and Elisabetta Mangano for their skilled contribution to participant enrollment and support in the follow-up study.

#### REFERENCES

- Sunderam S, Hollander L, Macaluso M, et al. Safe conception for HIV discordant couples through sperm-washing: experience and perceptions of patients in Milan, Italy. *Reprod Health Matters* 2008;16:211-9.
- Duerr A, Jamieson D. Assisted reproductive technologies for HIV-discordant couples. *Am J Bioeth* 2003;3:45-7.
- Gilling-Smith C, Smith JR, Semprini AE. HIV and infertility: time to treat. There's no justification for denying treatment to parents who are HIV positive. *BMJ* 2001;322:566-7.
- Ethics Committee of the American Society for Reproductive Medicine. Human immunodeficiency virus and infertility treatment. *Fertil Steril* 2002;77:218-22.
- American College of Obstetricians and Gynecologists. ACOG Committee Opinion no. 255. HIV: Ethical Guidelines for Obstetricians and Gynecologists, April 2001. *Obstet Gynecol* 2001;97:suppl 1-6.
- Centers for Disease Control and Prevention. Revised guidelines for HIV counseling, testing, and referral. *MMWR Recomm Rep* 2001;50:1-57.
- Ethics Committee of the American Society for Reproductive Medicine. Human immunodeficiency virus and infertility treatment. *Fertil Steril* 2010;94:11-5.
- Centers for Disease Control and Prevention. HIV-1 infection and artificial insemination with processed semen. *MMWR* 1990;39:249, 255-6.
- Sauer MV, Wang JG, Douglas NC, et al. Providing fertility care to men seropositive for human immunodeficiency virus: reviewing 10 years of experience and 420 consecutive cycles of in vitro fertilization and intracytoplasmic sperm injection. *Fertil Steril* 2009;91:2455-60.
- Semprini AE, Vucetich A, Morandi E, Paravicini CL, Pardi G. Removal of p18 immunoreactive cells from semen of HTLV-11/LAV seropositive men. *Colloque INSERM* 1987;154:462.
- Semprini AE, Levi-Setti P, Bozzo M, et al. Insemination of HIV-negative women with processed semen of HIV-positive partners. *Lancet* 1992;340:1317-9.
- Bujan L, Hollander L, Coudert M, et al. Safety and efficacy of sperm washing in HIV-1-serodiscordant couples where the male is infected: results from the European CREATe network. *AIDS* 2007;21:1909-14.
- Marina S, Marina F, Alcolea R, et al. Human immunodeficiency virus type 1-serodiscordant couples can bear healthy children after undergoing intrauterine insemination. *Fertil Steril* 1998;70:35-9.
- Anderson DJ, Politch JA, Oneta M, Tucker L, Semprini AE. Efficacy of conventional semen processing techniques in separation of motile sperm from HIV-1 and HIV-1 host cells. Presented at the 48th Annual Meeting of the American Fertility Society, New Orleans, LA: 1992; [abstract P-213, p. 107-8].
- Persico T, Savasi V, Ferrazzi E, Oneta M, Semprini AE, Simoni G. Detection of human immunodeficiency virus-1 RNA and DNA by extractive and in situ PCR in unprocessed semen and seminal fractions isolated by semen-washing procedure. *Hum Reprod* 2006;21:1525-30.
- Bujan L, Pasquier C, Labeyrie E, Lanusse-Crousse P, Morucci M, Daudin M. Insemination with isolated and virologically tested spermatozoa is a safe way for human immunodeficiency type 1 virus-serodiscordant couples with an infected male partner to have a child. *Fertil Steril* 2004;82:857-62.
- Nicopoulos JD, Almeida P, Vourliotis M, Goulding R, Gilling-Smith C. A decade of sperm washing: clinical correlates of successful insemination outcome. *Hum Reprod* 2010;25:1869-76.
- Kato S, Hanabusa H, Kaneko S, et al. Complete removal of HIV-1 RNA and proviral DNA from semen by the swim-up method: assisted reproduction technique using spermatozoa free from HIV-1. *AIDS* 2006;20:967-73.
- Antiretroviral Therapy Cohort Collaboration. Life expectancy of individuals on combination antiretroviral therapy in high-income countries: a collaborative analysis of 14 cohort studies. *Lancet* 2008;372:293-9.
- Guibert J, Leruez-Ville M, Dulioust E, et al. Assisted procreation technology and people with HIV. *Presse Med* 2008;37:998-1006.
- Support for sexual and reproductive health in people living with HIV/AIDS. Clinical protocol for the WHO European Region. Available at: [http://www.euro.who.int/\\_data/assets/pdf\\_file/0007/70099/E90840\\_Chapter\\_9.pdf](http://www.euro.who.int/_data/assets/pdf_file/0007/70099/E90840_Chapter_9.pdf). Accessed Feb. 20, 2013.
- Sauer MV. Providing fertility care to those with HIV: time to re-examine healthcare policy. *Am J Bioeth* 2003;3:33-40.
- California Code: health and safety code. Section 1644-1644.5. Available at: <http://www.leginfo.ca.gov/cgi-bin/displaycode?section=hsc&group=01001-02000&file=1644-1644.5>. Accessed Nov. 11, 2012.
- Barnhart N, Shannon M, Weber S, Cohan D. Assisted reproduction for couples affected by human immunodeficiency virus in California. *Fertil Steril* 2009;91:1540-3.
- van Leeuwen E, de Vries JW, Jurriaans S, et al. Intrauterine insemination with processed sperm for HIV serodiscordant couples in whom the man is HIV positive. *Ned Tijdschr Geneesk* 2005;149:423-4.
- Coll O, Vidal R, Martinez de Tejada B, Ballescá JL, Azulay M, Vanrell JA. Management of HIV serodiscordant couples. The clinician point of view. *Contracept Fertil Sex* 1999;27:399-404.



- 27.** Marina S, Marina F, Alcolea R, et al. Human immunodeficiency virus type 1-serodiscordant couples can bear healthy children after undergoing intrauterine insemination. *Fertil Steril* 1998;70:35-9.
- 28.** Williams RS, Hillard JB, De Vane G, et al. A randomized, multicenter study comparing the efficacy of recombinant FSH vs recombinant FSH with Ganirelix during superovulation/IUI therapy. *Am J Obstet Gynecol* 2004;191:648-51.
- 29.** Carroll N, Palmer JR. A comparison of intrauterine versus intracervical insemination in fertile single women. *Fertil Steril* 2001;75:656-60.
- 30.** Gray RH, Wawer MJ, Brookmeyer R, et al. Probability of HIV-1 transmission per coital act in monogamous, heterosexual, HIV-1-discordant couples in Rakai, Uganda. *Lancet* 2001;357:1149-53.
- 31.** Englert Y, Lesage B, Van Vooren JP, et al. Medically assisted reproduction in presence of chronic viral diseases. *Hum Reprod Update* 2004;10:149-62.
- 32.** Cohen MS, Chen YQ, McCauley M, et al. Prevention of HIV-1 infection with antiretroviral therapy. *N Engl J Med* 2011;365:493-505.
- 33.** Pasquier C, Sauné K, Raymond S, et al. Determining seminal plasma human immunodeficiency virus type 1 load in the context of efficient highly active antiretroviral therapy. *J Clin Microbiol* 2009;47:2883-7.
- 34.** Bujan L, Daudin M, Matsuda T, et al. Factors of intermittent HIV-1 excretion in semen and efficiency of sperm processing in obtaining spermatozoa without HIV-1 genomes. *AIDS* 2004;18:757-66.