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Effectiveness of semen washing to prevent HIV transmission and assist pregnancy in HIV-discordant couples: a systematic review and meta-analysis

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Abstract

Objective—To evaluate the effectiveness of semen washing in HIV-discordant couples in which the male partner is infected

Design—Systematic review and meta-analysis

Setting—All countries

Patient(s)—Forty single-arm, open label studies among HIV-discordant couples that underwent intrauterine insemination (IUI) or in vitro fertilization (IVF) with or without intracytoplasmic sperm injection (ICSI) using washed semen

Intervention(s)—Semen washing followed by IUI, IVF, or IVF/ICSI

Main outcome measure(s)—Primary outcome: HIV transmission to HIV-uninfected women; secondary outcomes: HIV transmission to newborns and proportion of couples achieving a clinical pregnancy

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Result(s)—No HIV transmission occurred in 11,585 cycles of assisted reproduction using washed semen among 3,994 women (95% confidence interval [CI] = 0–0.0001). Among the subset of HIV-infected men without plasma viral suppression at the time of semen washing, no HIV seroconversions occurred among 1,023 women following 2,863 cycles of assisted reproduction using washed semen (95%CI= 0–0.0006). Studies that measured HIV transmission to infants reported no cases of vertical transmission (0/1,026, 95% CI= 0–0.0029). Overall, 56.3% (2,357/4,184, 95%CI=54.8%–57.8%) of couples achieved a clinical pregnancy using washed semen.

Conclusion(s)—Semen washing appears to significantly reduce the risk of transmission in HIV-discordant couples desiring children, regardless of viral suppression in the male partner. There are no randomized, controlled studies or studies from low-income countries, especially those with a large burden of HIV. Continued development of lower-cost semen washing and assisted reproduction technologies is needed. Integration of semen washing into HIV prevention interventions could help further reduce the spread of HIV.

Keywords

HIV prevention; semen washing; assisted reproduction; serodiscordant; safer conception

INTRODUCTION

Approximately 37 million people are living with HIV worldwide (1) and over 80% of HIV-infected individuals are of childbearing age (2). A cornerstone of successful HIV prevention campaigns has included the promotion of consistent condom use (3). However, many heterosexual HIV-discordant couples desire pregnancy (4, 5) and consistent condom usage impedes this desire. Couples may risk sexual HIV transmission in order to achieve pregnancy if they do not have access to safer reproductive methods (4, 6, 7). Semen washing is a safer reproductive strategy that HIV-discordant couples in which the male is infected can use to achieve pregnancy (8).

Semen washing removes spermatozoa, which are not vectors for HIV, from surrounding seminal fluid, and the HIV-negative sperm fractions are used in assisted reproduction (8). The first study from 1989 offering semen washing to HIV-discordant couples with intrauterine insemination (IUI) found no HIV transmission to 29 uninfected female partners (9). In the two decades following the introduction of semen washing, many more studies have evaluated the effect of this method in conjunction with assisted reproductive technologies, such as IUI, in vitro fertilization (IVF), and IVF with intracytoplasmic sperm injection (ICSI), on HIV transmission in HIV-discordant couples (10–12). We conducted a systematic review and meta-analysis of these studies in order to estimate the safety and effectiveness of semen washing in reducing HIV transmission in HIV-discordant couples in which the male is infected.

Three systematic reviews addressing prevention of HIV transmission in HIV-discordant couples following semen washing have been completed to date. The first by Vitorino *et al.* (10) included 17 observational studies published through December 2007. The second review by Eke *et al.* (11) searched for randomized controlled trials published through

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December 2010 but did not identify any. The third review by Savasi *et al.* included 22 observational studies through May 2012 (12). Our systematic review expands on all three reviews by including observational study designs, studies of any size, and studies published in any language through December 2014. Barnes *et al.* (13) published a related systematic review in 2014 that reviewed 24 articles with the primary objective to evaluate reproductive outcomes among HIV-affected couples following IUI and IVF, specifically fecundability, miscarriage rates, and multiple gestation rates. Our systematic review and meta-analysis complements the review by Barnes *et al.* (13) by evaluating the effectiveness of semen washing in reducing HIV transmission in HIV-discordant couples.

MATERIALS AND METHODS

Using Cochrane Collaboration methods, we conducted a rigorous systematic review and meta-analysis. We assessed evidence quality with the GRADE methodology (14). We reported our findings in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (15).

We developed a search strategy to identify studies with abstracts published through December 2014 in four major electronic databases—MEDLINE (via PubMed), Cochrane Library, SCOPUS, and the WHO's Global Index Medicus. We also searched the International AIDS Conference, British HIV Association Conference, International Conference of Obstetricians and Gynecologists, American Academy of HIV Medicine Conference, American Society for Reproductive Medicine Conference, European Society for Human Reproduction and Embryology Conference, and British Fertility Society Conference for relevant abstracts. In addition to National Library of Medicine Medical Subject Heading (MeSH) terms and other specialized syntax, our search strategies used key terms related to "sperm washing", "assisted reproduction", and "HIV". We also hand searched the references of existing reviews and studies on semen washing. We considered articles irrespective of year of publication, language, or sample size.

The inclusion criteria for studies were: 1) studies that evaluated semen washing; 2) comparative and non-comparative observational and experimental studies, such as clinical trials, cohort studies, and pre-post-studies; 3) studies among HIV-discordant couples in which the male was infected and the female partner was attempting pregnancy; and 4) studies that reported the HIV status of the female partner before and after she underwent assisted reproduction with semen washing. Primary outcomes were serologic evidence of HIV infection in female partners following semen washing and virologic evidence of HIV infection in newborns following birth. We excluded studies that did not measure HIV status of the female partner before and after insemination with washed semen. Secondary outcomes included the proportion of women who achieved clinical pregnancy, the proportion of women who had spontaneous abortions/miscarriages, the proportion of infants born with low birth weight, and the proportion of deliveries that were premature. This review followed the "best available evidence approach" (16) and included single group, open label studies that evaluated all subjects before and after undergoing a single intervention. Although studies using a randomized, blinded control group are considered the

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highest quality, the best available evidence approach can be taken when these studies are not available (16).

Two authors (MZ and JB) independently screened abstracts gathered from electronic database and hand searches. Following discussion on discrepancies about abstract inclusion, the authors selected a list of articles for full text review. They independently extracted the following data from included studies and compiled them into pre-piloted data tables: 1) study details, including design, period of recruitment, setting, number of couples enrolled, eligibility criteria, method of semen washing and testing, and post-wash semen positivity; 2) time point for HIV testing of women and infants and the number of HIV seroconversions among both groups; 3) other clinical data, including viral loads and CD4 cell counts of male patients, and the proportion of male patients on antiretroviral therapy; 4) assisted reproductive techniques used (IUI, IVF, or IVF/ICSI); and 5) reproductive outcomes, including pregnancy, spontaneous abortions, low birth weight, and premature deliveries.

Our systematic review and meta-analysis did not involve human subjects and, therefore, did not require institutional review board approval.

Statistical analysis

We pooled data from the studies to derive an estimate of the total reported number of couples who have used semen washing, the total number of semen washing cycles that have been performed, and the total reported number of infants born among couples using this method. We calculated the 95% confidence intervals (CI) of HIV transmission risk per cycle and per couple for this pooled estimate according to the Jeffreys method (17). We used a one-sided exact binomial test to assess whether the overall probabilities of HIV transmission per cycle and per couple were lower than historical estimates of per-coital probability of HIV transmission, 0.1% (18, 19).

We calculated the proportion of women who acquired HIV for each study and a performed a proportion meta-analysis using the random effects methods of DerSimonian and Laird (20). We tested for heterogeneity in effects using the I^2 statistic.

We calculated the proportion of women achieving clinical pregnancy by dividing the number of reported clinical pregnancies by the total number of cycles initiated, which included cancelled and completed cycles (21). Not all studies in this review reported pregnancy results, and studies that reported pregnancy results did not always report results per couple and per cycle. Moreover, not all studies reported pregnancy results disaggregated by type of assisted reproductive procedure (e.g. IUI vs. IVF or IVF/ICSI). Therefore, numerators and denominators for the pregnancy outcomes vary from the numerators and denominators for the HIV outcomes, and do not consistently sum up to the total number of events observed.

We also conducted a subgroup analysis among those couples in which the HIV-infected male partner had not achieved viral suppression (determined by plasma viral load) at the time of semen washing. This analysis estimated the independent effect of semen washing on HIV prevention in the absence of viral suppression. The subgroup included men without

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viral suppression regardless of antiretroviral use. When articles reported the number of men without viral suppression, but not the explicit number of cycles of assisted reproduction performed on their partners, we estimated this number by assuming that the subgroup underwent a similar number of cycles as couples with viral suppression. The definition of viral suppression used by authors of the included studies varied over time from <50 to <400 copies/mL. In studies where neither viral load nor use of antiretroviral medication was reported, the authors contacted corresponding authors to request this information.

We conducted all data analyses using STATA software version 12.0 (StataCorp LP, College Station, Texas, USA).

Assessing the quality of evidence

In order to comment on the overall quality of evidence, we assessed the risk of bias in each study. This parameter is our main consideration because it informs how confidently we can believe the results of studies. There is no single generic instrument recommended for assessing bias risk in observational studies (22). To determine the risk of bias in each study, we adapted the GRADE Working Group (23) recommendations to assess the following limitations of observational studies: (1) failure to develop and apply appropriate eligibility criteria; (2) flawed measurement of both exposure and outcome; (3) failure to adequately control confounding; and (4) incomplete follow-up. GRADE is not typically used to assess evidence quality of outcomes reported in single-arm studies; therefore, we modified GRADE to evaluate evidence quality for HIV-related outcomes in our review.

RESULTS

Search results

The electronic database and conference website searches retrieved 249 relevant abstracts and hand searching of previous systematic reviews and studies, an additional six abstracts (Figure 1). Of these 255 abstracts, 12 were duplicates and after screening the remaining 243, we selected 47 for full-text review. These articles were published in English (n=40), Hebrew (n=2), Portuguese (n=2), Dutch (n=1), French (n=1), and Spanish (n=1). A total of 40 studies (37 published articles and three conference abstracts) met our eligibility criteria and were included in this review (Table 1).

We found no randomized controlled trials. All included studies were single arm, open-label, pre-/post-test designs. Eighteen studies were prospective, 21 retrospective, and one evaluated both retrospective and prospective cohorts. All studies took place in high and upper-middle income countries representing the North American, European, Asian, and Latin American regions.

Population studied

In the 40 included studies, a total of 4,257 HIV-discordant couples completed 11,915 cycles of assisted reproduction following semen washing (Table 2). Men utilizing assisted reproductive services ranged in age from 29 to 58 years and women from 29 to 40 years (Supplemental Table 1). The vast majority of women (93.8%, 3,994/4,257) and completed

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cycles (97.2%, 11,585/11,915) had an HIV test result available before and after exposure to washed semen (Table 2).

Twenty-one studies reported antiretroviral use among male participants; of the 2,326 men in these studies, 641 (27.6%) were not taking antiretrovirals at the time of semen washing. Twenty-eight studies reported men's plasma viral load; of the 1,890 men in these studies, 985 (52.1%) were not virally suppressed at the time of semen washing. Overall, a minimum of 24% (1,023/4,257) of the 4,257 couples in the 40 studies were estimated to not have achieved viral suppression at the time of semen washing; this includes men without viral suppression at the time of semen washing (n=985) plus men without a viral load measurement, who were known to not be taking anti-retroviral medications (n=38). Among the 21 studies that reported CD4 levels, the average CD4 count of HIV-infected men ranged from 200 to 608 cells/μL.

Semen washing technique

Twenty-nine studies in this review reported washing semen using a technique invented by Semprini in 1989 (Table 1) (8). Some studies used a polymerase chain reaction (PCR) to detect HIV DNA and RNA in the washed semen fractions (24). Five studies reported post-wash semen RNA positivity, ranging from 1.3% to 7.7% (25–29) (Table 1). Seminal fractions that tested positive for HIV were discarded.

HIV transmission following semen washing

There were no cases of HIV transmission following exposure to washed semen among 3,994 women undergoing 11,585 cycles of assisted reproduction (0/11,585, 95% CI = 0–0.0001). This per cycle HIV transmission risk is significantly lower ($P<0.001$) than the historical HIV transmission risk estimate of 0.1% per act of unprotected vaginal intercourse (18, 19). Results of the meta-analysis are presented in Figure 2. Given there were no cases of HIV transmission in any study, the I^2 score was 0% indicating no observed heterogeneity.

There were no HIV seroconversions among the subset of 1,023 couples in which the HIV-infected male was not virally suppressed. These couples underwent an estimated 2,863 cycles of assisted reproduction involving IUI, IVF, and IVF/ICSI (Table 2) and had an estimated per cycle risk of HIV seroconversion of 0 (0/2863, 95% CI = 0–0.0006). This per cycle HIV transmission risk is significantly lower ($P=0.05$) than the historical HIV transmission risk of 0.1% per act of unprotected vaginal intercourse (18, 19).

In studies that provided data on mother-to-child HIV transmission, there were no cases of vertical transmission among 1,026 newborns, either at birth or at the follow-up evaluations (0/1,026, 95% CI = 0–0.0029).

Pregnancy following semen washing with IUI, IVF, IVF/ICSI

Assisted reproduction techniques included IUI with ovarian stimulation or natural cycles (10), IVF or IVF/ICSI. In studies that reported pregnancy outcomes per women, of the 4,184 couples that initiated a cycle of reproduction, 2,357 (56.3%, 95% CI=54.8%–57.8%) had a clinical pregnancy (Supplemental Table 1). Based on reported data, the proportions of

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couples achieving pregnancy undergoing IUI (56.4%, 95%CI=54.2%, 58.5%) and IVF or IVF/ICSI (58.1%, 95%CI=55.0%, 61.1%) were similar (*P*=0.37). In studies that reported pregnancy outcomes per cycle, 19.9% (95%CI=19.1%, 20.6%) of initiated assisted reproduction cycles resulted in a clinical pregnancy (Supplemental Table 1). In studies that reported data on spontaneous abortions, 17.0% (95%CI=15.4%, 18.6%) of clinical pregnancies ended with a spontaneous abortion. Rates of spontaneous abortions following IUI (15.5%, 95%CI=13,4%, 17.7%) and IVF or IVF/ICSI (17.7%, 95%CI=13.9%, 22.0%) were similar (*P*=0.32).

Four studies reported birth weight and preterm delivery outcomes (30–32). Of 259 infants, 115 (44.4%) were born with low (<2500g) or very low (<1500g) birth weight and 107 (41.3%) were born prematurely (prior to 37 weeks of gestation). All women who experienced premature delivery or gave birth to infants with low birth weight had undergone IVF or IVF/ICSI. The rate of multiple gestations among ongoing/delivered pregnancies was 43.5% (81/186).

Quality of evidence

All of the 40 included studies enrolled populations of HIV-discordant couples that addressed the study question. Thirty-nine studies were conducted in a controlled manner with rigorous biological testing for HIV before and after semen washing to measure HIV seroconversion accurately. Individual studies did not calculate effect sizes, nor did they use statistical methods to adjust effect estimates. The risk of missing data was very low overall, with HIV results before and after exposure to washed semen available for 93.8% of women and 97.2% of cycles included in this review. Thirty-nine studies reported no loss to follow-up. Duration of follow-up ranged from 3 months to 12 months, which are appropriate lengths of follow-up to monitor for HIV seroconversion.

DISCUSSION

This is the most comprehensive systematic review and meta-analysis to date evaluating the effect of semen washing on HIV transmission among HIV-serodiscordant couples. We found that semen washing provides a safe and effective method for HIV serodiscordant couples to become pregnant. There were no instances of HIV seroconversion among HIV-uninfected women inseminated with washed semen from their HIV-infected partners. The estimated per cycle HIV transmission risk following semen washing is significantly lower than historical estimates of HIV transmission risk per act of unprotected intercourse in both the overall population reviewed and the subgroup of men without viral suppression at the time of semen washing. Over half of couples in this review achieved a clinical pregnancy, and the rate of spontaneous abortions reported was similar to general population estimates (33). There were no cases of vertical transmission. HIV prevention programs that encourage couples to attempt pregnancy with washed semen as an alternative to intercourse without condoms may help to prevent the incidence of sexual transmission of HIV (6).

Approximately half, 52.1%, of men in studies that reported viral loads of participants were not virally suppressed at the time of semen washing. This number is an underestimate of the true number of men who were virally unsuppressed, as 12 of studies we reviewed did not

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report on viral load, and 19 did not report on antiretroviral use. The absence of HIV transmission in this subgroup of men without viral suppression suggests that semen washing may be a safer and more effective reproductive method in settings where men are unable or unwilling to initiate antiretroviral therapy, are non-adherent, or are not virally suppressed. For example, in sub-Saharan Africa it is estimated that at least one-third of individuals who have been taking antiretrovirals for 12 months do not attain viral suppression (34). Furthermore, up to 48% of men taking effective antiretroviral therapy with undetectable viral load in blood plasma samples have detectable virus in their semen (35, 36). Semen washing may be relevant in such settings where men can access antiretroviral therapy and are highly adherent to it, but remain at risk of transmitting HIV to their partners. Semen washing may offer a safer alternative to intercourse without condoms to prevent HIV transmission to the uninfected female partner.

Some have argued that IVF and IVF/ICSI have better fertility outcomes than IUI (31); however, the overall pregnancy success rates were similar between the methods in the HIV-discordant population reviewed. Additionally, some have argued that IVF or IVF/ICSI poses less risk of HIV transmission than IUI because it uses a single spermatozoon (37). However, neither women nor newborns in the reviewed studies acquired HIV following IUI with washed semen. Additionally, the vast majority of assisted reproduction cycles performed used IUI. While lower cost IVF procedures are being developed and evaluated, the method is currently at least 10 times costlier than IUI in most settings (38, 39). Moreover, IVF is more invasive, carries some surgical risk, and requires additional clinic and laboratory capacity that may not exist in many low-resource settings. Therefore, IUI with washed semen may offer an effective, affordable, feasible, and safe strategy for preventing HIV transmission among HIV-discordant couples desiring children (40).

Traditionally, semen washing followed by assisted reproduction has been used to meet the needs of couples with infertility or subfertility. A 2012 WHO study reported that infertility affects one in four couples in developing countries (41). This study estimated that infertility globally affected 48.5 million heterosexual stable couples that had been attempting pregnancy for five or more years, of which 10 million lived in sub-Saharan Africa, the region most impacted by HIV (41). Safer conception strategies in these areas must consider not only the risk of HIV transmission but also underlying infertility.

Assisted reproduction with washed semen may help both fertile and infertile couples achieve pregnancy, while simultaneously reducing the risk of HIV transmission to the woman and her newborn. However, the availability of semen washing must be considered. Semen washing is currently provided by only a limited number of fertility or reproductive health centers worldwide. Establishing capacity for semen washing in any part of the world will depend on the availability of financial and clinical resources and expertise of clinical staff (40). Efforts to scale-up capacity for semen washing and the development of lower-cost procedures are warranted, particularly in HIV endemic settings.

Despite a comprehensive search of the scientific literature, without language restrictions, limitations to include only published studies, or sample size constraints, we did not find any published randomized control trials or cohort studies with an internal comparison group to

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test the effect of semen washing on HIV prevention in HIV-discordant couples. Without a matched and untreated comparison group, it is difficult to determine whether there would be a significant difference in the rate of HIV transmission between women inseminated with washed semen compared to those who were not. Given the absence of a direct comparison group, studies have evaluated their results against historical estimates of the overall risk of HIV transmission during unprotected intercourse. This comparison has its limitations (42). Furthermore, the lack of studies without a comparator group impacts the quality of our evidence. The GRADE approach to assessing evidence quality by outcome denotes data from observational studies with comparators as “low quality evidence” (23). Evidence quality can be graded down to very low due to a lack of internal comparators in the studies evaluated. Because our included studies are single-arm, observational trials, we assigned them a high risk of bias and graded the evidence quality down to very low (Supplemental Table 2).

The majority of studies included in this review did not report on differences in semen quality between patients with or without previous viral suppression. However, one study by Nicopollous *et al.* noted that semen parameters were not significantly different between men with detectable or undetectable viral loads, despite significantly lower CD4 counts among unsuppressed men. There is evidence in the literature that while HAART impairs semen parameters, resulting in lower ejaculate volume and sperm with less motility (43), HIV parameters such as CD4 cell count, viral load, and duration of antiretroviral therapy, are not significantly correlated with semen quality (44).

Studies included in this review did not report whether there were significant differences in pregnancy rates in the different techniques (IUI, IVF, ICSI) between patients with or without viral suppression. However, one study by Savasi *et al.* calculated the rates of clinical pregnancy following IUI among participants taking antiretroviral therapy and those not. The rate of clinical pregnancy per cycle in the group taking antiretroviral medication (17.4%, 332/1902) was not significantly different ($p = 0.105$) from the rate of clinical pregnancy in the group not taking antiretroviral medication (25%, 124/498). Because IUI and IVF procedures typically wash sperm in order to prepare it for insemination regardless of the HIV status of the patient, this review is unable to comment on rates of birth outcomes following assisted reproduction without semen washing.

A future direction of research may explore the utility of conducting post-wash semen HIV testing. Very few (n=5) of the studies included in this review reported on this method. Additionally, no study compared rates of HIV transmission following assisted reproduction with or without post-wash semen HIV testing. Therefore, we are unable to comment on the utility of conducting post-wash semen HIV testing prior to IUI or IVF in this context.

This review has numerous strengths, including an exhaustive search strategy, inclusion of 20 years’ of multi-country and multi-language studies, and the consistency of results across the included studies. Additional strengths of the studies included in this review include the use of serological and virologic testing of women before and after semen washing and extremely high rates of participant retention. Finally, a major strength of this review is its large sample

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size; this review includes 11,585 completed cycles of assisted reproduction with known HIV outcomes, and 2,863 cycles in which HIV-infected men had not attained viral suppression.

CONCLUSION

The absence of HIV seroconversion in the studies reviewed suggests that semen washing prevents HIV transmission in HIV-discordant couples attempting pregnancy where the male is infected. There is a lack of studies on semen washing from low-income and lower-middle income countries, including countries in Sub-Saharan Africa with a high HIV prevalence. Efforts to develop lower-cost semen washing and assisted reproduction technologies that can be used in less resourced settings are therefore warranted. Integration of semen washing into HIV prevention protocols may help curb the incidence of sexual HIV transmission.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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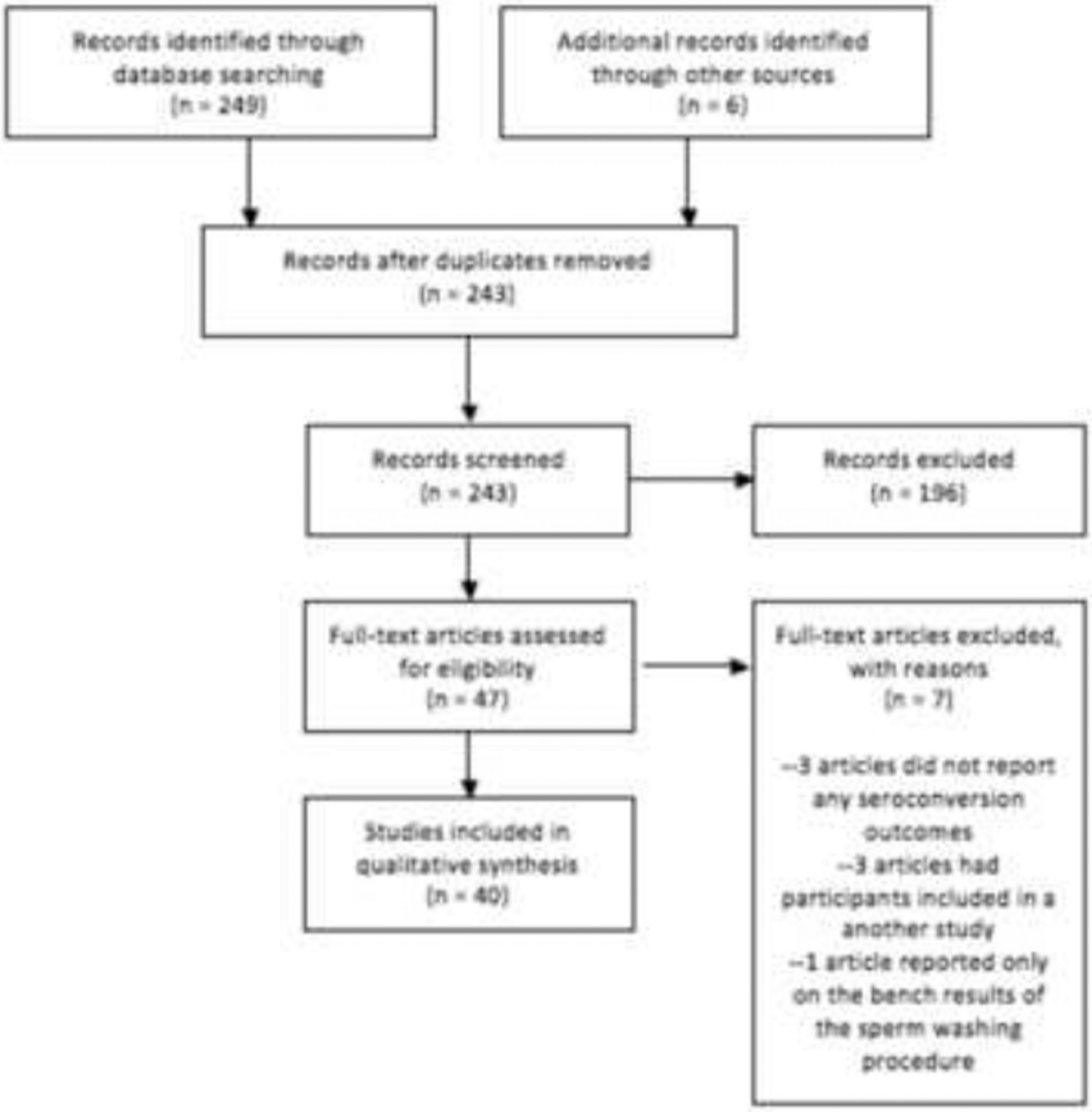

Figure 1. PRISMA Flow Chart
Article selection process using the PRISMA guidelines flowchart

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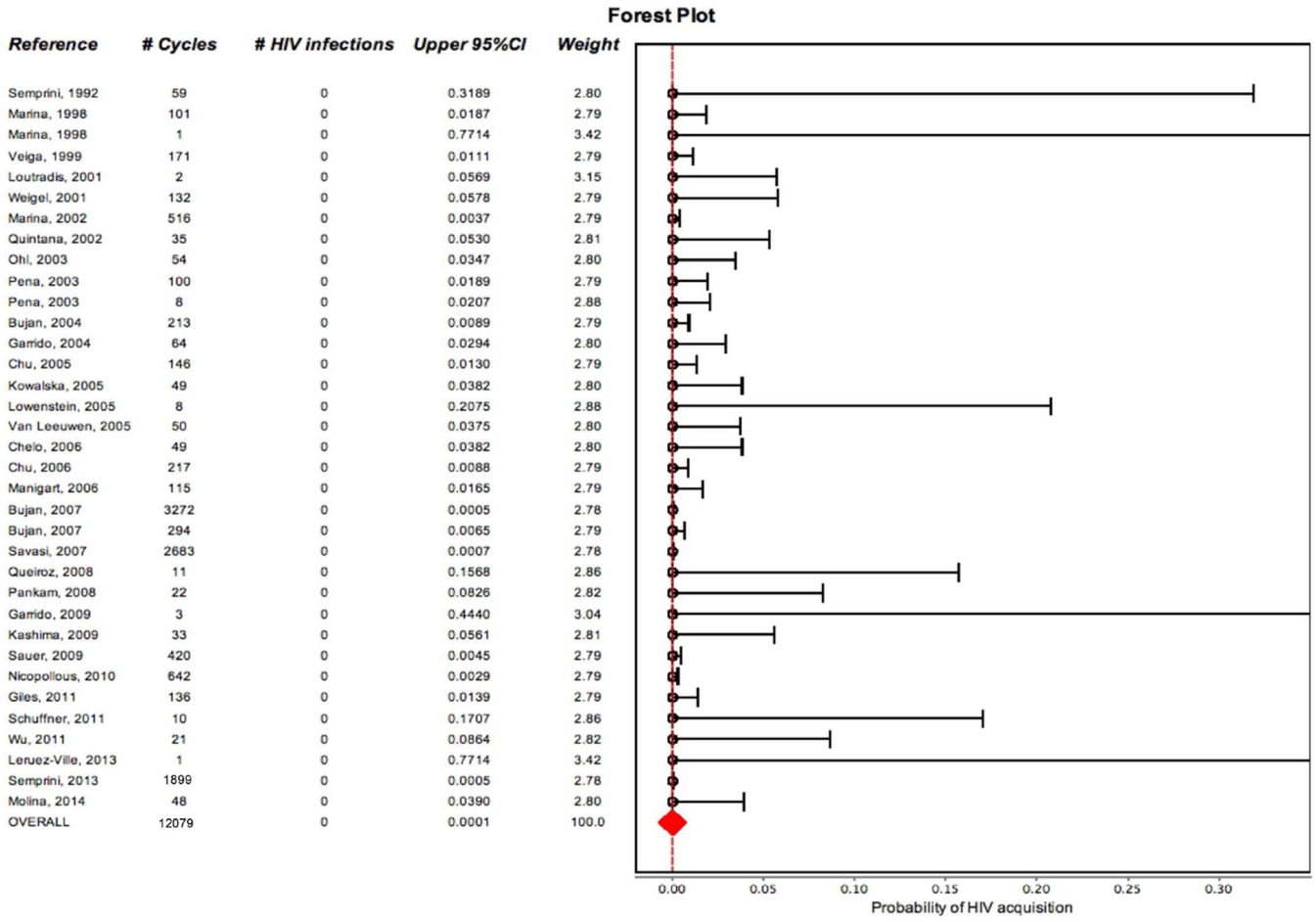

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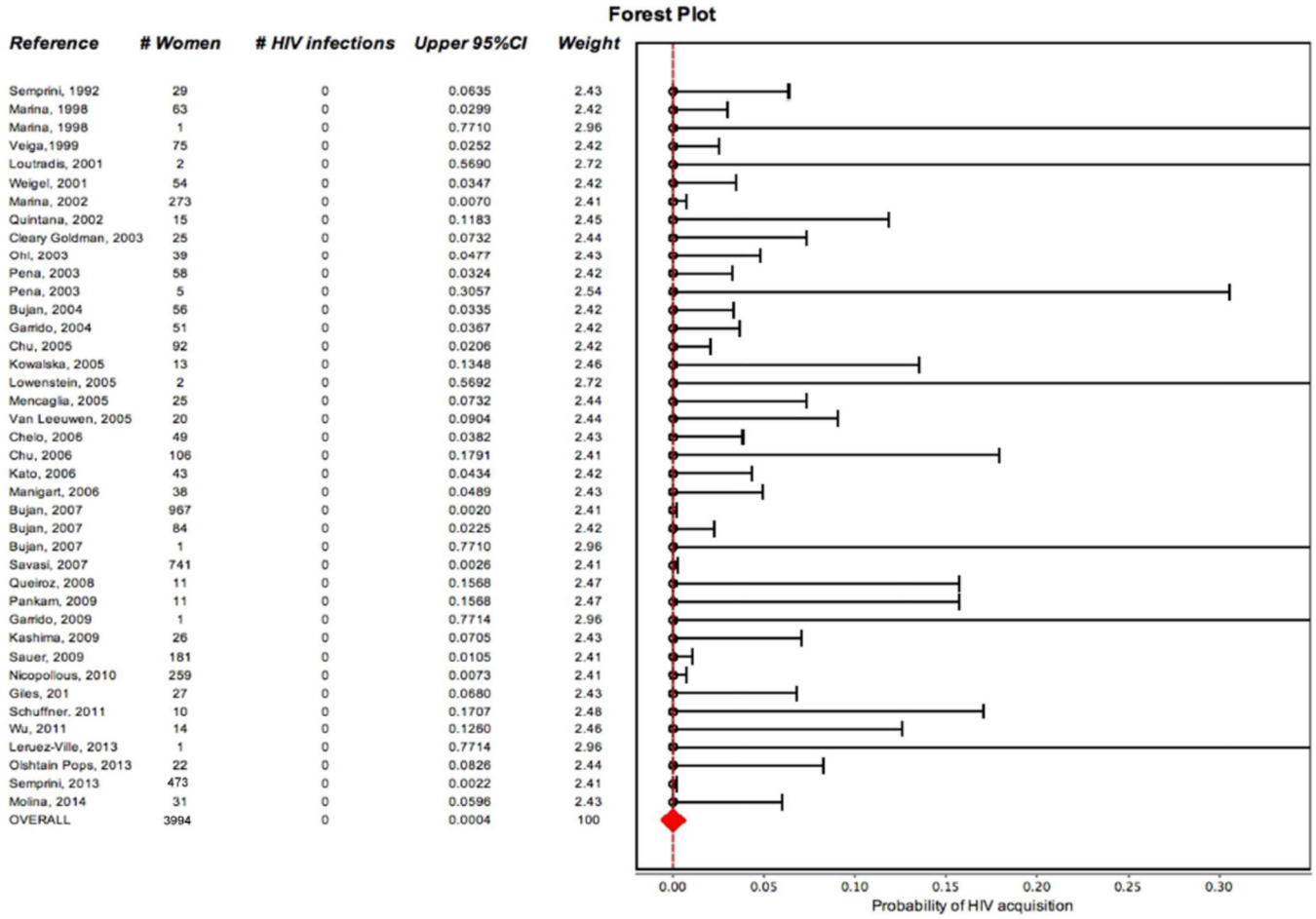

Figure 2. Figure A—Forest plot of HIV Transmission per cycle; Figure B—Forest plot of HIV transmission per woman

Proportion meta-analysis plot for HIV transmission probability and upper 95% confidence interval (CI) following sperm washing per cycle (a) and per woman (b)

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Table 1

Description of 40 studies included in this review, with assisted reproduction technique and semen washing technique used

Study	Location	Period of Recruitment	Study Design	Couples (n)	Assisted Reproduction Technique	Technique used in semen preparation	Technique used in post-wash semen testing	Post-wash semen positivity (%)
Semprini 1992 (9)	Italy	NR	Single-arm open trial	29	IUI	Density gradient & swim-up	mAb HIV antibody	NR
Marina 1998 (25)	Spain	NR	Single-arm open trial	63	IUI	Density gradient & swim-up	PCR, RT-PCR	5.6 (DNA)
Marina 1998 (45)	Spain	NR	Case report	1	IVF+/−ICSI IUI	Density gradient & swim-up	PCR, RT-PCR	NR
Veiga 1999 (46)	Spain	02/1997–12/1998	Single-arm open trial	75	IUI IVF+/−ICSI	Density gradient & swim-up	PCR, RT-PCR	NR
Loutradis 2001 (47)	Greece	1999–2000	Case series	2	IVF+/−ICSI	Density gradient & swim-up	NR	NR
Weigel 2001 (48)	Greece	1991–1999	Retrospective chart review	54	IUI IVF+/−ICSI	Density gradient & swim-up	PCR	NR
Marina 2002 (26)	Spain	NR	Single-arm open trial	273	IUI IVF+/−ICSI	Density gradient & swim-up	PCR, RT-PCR	2.5 (DNA), 1.3 (RNA)
Quintana 2002 (49)	Argentina	NR	Single-arm open trial	15	IUI IVF+/−ICSI	Density gradient	PCR	NR
Cleary-Goldman 2003 (31)	USA	01/1997–06/2002	Retrospective chart review	25	IVF+/−ICSI IUI	Double swim-up	NR	NR
Ohl 2003 (50)	France	01/2001–07/2002	Single-arm open trial	39	IUI IVF+/−ICSI	Density gradient & swim-up	PCR	NR
Pena 2003 (31)	USA	07/1997–07/2002	Retrospective chart review	58	IVF+/−ICSI	Density gradient & swim-up	NR	NR
Pena 2003 (51)	USA	08/1997–02/2002	Case series	5	IVF+/−ICSI	—	NR	NR
Bujan 2004 (52)	France	12/1999–12/2001	Single-arm open trial	56	IUI	Density gradient & swim-up	PCR, RT-PCR	NR
Garrido 2004 (27)	Spain	08/2001–10/2003	Retrospective chart review	51	IVF+/−ICSI	Density gradient & swim-up	Nested PCR, RT-PCR	7.7 (RNA), 2.6 (DNA)
Chu 2005 (53)	USA	07/1997–04/2004	Retrospective chart review	92	IVF+/−ICSI	Density gradient & swim-up	PCR	NR

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Study	Location	Period of Recruitment	Study Design	Couples (n)	Assisted Reproduction Technique	Technique used in semen preparation	Technique used in post-wash semen testing	Post-wash semen positivity (%)
Kowalska 2005 (54)	Poland	05/2002–03/2005	Case series Single-arm	13	IUI	Density gradient & swim-up	PCR, RT-PCR	NR
Lowenstein 2005 (55)	Israel	NR	Single-arm open trial	2	IUI	Density gradient	RT-PCR	NR
Mencaglia 2005 (56)	Italy	01/2001–12/2003	Single-arm open trial	25	IVF+/−ICSI	Density gradient & swim-up	NR	NR
Van Leeuwen 2005 (57)	The Netherlands	2003–10/2004	Single-arm open trial	20	IUI	Density gradient & swim-up	RT-PCR	NR
Chelo 2006 (58)	Italy	NR	Single-arm open trial	49	IVF+/−ICSI	Density gradient & swim-up	RT-PCR	NR
Chu 2006 (59)	USA	08/1997–03/2004	Retrospective chart review	106	IVF+/−ICSI	—	NR	NR
Kato 2006 (60)	Japan	NR	Single-arm open trial	43	IVF+/−ICSI	Density gradient & swim-up	RT-nested PCR	NR
Manigart 2006 (61)	Belgium	01/2000–06/2005	Single-arm open trial	38		Density gradient & swim-up	RT-PCR	NR
Bujan 2007 (62)	Europe	1989–2003	Retrospective multicentre study	1036	IUI IVF+/−ICSI	Density gradient & swim-up	NR	NR
Bujan 2007 (63)	France	06/2000–08/2003	Retrospective chart review	84	IUI	Density gradient & swim-up	PCR, RT-PCR	NR
Bujan 2007 (64)	France	2004	Case report	1	IVF+/−ICSI	Density gradient & swim-up	RT-PCR	NR
Savasi 2007 (28)	Italy	01/2002–01/2006	Retrospective chart review	741	IUI IVF+/−ICSI	Density gradient & swim-up	Real-time PCR	4.0 (RNA)
Queiroz 2008 (65)	Brazil	06/2001–05/2007	Retrospective chart review	11	IVF+/−ICSI	Density gradient	RT-PCR	NR
Pankam 2008 (66)	Thailand	08/2006–12/2007	Single-arm open trial	43	IUI	Density gradient & swim-up	NR	NR
Garrido 2009 (67)	Spain	08/2007-11/2008	Case report	1	IVF+/−ICSI	Density gradient	PCR	NR
Kashima 2009 (68)	Japan	01/2001–07/2007	Single-arm open trial	26	IVF+/−ICSI	Density gradient & swim-up	Nested PCR	NR
Sauer 2009 (30)	USA	01/1998–12/2007	Retrospective chart review	181	IVF+/−ICSI	Density gradient & swim-up	PCR	NR
Nicopollous 2010 (69)	UK	1999–2008	Retrospective chart review	259	IUI IVF+/−ICSI	Density gradient & swim-up	PCR	NR

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Study	Location	Period of Recruitment	Study Design	Couples (n)	Assisted Reproduction Technique	Technique used in semen preparation	Technique used in post-wash semen testing	Post-wash semen positivity (%)
Giles 2011 (70)	Australia	2003–06/2010	Single-arm open trial	27	IUI IVF+/−ICSI	Density gradient	PCR, RT-PCR	NR
Schuffner 2011 (71)	Brazil	NR	Case Report	10	IUI	Density gradient & swim-up	RT-PCR	NR
Wu 2011 (72)	Taiwan	2005–2009	Single-arm open trial	14	IVF+/−ICSI	Density gradient & swim-up	Real-time PCR	NR
Leruez-Ville 2013 (73)	France	NR	Case report	1	IVF+/−ICSI	Density gradient	Real-time PCR, RTPCR	NR
Olshtain-Pops 2013 (29)	Israel	NR	Single-arm open trial	22	IUI	Density gradient	PCR	2.9 (DNA)
Semprini 2013 (8)	Italy	07/1989–04/2005	Single-arm open trial & Retrospective chart review	635	IUI	Density gradient & swim-up	RT-PCR	NR
Molina 2014 (32)	Spain	11/2005–12/2009	Retrospective chart review	31	IVF+/−ICSI	Density gradient	Real-time RT-PCR	NR

NR = not reported in the study; IUI = Intrauterine insemination; IVF+/−ICSI= In vitro fertilization with or without intracytoplasmic sperm injection; RT-PCR = Reverse transcriptase Polymerase Chain Reaction

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Table 2

Numbers of couples and cycles included in this review, and number of HIV seroconversions

Number of couples and cycles	N *or* % (n/N)
Initiated cycles of assisted reproduction with washed semen	12,079
Completed cycles of assisted reproduction with washed semen	11,915
Couples with at least one completed cycle of assisted reproduction with washed semen	4,257
Women with known HIV results after exposure to washed semen	93.8 (3,994/4,257)
Completed cycles of assisted reproduction among women with known HIV results after exposure to washed semen	97.2 (11,585/11,915)
Men known to be taking antiretroviral therapy at time of semen washing	39.5 (1,685/4,257)
Men who were known to have not achieved viral suppression at time of semen washing (from plasma testing)	27.7 (985/4,257)
Completed cycles of assisted reproduction using washed semen among subgroup of couples with a male partner who was not virally suppressed	24.0 (2863/11,915)
Number of HIV seroconversions	n/N (95% CI)
Per completed cycle of assisted reproduction, overall	0/11,585 (0, 0.0001)
Per woman with known HIV outcome, overall	0/3,994 (0, 0.0004)
Per completed cycle, among subgroup of couples with a male partner who was not virally suppressed	0/2,863 (0, 0.0006)
Per infant	0/1026 (0, 0.0029)