

# Reproductive assistance in HIV serodiscordant couples

V. Savasi<sup>1,\*</sup>, L. Mandia<sup>1</sup>, A. Laoreti<sup>1</sup>, and I. Cetin<sup>1,2</sup>

<sup>1</sup>Unit of Obstetrics and Gynecology, Department of Clinical Sciences, Hospital 'L. Sacco', University of Milan, Via G. B. Grassi, 74, 20157 Milan, Italy <sup>2</sup>Centre for Fetal Research Giorgio Pardi, University of Milan, Milan, Italy

\*Correspondence address. E-mail: valeria.savasi@unimi.it

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**BACKGROUND:** Three quarters of individuals infected with human immunodeficiency virus (HIV) are in their reproductive years and may consider pregnancy planning. Techniques have been developed which can minimize the risk of HIV transmission in these couples, and the current literature on this topic is reviewed here.

**METHODS:** We reviewed the literature for the following topics: risk of HIV transmission, effects of HIV infection on fertility, reproductive assistance in industrialized and low-income countries, pre-exposure chemoprophylaxis (PrEP) and timed intercourse in HIV-discordant couples for both male and female positivity. Relevant publications were identified through searches of the EMBASE Medline and PubMed databases, the Google-indexed scientific literature and periodic specialized magazines from the on-line Library Service of the University of Milan, Italy.

**RESULTS:** In serodiscordant couples in which the man is positive, the primary method used to prevent HIV transmission is 'sperm washing', followed by IUI or IVF. Data show that sperm washing in HIV-positive men has not produced seroconversion in women or their offspring; however, the evidence is limited. Recently, increasing evidence describing PrEP for HIV prevention has been published and PrEP could be an alternative to ART for fertile couples. Usually HIV-infected women undergo self-insemination around the time of ovulation. Few studies have been published on IVF outcome in HIV-infected women.

**CONCLUSIONS:** Assisted reproduction programmes should be integrated into global public health services against HIV. For HIV serodiscordant couples with infected men, sperm washing should be the first choice. However, timed intercourse and PrEP for HIV prevention has been reported. Recent data highlight the possible impairment of fertility in HIV-infected women. Efforts to design a multicentric study should be strengthened.

**Key words:** human immunodeficiency virus / sperm washing / IVF / intrauterine insemination / pre-exposure chemoprophylaxis

## Introduction

At the beginning of the acquired immune deficiency syndrome (AIDS) epidemic, because of the poor prognosis of those infected, couples with an infected human immunodeficiency virus (HIV) partner were discouraged from planning a pregnancy. Nowadays, AIDS remains worldwide a serious condition with a continuing morbidity and mortality, even in industrial countries where efficient and innovative treatments are available. The number of people living with HIV worldwide continued to grow in 2010, reaching an estimated 35 million people, with ~2.7 million new infections.

The total number of people living with the virus in 2010 was >20% higher than the number in 2000, and the prevalence was roughly 3-fold higher than in 1990 (AIDS Global Report, 2010). On the other hand, there has been an unprecedented increase in access to HIV treatment in 2000–2010, also in resource-limited settings where antiretroviral medications were previously unavailable [World Health Organization (WHO), United Nations Children's Fund, UNAIDS, 2009].

So, with the introduction of antiretroviral therapies, life expectancy of seropositive patients as well as their quality of life have dramatically improved during the last 10 years, and many couples with an HIV-positive partner can consider pregnancy planning (Minkoff and Santoro, 2000; Englert et al., 2001; Bujan et al., 2004). Assisted reproductive technology (ART) reduces the risk of contamination of the uninfected partner and helps couples to conceive (Minkoff and Santoro, 2000; Garrido et al., 2004; Semprini and Fiore, 2004; Savasi et al., 2007). The ASRM Committee on Ethics (Ethics Committee of the American Society for Reproductive Medicine, 2010), and the International Federation of Gynecology and Obstetrics (FIGO Committee for the Ethical Aspects of Human Reproduction and Women's Health, 2006) modified their guidelines concerning ART for people infected by HIV to allow assisted reproduction in HIV discordant couples.

## Methods

The EMBASE Medline and PubMed databases, the Google-indexed scientific literature and periodic specialized magazines from the on-line Library Service of the University of Milan were searched to identify relevant publications. Searches were performed using the following keywords: 'HIV and reproductive assistance', 'HIV and reproductive health', 'HIV and assisted reproductive technology (ART)', 'sperm washing', 'HIV and *in vitro* fertilization (IVF)', 'HIV and intrauterine insemination (IUI)', 'HIV serodiscordant couples', 'pre-exposure chemoprophylaxis (PrEP)', 'HIV positive women and fertility' and 'timed intercourse'. The search was performed up to May 2012 with no lower date limit.

Each author performed the search independently and the other authors subsequently checked the included articles. Reference lists of all primary and review articles were reviewed for relevant citations. Articles in languages other than English were excluded.

## Reproductive assistance in HIV serodiscordant couples where the man is positive

### HIV in semen

Stewart et al. (1985) first reported that semen used for donor artificial inseminations can transmit HIV-1. HIV-1 is present in the semen of

infected men as free HIV-1 RNA particles in the seminal plasma and as cell-associated virus in non-spermatozoal cells (NSC), such as CD4-positive lymphocytes and macrophages, which represent the principal reservoirs. Studies on the presence of HIV in spermatozoa provided contradictory results. Several reports indicated that proviral HIV-1 DNA can be detected in spermatozoa of infected men by extraction PCR, or by *in situ* PCR (IS-PCR) (Bagasra et al., 1988, 1994; Miller et al., 1989; Gobert et al., 1990; Baccetti et al., 1991; Nuovo et al., 1994; Scofield et al., 1994; Muciaccia et al., 1998) but other studies contradicted these findings demonstrating that HIV viral particles cannot be found in washed spermatozoa isolated from NSC and seminal plasma (Lasheeb et al., 1997; Quayle et al., 1997; Pudney et al., 1990; Bujan et al., 2004).

Persico et al. (2006) published a paper where all samples of spermatozoa recovered after separation by gradient centrifugation and swim-up (sperm washing) were free of HIV-1 RNA above the threshold of 50 copies/ml and of proviral DNA by highly sensitive extractive nested PCR. This confirms the findings of previous reports in which nested PCR (Ohl et al., 2003; Bujan et al., 2004; Garrido et al., 2004) was used to assess the validity of sperm washing in HIV-infected semen. IS-PCR was not used in recent works owing to its methodological limitations (Persico et al., 2006). Nevertheless, Muciaccia et al. (2007) reported the presence of HIV-1 DNA in a small number of abnormal spermatozoa from HIV-1 infected subjects.

In untreated HIV-1 infection, the concentration of HIV-1 RNA in semen is, on average, 10-fold lower than that in blood plasma and in general, HIV-1 RNA concentrations in the blood and seminal plasma show a parallel decrease in response to highly active antiretroviral therapy (HAART). Nevertheless, in some individuals, HIV-1 RNA can be detected sporadically in the semen despite stable levels or even undetectable levels of HIV-1 RNA in blood. Persico et al. (2006) found that six out of the seven seminal plasma samples which tested positive for HIV-1 RNA were from patients on HAART. Four men had elevated blood viral load and three presented an undetectable viremia. These findings confirm previous reports of discrepancies between hematic and seminal HIV-1 concentrations (Bujan et al., 2004; Xu et al., 2005), either related to subtherapeutic concentrations of antiretroviral drugs in the male seminal tract or to local production of HIV-1 RNA from localized cells, which respond poorly to treatment.

In conclusion, while the debate on whether or not spermatozoa harbor HIV remains open, only two cases of viral transmission using only sperm centrifugation have been reported (Englert et al., 2004). Couples who participate in the programme of ART should be informed that a theoretical risk of infection remains (Lesage et al., 2006). However, a reduction of viral load to undetectable levels, or even 1% of the original viral load, can be achieved and should certainly reduce, if not eliminate, the risk of viral transmission, as shown by the cumulative clinical data.

### Semen handling and processing

Sperm washing is the semen-processing method developed 20 years ago in Milan by Semprini et al. (1992) with the goal of separating infected NSC and free HIV-1 particles from a motile fraction of spermatozoa. Semen samples are obtained by masturbation after 3–5 days of sexual abstinence and semen parameters are assessed as outlined

by the WHO criteria (WHO, 2010). Handling the semen samples of HIV-seropositive men requires specific precautions and facilities dedicated to the processing of an infectious agent. Potentially infected gametes and embryos must be handled separately in a special biosafety cabinet workstation (Muciaccia *et al.*, 2007). Dedicated-use incubators and storage tanks should be devoted solely to specimens from men known to be HIV positive. The standard semen-washing method devised in Milan is a three-step system. Samples are processed using a 40–80% density gradient to separate motile spermatozoa from NSC, immotile spermatozoa and seminal plasma. The ejaculate is layered over the gradient and centrifuged at 400 g for 30 min. After centrifugation, the supernatant is removed and the sperm pellet recovered and resuspended in 3 ml of fresh medium. A washing at 400 g for 10 min is performed and the supernatant is discarded. One ml of medium is then gently layered on the pellet and the tube is incubated at 37° for 1 h. After swim-up the washed sperm is used for IUI or IVF procedures. Since 1992, several different methods of semen processing have been proposed. In fact, media, steps of processing, concentration of gradient solutions, time of centrifugation and method of collection of the bottom layer vary among laboratories (Table I).

It has been demonstrated that ~5% of all motile sperm fractions from HIV-1 seropositive men remain positive for HIV-1 following the gradient/swim-up procedure (Politch *et al.*, 2004) and the gradient/swim-up method is a relatively long procedure that requires advanced technical expertise. For this reason, Politch developed a 'double tube gradient' sperm separation technique that uses the same discontinuous gradient approach but the gradient is formed within a tube insert (inner tube) concluding that this method is a

relatively simple and quick technique, superior in terms of excluding HIV-1 from the motile sperm fraction and resulting in greater sperm yield compared with the standard method (Politch *et al.*, 2004). Tachet *et al.* (1999) using a two-step density gradient reported that 14.6% of sperm-enriched fractions tested positive for HIV-1 RNA. Hanabusa *et al.* (2000) suggest that sperm washing by density gradient centrifugation alone is insufficient to remove HIV-1 RNA from semen and that the procedure should be combined with an additional swim-up separation step. Other authors proposed variants of the classic sperm-washing technique (Marina *et al.*, 1998a, b; Garrido *et al.*, 2005; Mencaglia *et al.*, 2005) (Table I). Performing a variant of sperm washing, Garrido reported 10% of the samples positive by nested PCR and the probabilities were higher as the number of determinations increases. In the same year, Loskutoff *et al.* (2005) published a novel method. He hypothesized that the critical issue of the standard method is removing the upper density gradient layers (including the potentially infected seminal plasma) by aspiration. So he designed and produced a novel polypropylene [U.S. Food and Drug Association (FDA) medical grade] tube insert that not only allows access to the pellet without any risk of exposing the treated sperm to the upper (potentially contaminated) layers but also facilitates the layering of multiple density gradients. Kato *et al.* (2006) modified again the sperm-washing method and spermatozoa obtained were tested by nested PCR with a detection limit of one copy (Table I). Sauer and Chang (2002) simplified processing the whole semen with a double-density gradient and two washes. All the researchers agree that it is not possible to guarantee that all viral particles are absent from a washed sperm preparation.

The key points to note are: the molecular technique used for detection of RNA and DNA HIV in semen, the sensitivity of laboratory assays for detecting virus, that usually varies between 50 and 800 copies/ml, and the presence of inhibitors of PCR in the semen, such as lactoferrin, peroxides and mostly zinc residues, that might interfere with the action of Taq polymerases (Sauer and Chang, 2002; Loskutoff *et al.*, 2005; Savasi *et al.*, 2010). These inhibitors could be removed by silica bead extractions (Fiscus *et al.*, 2000). The bDNA assay is less likely to be affected by inhibitory substances in the seminal plasma as the assay does not amplify targeted HIV-1 RNA molecules (Dunne *et al.*, 2003).

## Sexual transmission of the virus

Worldwide, the predominant mode of HIV transmission is heterosexual intercourse. Knowledge of the rates and risk factors of transmission is essential for the design and the evaluation of prevention programmes (Shattock and Moore, 2003). A longitudinal study on HIV transmission by heterosexual partners calculated that the rate for transmission per contact was 5 per 1000 if the index partner was in the advanced stage of infection and 0.7 per 1000 if the index partner was asymptomatic (De Vincenzi, 1994). The viral load is the chief predictor of the risk of transmission of HIV-1, and transmission is rare among individuals with levels of <1500 copies of HIV-1 RNA (Quinn *et al.*, 2000). The viraemia load is correlated, even if not directly, with virospermia. Chakraborty *et al.* (2001) studied a model to predict the transmission of HIV-1 from men to women. When the semen contains 100 000 copies of HIV RNA, the probability of HIV is 1 per 100 intercourses; with 1000 copies of HIV RNA in

**Table I** Published studies on washing technique for human sperm.

Study	Sperm-washing technique
Semprini <i>et al.</i> (1992); Savasi <i>et al.</i> (2007)	Whole semen, double-density gradient, one wash, swim-up
Hanabusa <i>et al.</i> (2000)	Semen dilution 1:1, quadruple-density gradient in double tube (glass capillary tube), swim-up
Sauer and Chang (2002)	Whole semen, double-density gradient, two washes
Marina <i>et al.</i> (1998a, b); Mencaglia <i>et al.</i> (2005); Garrido <i>et al.</i> (2005)	Semen dilution 1:1, one wash, triple-density gradient, one wash, swim-up
Politch <i>et al.</i> (2004)	Whole semen, double-density gradient in a double tube, removal of inner tube, one wash
Bujan <i>et al.</i> (2004)	Whole semen, triple-density gradient, two washes, swim-up
Loskutoff <i>et al.</i> (2005)	Semen dilution 1:4, one wash, triple-density gradient (trypsin added) in double tube, two washes
Kato <i>et al.</i> (2006)	Semen dilution 1:2, precipitation of debris, filtration of suspension, 1 Percoll centrifugation, double-density gradient, tube cut, swim-up

semen, transmission probability is 3 per 10 000 intercourses. On the other hand, men with acute HIV-1 infection are biologically hyperinfectious because of increased genital shedding of HIV-1 (Pilcher et al., 2004). In addition, during acute infection, the HIV-1 load increases and decreases in semen approximately in parallel with changes occurring in blood. HAART has been shown to be highly effective in reducing plasma levels of HIV RNA and in diminishing the risk of transmission (Castilla et al., 2005). Vernazza et al. (2000) demonstrated that <4.2% of men on HAART who have HIV RNA below detectable levels in blood are likely to have detectable virus in semen. Nevertheless, the absence of detectable HIV-RNA in semen does not prove that such patients cannot transmit HIV, because it is important to consider the relative importance of cell-associated virus in sexual transmission (Vernazza et al., 2000). Baeten et al. (2011) reported that higher genital HIV-1 RNA concentrations are associated with greater risk of heterosexual HIV-1 transmission, and this effect was independent of plasma HIV-1 concentrations. Not all viruses are transmitted with the same modalities and some mucosally transmitted viruses are biologically different from non-mucosally transmitted viruses. A genetically and phenotypically diverse quasi-species of virus is present in the semen, cervicovaginal secretions or blood of individuals with chronic HIV-1 infection but, most often, only a single virion or virally infected cell is transmitted and leads to productive clinical infection.

The results of one study, in which 648 stable serodiscordant heterosexual couples were enrolled, showed sexual relationship with the index partner as the only risk of exposure (Del Romero et al., 2010). In couples in which the HIV partner was taking antiretroviral treatment no infection of the seronegative partner was observed, whereas in couples with the index partner not on antiretroviral therapy 9.2% of partners was infected: during follow-up, in the first group, for over 7000 unprotected intercourses and 47 natural pregnancies, no HIV seroconversion was observed, while in the second group for about 11 000 unprotected intercourses and 50 natural pregnancies the HIV seroconversions numbered five. So the avoidance of unprotected intercourse and combined antiretroviral treatment for the infected partner, in accordance with protocols, are complementary measures to prevent HIV transmission.

In conclusion, antiretroviral treatment is a powerful measure to prevent HIV transmission in discordant couples. More recent studies found even larger effects, suggesting that stronger treatment regimes are associated with even greater reductions in transmission, especially if the HIV-1 positive partner has  $\leq 550$  CD4 cells/ $\mu\text{l}$  (Donnell et al., 2010; Cohen et al., 2011; Reynolds et al., 2011). Questions remain about durability of protection, the balance of benefits and adverse events associated with earlier therapy, long-term adherence and transmission of ART-resistant strains to partners (Anglemyer et al., 2011).

## Assisted reproduction

The ART programme in Italy has been offered to serodiscordant couples for male HIV infection seeking medical assistance since 1992 (Semprini et al., 1992). After the sperm-washing procedure, there are three main options to achieve a pregnancy: IUI, IVF and

ICSI. There is wide experience with IUI and IVF in HIV serodiscordant couples in Europe and in the UK (Riley and Yawetz, 2005; Savasi et al., 2007, etc.), while ICSI is the only recommended option in some countries, such as the USA. Each centre has its own inclusion criteria in order to determine whether the infected man is an appropriate candidate for treatment. In some UK (Nicolopoulos et al., 2010b) and US centres, men are required to show evidence of stable HIV disease for at least 6 months on the basis of stable viral load ( $<50\,000$  copies per ml) and CD4 counts  $>250$  cells/ $\text{mm}^3$  (Sauer et al., 2009). In other centres, such as Milan (Savasi et al., 2007), there are no limits regarding viral load and CD4 lymphocyte figures. In fact, access to the ART programme is unrestricted as the method was originally conceived as a risk-reduction strategy and therefore most necessary in those individuals who have the highest risk of transmission. One important aspect involves the effects of antiretroviral medications on seminal fluid parameters. Data so far achieved show that HIV may have a detrimental effect on semen parameters, as there is a negative correlation between CD4 cell count and the progression of the disease and semen parameters (Politch et al., 1994). Nicolopoulos et al. (2011) demonstrated the potential negative effect of the use of HAART on sperm, which may counteract the benefits of a reduction in viral load and lead to an increase in CD4 cell count. Another study assessed 26 males and reported an overall increase in sperm motility and normal morphology, with no effect on sperm count after HAART (Robbins et al., 2001). Our preliminary data suggest that HAART reduces DNA integrity in the spermatozoa causing DNA damage (Oneta et al., 2011). There is sufficient evidence showing that sperm washing in HIV-positive men has not produced any seroconversion in the women and in their offspring but the strength of the evidence is limited to observational studies (Bujan et al., 2004; Vernazza et al., 2006; Savasi et al., 2007). Systematic reviews were conducted to analyse the effectiveness and safety of ART in serodiscordant couples with male HIV infection (Eke and Oragwu, 2011; Vitorino et al., 2011). There are certain reasons why a randomized controlled trial has not been performed on sperm washing, the most important being ethical concerns about possible HIV transmission. More studies have recently been carried out on the cumulative pregnancy and ongoing pregnancy rates (PR) following assisted conception after sperm washing. The studies show an overall PR and ongoing PR per couple of 45.4 and 36.3%, respectively, with no reported seroconversions (Nicolopoulos et al., 2010b). For combined IVF, ICSI and frozen embryo transfer cycles, cumulative PR and ongoing PR per transfer were 33.0 and 26.8%, respectively (Nicolopoulos et al., 2010b). In the USA, an overall clinical PR and ongoing PR per transfer of 46 and 39%, respectively, has been reported (Sauer et al., 2009).

In conclusion, in over 19 years since the development of sperm washing, no RCTs have been carried out to assess the efficacy of the procedure. This leaves observational studies and systematic reviews to assess this intervention. In Table II we present the major published studies in the literature on ART in serodiscordant couples with an HIV-infected male partner.

To date, the cumulative number of reproductive techniques is 3215 couples treated, 6220 with IUI and 1686 with IVF-ICSI, leading to 1320 children born. No seroconversion has been reported using sperm washing, so neither women nor children were infected.

**Table II** Published studies on ART in serodiscordant couples with an HIV-infected male partner.

Study	Method	Couples (n)	Cycles (n)	Pregnancies (n or PR %)	Miscarriages (n)	Multiple pregnancies (n)	Delivery (n)	Children (n)	HIV screening women	HIV screening children
Semprini <i>et al.</i> (1992)	IUI	29	59	17	2	3	7	10	Neg	Neg
Marina <i>et al.</i> (1998a)	IUI	63	101	31	3	8	28	37	Neg	Neg
Marina <i>et al.</i> (1998b)	ICSI	1	1	1	0	0	NR	NR	Neg	NR
Gilling-Smith (2000)	IUI	19	40	8	3	NR	1	1	Neg	
Loutradis <i>et al.</i> (2001)	ICSI	2	2	2	0	0	2	2	Neg	Neg
Guibert <i>et al.</i> (2001)	ICSI	68	97	41	13 + 1 EP	5	26	26	Neg	Neg
Peña <i>et al.</i> (2002)	ICSI	1	2	2	0	0	2	2	Neg	Neg
Sauer and Chang (2002)	ICSI	34	55	25	8	6	17	25	Neg	Neg
Ohl <i>et al.</i> (2003)	IUI	39	5	0	0	0	0	0	Neg	NR
	IVF/ICSI		49	20	4	2	12	14	Neg	Neg
Peña <i>et al.</i> (2003a)	IVF	11	25	9	NR	4	5	8	Neg	Neg
Peña <i>et al.</i> (2003b)	IVF	58	96	35	NR	20	26	39	Neg	Neg
Marina <i>et al.</i> (2003)	ICSI	156	219	92	25	NR	58	75	Neg	Neg
Bujan <i>et al.</i> (2004)	IUI	56	213	37	7	4	28	33	Neg	NR
Garrido <i>et al.</i> (2004)	ICSI	51	64	29	NR	NR	NR	19	Neg	NR
Nicopoulos <i>et al.</i> (2004a)	IUI	105	133	25	NR	NR	NR	NR	NR	NR
Mencaglia <i>et al.</i> (2005)	ICSI	35	NR	27.7%	NR	NR	NR	NR	Neg	Neg
Chu <i>et al.</i> (2005)	ICSI	92	146	54	NR	NR	NR	NR	Neg	Neg
Savasi <i>et al.</i> (2007)	IUI	581	2400	456	54 + 5 EP	18 (4%)	325	337	Neg	Neg
	IVF-ICSI	160	278	65		7 (10%)	NR	NR	Neg	Neg
Bujan <i>et al.</i> (2007b)	IUI	853	2840	15.1%	112 + 8 EP	4.9%	410	463	Neg	NR
	IVF	76	107	29%		17.2%				
	ICSI	262	394	30.6%		20.8%				
	FET	40	49	17.5%		20%				
Kashima <i>et al.</i> (2009)	IVF-ICSI	27	33	20	3	5	17	22	Neg	Neg
Sauer <i>et al.</i> (2009)	ICSI	181	347	161	27	48	116	170	Neg	Neg
Nicopoulos <i>et al.</i> (2010a)	IUI	151	429	61	20	3.4%	35	37	Neg	

ART, assisted reproduction techniques; HIV, human immunodeficiency virus; IUI, intrauterine insemination; FET, frozen embryo transfer; NR, not reported; EP, ectopic pregnancy; Neg, negative; PR, pregnancy rate.



These results might be approximate owing to possible overlapping in reported cycles of treatment.

### Azoospermia in HIV seropositive men

In recent years the clinicians have received an increasing number of requests for reproductive assistance in azoospermic HIV-positive men. One of the major problems in these patients is that sperm-washing technique cannot be carried out in oligo-azoospermic patients, where spermatozoa retrieval from the epididymis and testis are often not sufficient. Microsurgical epididymal sperm aspiration (MESA) or testicular sperm aspiration (TESA) can be offered if there is a high probability of obtaining virus-free spermatozoa for ICSI. The first case of synchronous sperm retrieval followed by sperm washing in an ICSI cycle in an azoospermic HIV-positive man was published by [Nicopoulos et al. \(2004b\)](#). In this case the physicians proceeded with MESA and retrieved sufficient viable sperm for sperm washing but not for cryopreservation because of poor motility. Three embryos were transferred and no pregnancy was obtained. A second paper published in 2007 reported the first live birth following ICSI in a serodiscordant couple using frozen epididymal spermatozoa from an HIV-1 infected man with obstructive azoospermia ([Bujan et al., 2007c](#)). In a small percentage of such patients, it is impossible to recover spermatozoa after surgical procedures because of the highly impaired spermatogenesis. Some authors proposed less rigorous methods to wash the sperm in order to retrieve some spermatozoa for ICSI. One of these methods was proposed by [Garrido et al. \(2006\)](#), in which ejaculates were diluted and then were processed by centrifuge for 10 min at 400g and supernatants were carefully discarded. This procedure was repeated twice. [Bostan et al. \(2008\)](#) developed a single-sperm-washing technique, where the spermatozoa, after the retrieval, were washed with the aid of a micromanipulator to obtain virus decontamination and then used for ICSI: their data demonstrated that single sperm washing could be performed in cases of extreme male sterility and concluded that couples with an HIV positive and oligoazoospermic male, could be included in their ICSI programme. The MESA technique could be inappropriate for some azoospermic men, for example, it should not be applied if there is obstruction in the genital tract or when there is non-obstructive azoospermia with no spermatozoa available in the epididymal reservoir ([Gil-Salom et al., 1996](#)). Moreover, although open testicular biopsies increase the chances of locating motile sperm cells in azoospermic patients, the blood and round cell presence could increase the risk of viral particles after wash. From data available in the literature the testicular compartment seems to behave differently to other tissues regarding antiretroviral treatment and viral spread ([Speck et al., 1999](#); [Tachet et al., 1999](#)).

### Pre-exposure prophylaxis and timed intercourse

Among evidence-based strategies to reduce transmission, HAART has a pivotal role, and recently a multi-national RCT, HPTN 052, definitively demonstrated that early initiation of ART reduces the risk of transmission of HIV ([Cohen et al., 2011](#)). In order to decrease incident infections, new strategies have emerged and pre-exposure

chemoprophylaxis (PrEP) with HAART represents a potential way to prevent new infections.

PrEP involves the use of topical or oral agents in HIV-uninfected individuals prior to exposure to the virus in order to prevent HIV acquisition. The current understanding of mucosal HIV transmission suggests that HIV first replicates at a low level at the mucosal point of entry in the new host and PrEP can be designed to exploit this brief period of virus vulnerability and block HIV from establishing as a persistent infection ([Heneine and Kashuba, 2012](#)). Agents active at the pre-integration stage of viral replication that may prevent the establishment of HIV infected cells are thought to be more suitable than post-integration drugs such as protease inhibitors, although data to support this supposition are limited ([Paxton et al., 2007](#); [McMichael et al., 2010](#)). The most promising antiretroviral agent is tenofovir disoproxil fumarate (TDF), a nucleoside reverse transcriptase inhibitor (NRTI), alone or coformulated with another NRTI, emtricitabine. Both are well tolerated, have a long intracellular and plasma half-life providing the pharmacokinetic–pharmacodynamic rationale for once-daily dosing and achieve higher concentrations in genital tract secretions than in blood ([Wang et al., 2004](#); [Dumond et al., 2007](#)).

PrEP has been studied extensively in animal models and an increasing number of clinical trials describing chemoprophylaxis for HIV prevention in high-risk patient populations are now published or about to be ([Romanelli and Murphy, 2010](#); <http://www.avac.org/ht/a/GetDocumentAction/i/3113>). Data on PrEP are still controversial. Concerning vaginal administration, the CAPRISA 004 trial showed that the use of pericoital microbicide containing tenofovir gel reduced HIV acquisition by an estimated 39% overall ([Abdool Karim et al., 2010](#)). Along with these results, the VOICE Study—Vaginal and Oral Interventions to Control the Epidemic—compared the safety and efficacy of oral versus topical PrEP for prevention of sexual transmission of HIV. An interim data review conducted by the National Institute of Allergy and Infectious Diseases (NIAID) independent Prevention Trials Data and Safety Monitoring Board (DSMB) concluded that tenofovir gel was not effective in preventing HIV in the women enrolled in the trial. The full results are expected to be available in late 2012 or early 2013 (<http://www.mtnstopshiv.org/node/3909>).

More promising data on oral PrEP are now available. [Grant et al. \(2010\)](#) in the placebo-controlled randomized efficacy trial of PrEP with emtricitabine/tenofovir, known as iPrEX, showed favourable results in men who have sex with men on oral chemoprophylaxis. The study subjects were randomly assigned to either PrEP or placebo once daily, and followed for 3324 person-years. Out of these subjects, 10 were found to have been infected with HIV at enrollment and 100 were infected at the follow-up (36 in the PrEP group and 64 in the placebo group), indicating a 44% reduction in the incidence of HIV, with a significant protective effect, showing a relationship between drug adherence and efficacy, as subgroup analyses indicated higher efficacy among those with at least 90% adherence. One of the largest trials to date, the Partners-PrEP trial, a randomized, double-blind placebo-controlled clinical with 4758 couples enrolled, compared TDF or emtricitabine (FTC) and TDF. Even if final results are still expected, interim analysis by the DSMB found a higher number of transmissions in the placebo group and recommended that the Partners PrEP Study results be made public and the placebo arm of the study be discontinued.

Of particular interest, adherence to the daily PrEP medication in this study was very high, with >97% of dispensed doses of the study medications taken. More than 95% of participants were retained in the study follow-up ([http://depts.washington.edu/uwicrc/research/studies/files/PrEP\\_PressRelease-UW\\_13Jul2011.pdf](http://depts.washington.edu/uwicrc/research/studies/files/PrEP_PressRelease-UW_13Jul2011.pdf)).

Similar results in terms of efficacy come out from other studies, such as the TDF2 study (<http://www.cdc.gov/nchhstp/newsroom/PrEPHeterosexuals.html>).

On the contrary, a phase II randomized, double-blind, placebo-controlled trial investigating the safety and effectiveness of a daily dose of 300 mg of TDF versus placebo in preventing HIV infection via vaginal intercourse showed no differences but the effectiveness could not be conclusively evaluated because of the small number of HIV infections observed during the study owing to premature closure of study sites (Peterson *et al.*, 2007). Similar results come out from the FEM-PrEP clinical trial, a phase III clinical trial of FTC/TDF with the same dosing strategy used in iPrEX, with 1951 high-risk HIV-uninfected women enrolled. The study was interrupted by its Independent Data Monitoring Committee in April 2011, because an equal number of AQuinfections was observed in the two study arms (<http://www.cdc.gov/hiv/prep/femprep.htm>). Limitations and potential explanations for the lack of efficacy include low adherence, as evaluated by drug levels, differential adherence by arm and tolerability or drug–drug interactions with hormonal contraception (Baeten *et al.*, 2011; Karim *et al.*, 2011; Celum and Baeten, 2012). Although some trial results appear conflicting, behavioral factors, adherence to dosing and pharmacokinetic properties of the different tenofovir formulations and dosing approaches offer plausible explanations for most of the variations in effectiveness observed in different trials (Gengiah *et al.*, 2012).

While Centers for Disease Control and Prevention has already developed interim guidance for physicians electing to provide PrEP for HIV prevention among men who have sex with men, many questions remain regarding optimal strategies for heterosexual couples (<http://www.cdc.gov/hiv/prep/>). Efficacy trials have demonstrated high safety and moderate-to-high efficacy of topical and oral PrEP but ongoing and planned PrEP trials and analyses need to be completed to have a more thorough understanding of the effectiveness in different populations and the relationship between adherence and efficacy (Celum and Baeten, 2012). Then, even if these drugs present a stable resistance profile, a significant concern is the potential acquisition of drug resistance either to the specific drug or to the entire class of agent (Hurt *et al.*, 2011).

Barreiro *et al.* (2007) published a paper in favour of conception by unprotected sexual intercourse during fertile days for HIV serodiscordant couples treated by HAART with an undetectable viral load. Recently, the Swiss HIV commission stated in its guidelines this possibility under specific conditions: (i) the HIV-infected patient is receiving antiretroviral therapy with excellent adherence; (ii) blood viral load has consistently been undetectable (<40 copies per ml) for >6 months and (iii) no sexually transmitted diseases (STDs) are present in either of the partners (Vernazza *et al.*, 2008). This point of view has been criticized by Wilson *et al.* (2008) as the risk of HIV transmission in heterosexual partnerships in the presence of effective treatment is low but not zero. In fact, using a theoretical model these authors showed that if the claim of non-infectiousness in effectively treated patients was widely accepted and condom use declined, there is the

potential for a substantial increase in HIV incidence, with a significant negative effect in terms of public health. Nevertheless, the authors agree that the risk of contamination by sexual intercourse is extremely low in this population and that it does not address the specific question of the legitimacy of having recourse to limited acts of sexual intercourse, centred optimally around ovulation, in order to conceive. In any case this evidence and data on PrEP suggest different options of conception than sperm washing. Vernazza *et al.* (2011) has described a protocol of PrEP and timed intercourse studying 46 HIV-discordant couples. In order to reduce the risk of transmission, the following guidelines were proposed:

- (i) Male partner being successfully treated, with undetectable HIV-RNA in the plasma (<50 copies/ml) for at least 6 months, without the need of HIV-RNA testing in semen.
- (ii) No current symptoms of genital infections, no unprotected sex with other partners.
- (iii) Use of an LH test in the urine to determine the optimal time of conception (36 h after LH peak).
- (iv) PrEP with tenofovir 300 mg, first dose at LH peak and second dose 24 h later with intercourse the evening of the second dose.
- (v) After six unsuccessful attempts a fertility evaluation is suggested.

None of the female partners had seroconverted for HIV and they reported pregnancy rates higher than previously reported for IUI with processed semen.

In this perspective, timed intercourse and PrEP could represent a potential alternative to ART for fertile couples. It is very comforting to observe that the rate of transmission of HIV in serodiscordant couples, under precise conditions, such as an undetectable viral load on treatment by HAART and sexual intercourse limited to the fertile days, is very low. However, various factors can increase the risk of seroconversion, and a non-negligible number of variables must be taken into account when discussing in which conditions unprotected intercourse would have negligible risk. The physicians should discuss all options with the couple showing available scientific data on the different opportunities.

## HIV serodiscordant couples where the woman is positive

In contrast with the first two decades of the HIV pandemic, currently women comprise approximately one-half of all adults with HIV infection or AIDS worldwide (Elford *et al.*, 2007; AIDS Global Report, 2010) and heterosexual transmission accounts for up to 80% of all new HIV infections in women (ACOG Practice Bulletin, 2010). Women acquire HIV infection at least 5–7 years earlier than men and young women aged 15–24 years have a 4- to 7-fold increased risk of becoming infected with HIV, when compared with young men of the same age (Simon *et al.*, 2006). Most of these are women of reproductive age and are likely to consider pregnancy (Watts *et al.*, 2004; McGarrigle *et al.*, 2006; Cliffe *et al.*, 2011). In fact HAART effectively and substantially extends life expectancy and improves the quality of life due to the ability of reaching undetectable maternal viral loads during pregnancy. Along with the liberal use of Caesarean section and restricted breastfeeding, HAART drastically reduces the risk of mother-to-child transmission to <2% (Vittinghoff

et al., 1999; Chen et al., 2001; Hogg et al., 2001; Mocroft et al., 2003; Porter et al., 2003; Charurat et al., 2004; European Collaborative Study, 2005; Smit et al., 2006; Heard et al., 2007; Volmink et al., 2007; Fiore et al., 2008; Siegfried et al., 2011). Furthermore, certain authors have observed that pregnancy does not worsen the progression of HIV infection or its immunological parameters even in women with advanced HIV infection (Brettle et al., 1995; Saada et al., 2000; Baroncelli et al., 2011). In addition, many HIV-infected women see pregnancy and childbirth as a way to regain their sense of womanhood and sexuality, often making childbearing a highly personal priority. A European study (Fiore et al., 2008) analysed the reproductive experiences of 500 HIV-infected women living in Europe. The authors reported the multivariable logistic regression analysis that determines factors associated with being pregnant at the time of the survey: maternal well-being, no previous live birth and having an uninfected partner were strongly associated with the likelihood of being pregnant.

## Female fertility and HIV infection

Several studies suggest that HIV-infected women may have a decreased fertility rate (Stephenson and Griffioen, 1996; Gray et al., 1998; Zaba and Gregson, 1998; De Simone et al., 2000; Lo and Schambelan, 2001; Zaba et al., 2003). Massad et al. (2004) presented a prospective cohort study in which they determined the frequency and outcomes of pregnancy in US women with HIV, before and after the introduction of HAART. Pregnancy rates were 7.4 and 15.2 per 100 person-years in seropositive and seronegative women, respectively ( $P < 0.0001$ ). Disparity persisted even after adjusting for age and after introduction of HAART, concluding that women with HIV were less likely to conceive than at-risk uninfected women. Advanced disease and low CD4 cell count result in a dramatic decline in pregnancy and live birth rate (Yaro et al., 2001; Hinz et al., 2002; Hunter et al., 2003; Loko et al., 2005; Sedgh et al., 2005) and a recent nested case-control study, conducted on sexually active infected women using no contraception, found an association between HIV-1 viral load and the likelihood of live birth (Nguyen et al., 2006).

The mechanisms by which HIV may interfere with fertility are both direct and indirect. As a direct mechanism we have to consider that 6–22% of American women diagnosed with pelvic inflammatory disease (PID) are HIV infected (Safrin et al., 1990; Shannon and Benrubi, 1991). These numbers are up to 10-fold greater than those among sexually active women without PID (Hoegsberg et al., 1990; Barbosa et al., 1997; Irwin et al., 2000). Cohort studies have also reported a high prevalence of STDs in HIV-1-infected women and they may, therefore, also be at risk for tubal infertility (Frankel et al., 1997; Sobel, 2000; Coll et al., 2007).

HIV-related immunodeficiency might facilitate ascent of vaginal flora to the upper genital tract, induce upper-tract disease from lower-tract flora, leading to increased severity or impairment of therapeutic response. Cohen et al., studying 133 women with laparoscopically verified salpingitis, found 33% of tubo-ovarian abscesses in HIV-1-infected versus 15% in HIV-1-uninfected women (OR 2.8) (Cohen et al., 1998). Several factors may contribute to the greater severity of salpingitis in HIV-1-infected women. Decreased phagocytosis by polymorphonuclear leukocytes, a defect associated with abscess formation, as well as impaired cellular antigen-presenting function and primary

humoral immune responses to bacterial infection have been found in HIV-1-infected persons (Ellis et al., 1988). Other hypotheses are that HIV-1 infection may lead to a blunted inflammatory response, thereby delaying onset of symptoms and prolonging the course of infection. However, we have to consider that most available data are collected from African women who are infected and this could represent an important bias.

As for the endocrinologic effect in infected individuals, severe ovarian dysfunction has been reported (Clark et al., 2001; Englert et al., 2004). Changes in menstrual function have been described, showing that amenorrhea, intervals  $>6$  weeks between menstrual cycles, and lower rates of premenstrual breast symptoms and dysmenorrhea were significantly more common in HIV-infected women (Chirgwin et al., 1996). Cejtin et al. (2006) found a prevalence of prolonged amenorrhea greater than expected among seropositive women and more than one-half of the HIV-positive women with prolonged amenorrhea of at least 1 year did not have ovarian failure. When adjusted for age, HIV seropositive women were about three times more likely than seronegative women to have prolonged amenorrhea without ovarian failure and Schoenbaum et al. (2005) demonstrated that HIV infection and immunosuppression are associated with an earlier age at the onset of menopause. The mechanisms underlying these observations are unknown. As HIV infection could influence ovarian reserve, Seifer et al. (2007) evaluated the markers of ovarian follicle reserve and reproductive aging in HIV-positive women in a cohort of 187 HIV women not pre-selected for infertility, measuring early follicular FSH, estradiol, inhibin B and anti-Müllerian hormone (AMH) levels. The mean values of inhibin B, FSH and estradiol were lower among HIV-infected women but none of these differences were statistically significant. AMH was highly correlated with early follicular FSH and inhibin B in women with and without HIV, demonstrating that AMH covaries with ovarian aging and biological measures of ovarian reserve. They concluded that using measures of reproductive aging, no evidence that HIV infection influences ovarian aging can be found and that an untimed assessment of serum AMH within as well as between cycles may be useful in a clinical setting for women without a history of infertility. In the same perspective, Ohl et al. (2010) recently studied serum markers of ovarian reserve, using FSH, inhibin B and AMH and the antral follicle count (AFC), in 78 HIV-positive women. The hormonal markers were concordant with a 36, 57 and 23% abnormal rate for FSH, inhibin B and AMH, respectively, and AFC showed a high rate of abnormal values (63%), occurring surprisingly early. They concluded that HIV seropositivity was associated with markers of premature ovarian insufficiency and this may contribute to explain impaired fertility. Endocrine perturbations should be considered along with the role of HAART and its impact on lipid metabolism and insulin resistance that could have consequences on folliculogenesis and ovulation regulatory processes (Englert et al., 2004).

## Fertility choices and management for HIV-positive women

### Conception under HAART

Preconception counselling is strongly recommended among HIV-infected women to minimize the risk of transmission, both to their infants and to an HIV-negative partner, and the risk of adverse



maternal and fetal outcomes. Pregnancy should be achieved under optimal clinical and infection-prevention conditions. Currently, the majority of infected women in developed countries are on HAART, and it is known that it has a folate antagonist effect. To reduce the risk of fetal neural tube defects, folic acid should be supplemented pre-conceptionally. Unfortunately, although one-third of HIV-infected people have a fertility desire when specifically asked, over half of the pregnancies are unintended (Stanwood *et al.*, 2007; Myer *et al.*, 2010) and the first antenatal appointment usually occurs when organogenesis has already been completed. Antiretroviral treatment during pregnancy has been the main contributor to reducing mother-to-child transmission of HIV. Nevertheless, during the conceptional period, HAART regimens should only include drugs with known safety. Currently, there is no evidence of a significantly increased risk of birth defects associated with antiretroviral treatment before conception or during the first trimester but changes into safer therapy may be required (Coll *et al.*, 2008). According to the current evidence, benefits of HAART far outweigh the risks of potential congenital abnormalities and the other adverse perinatal outcomes (Thorne and Newell, 2007). In conclusion, all HIV-infected women of reproductive age should be asked about fertility desire and preconception counselling should be encouraged. Moreover, while HAART indications are not influenced by fertility desire, regimen modifications may be needed.

#### *Unprotected sexual intercourse or medically assisted conception*

HIV-infected women usually do not require ART regardless of male HIV status. If the man is uninfected, the woman should undergo self-insemination around the time of ovulation. This procedure is simple, inexpensive and available for all couples. The male provides a fresh semen sample into a collection cup and the semen is then inserted in the vagina using a needleless syringe. For couples who are both infected, with effective treatment they can conceive naturally, although the impact of HIV-1 superinfection may not be negligible (Van der Kuyt *et al.*, 2005).

Regardless of the male HIV status, if conception does not occur or if there is a pre-existing fertility problem, the use of ART should be envisaged. It is important to stress that, considering the high prevalence of fertility problems among HIV-1 infected women, a scrupulous fertility

assessment is mandatory if more than six cycles of self-insemination have failed (Gilling-Smith and Almeida, 2003; Coll *et al.*, 2007).

To our knowledge few studies have been published about IVF outcome in HIV-infected women and in a recent review on HIV and infertility, Kushnir and Lewis (2011) concluded that additional data are needed to address the effect of infection and its treatment on fertility and reproductive outcomes.

Globally, Table III summarizes the results of nine retrieved published papers evaluating the outcome of IVF-ICSI in HIV serodiscordant couples for female positivity from 2003 until 2011 with a total of 306 couples assessed for 399 cycles.

The study by Coll *et al.* (2006) on IVF among HIV-infected women raised concerns about the ability to conceive: in these patients, reduced pregnancy rate after IVF was observed if the patient's own oocytes were used. The results of this study support the finding that HIV-infected women undergoing IVF have an adjusted lower pregnancy rate. In order to evaluate whether the reduction in the pregnancy rate was caused by the maternal environment or by oocyte exposure—either to HIV infection or to antiretroviral treatment—the author conducted a parallel study on patients who required oocyte donation, and no significant reduction in the pregnancy rate was found if donated oocytes were used.

Ovarian resistance to hyperstimulation may be involved in this effect because a greater number of units of gonadotrophins were needed to adequately stimulate these patients. This resistance may reflect an underlying subclinical hypogonadism (normal menses and comparable basal FSH values), and ovulation induction may be considered as a functional stress test on the ovary. HIV should not have a direct impact on the human oocyte because no receptors for HIV have been described on either the cumulus cells or on the surface of the oocyte (Baccetti *et al.*, 1998). A potential hypothesis might be mitochondrial dysfunction as a result of the use of antiretroviral drugs (Brinkman *et al.*, 1998; Lewis *et al.*, 2003; de Mendoza *et al.*, 2004). This hypothesis has also been supported by López *et al.* (2008) who founded that oocytes from infertile HIV-infected women on HAART have decreased mtDNA levels compared with infertile uninfected controls. One possible explanation is that HAART combinations used to treat HIV, especially those containing nucleoside

**Table III** Published studies on IVF-ICSI in serodiscordant couples with an HIV-infected female partner.

Study	Couples (n)	Cycles (n)	Mean female age (years)	Fertilization rate (%)	Cancellation rate (%)	Transferred embryos/ET (n ± SD)	Clinical pregnancies/ET (%)	Children born (n)
Ohl <i>et al.</i> (2003)	9	15	35.9	71.4	NR	1.9 ± 0.6	9.1	0
Ohl <i>et al.</i> (2005)	50	62	35	63.8	NR	1.8 ± 0.6	23.9; 33.3 (FET)	8
Terriou <i>et al.</i> (2005)	29	66	35.8	67	15.2	2	16.1	8
Coll <i>et al.</i> (2006)	35	50	NR	NR	26	NR	16.2	NR
Manigart <i>et al.</i> (2006)	33	56	35.6	73	42.9	NR	28.1	NR
Martinet <i>et al.</i> (2006)	27	27	35.5	67	18.5	1.3	11	NR
Douglas <i>et al.</i> (2009)	14	29	36.5	58	27.6	2.7 ± 0.3	33	9
Prisant <i>et al.</i> (2010)	52	94	34.7	68.2	NR	1.96 ± 0.5	17.65	14
Santulli <i>et al.</i> (2011)	57	NR	34.2	NR	16.2	1.5 ± 0.7	26.3	NR

reverse transcriptase inhibitors, could cause mitochondrial toxicity. In particular, oocytes are post-mitotic cells with no ability to eliminate damaged mitochondria and with a high dependence on the oxidative phosphorylation system. Moreover, because oocytes contain a large number of mitochondria with only one molecule of mtDNA per organelle, they are more sensitive to mtDNA-depleting factors. In this scenario, oocytes would be especially prone to decreased mtDNA levels. The most plausible hypothesis is that the underlying mechanism that causes oocyte mtDNA depletion and reduced fertility among HIV-infected women on HAART is the antiretroviral therapy. No data are available on mtDNA content of oocytes from HIV-infected women who have not undergone HAART.

On the contrary, [Martinet et al. \(2006\)](#) suggested that there is no difference between HIV-positive and HIV-negative women in ovarian responses to an IVF programme. This study evaluated the ovarian response to IVF stimulation in 27 HIV-positive patients compared with 77 control patients. The results indicated that HIV-infected patients who are in good general health and who are matched to a control group (for age, infertility etiology, length and type of infertility and history of pelvic surgery) present a similar ovarian response to stimulation, suggesting similar ovarian reserve. The authors argue that the clinical impression of physicians that HIV-infected patients respond less well to IVF stimulation might be related to a bias and to confounding factors, such as a more advanced age and a high prevalence of tubal pathologies among HIV-infected women. Nevertheless the authors concluded that further studies, including larger numbers of patients, should be carried out.

## Accessibility to reproductive assistance in low-income countries

The majority of people who are infected with HIV live in low-income countries, where reproductive technologies are neither geographically nor economically accessible ([Frodsham et al., 2006](#); [Stanitis et al., 2008](#); [Chadwick et al., 2011](#)) and simply encouraging HIV-affected couples to abstain from procreation may no longer be a realistic strategy. In the absence of counseling, couples may knowingly take on the risks of transmission in order to have children, engaging in unprotected intercourse. In this context, an increasingly crucial issue is the introduction of harm reduction and safer conception methods for people with HIV infection in settings where ART cannot be easily obtained.

Most international research on safer conception interventions has been based on settings from industrialized-world contexts and has concentrated on options for couples in which the male partner is infected with HIV and the female partner is not, therefore focusing on 'high-technology' methods such as sperm washing with IUI or IVF/ICSI, in laboratory settings. However, in low-income countries, these interventions are not feasible and most couples are serodiscordant for HIV female positivity. As a result, there are considerable data on the efficacy of sperm washing, but limited data on timed unprotected sex and no available data on vaginal insemination ([Chadwick et al., 2011](#)).

In resource-limited settings, before any safer conception intervention, couples should be screened for viral load, CD4+ cell count, sexually transmitted infections and counselled for the need of a

close adherence to antiretroviral drugs ([Matthews and Mukherjee, 2009](#)). The most feasible method in low-income countries for HIV-serodiscordant couples for female positivity seems to be vaginal self-insemination with sperm from the uninfected partner, timed to the woman's fertile period ([Chadwick et al., 2011](#)). To date, no published studies are available on acceptability, feasibility and efficacy of vaginal self-insemination in HIV-discordant couples. Nevertheless, the routine use of vaginal self-insemination is of significant public health importance because it is expected to reduce the likelihood of riskier sexual practices (the inconsistent use of male condoms) for childbearing and decrease the incidence of HIV in low-income countries. Systematic research on self-insemination is needed to establish pregnancy rate and outcomes, HIV transmission route to infants and acceptability for couples and health-care providers.

For couples in which the man or both partners are positive, the only feasible option is careful, informed natural conception ([Matthews and Mukherjee, 2009](#)). Timed intercourse for HIV-seroconcordant couples should form part of a harm-reduction strategy to reduce exposure to HIV when planning conception in resource-limited settings. As regards HIV-serodiscordant couples with male infection, the use of periconception PrEP for the seronegative female partner during timed and limited intercourse represents an important implementation of safer conception. A recent study found strong evidence of the cost-effectiveness of PrEP in South African women, with a reduced mean lifetime HIV risk from 40 to 27% ([Walensky et al., 2012](#)).

In conclusion, assuring that HIV-affected couples can undergo safer childbearing is crucial in decreasing both mother-to-child HIV transmission and infection of seronegative partners. Further research is needed to establish the awareness, understanding and acceptability of low-technology, safer conception strategies among people with HIV infection.

## Conclusions

Not surprisingly, HIV-infected adults desire and expect to have children. This behaviour has important implications for the prevention of vertical and heterosexual transmission of HIV virus. In this perspective, the need for counselling to facilitate informed decision-making about safe childbearing becomes vital. In western countries, the issue is that ART programmes should be integrated into global public health services against HIV. For the HIV serodiscordant couples with HIV-infected men, sperm washing should be the first choice. To date, there are no RCTs evaluating sperm washing to prevent HIV sexual transmission but the majority of clinical data and follow-up for mothers and children born using this technique are reassuring.

In the near future, physicians might consider PrEP in order to control the risk of HIV sexual transmission in couples wishing to conceive. Efficacy trials have demonstrated high safety and moderate-to-high efficacy of topical and oral PrEP but remaining trials and analyses need to be completed to have a more thorough understanding about the effectiveness in different populations, the relationship between adherence and efficacy, and the problem of drug resistance.

When women are infected in HIV serodiscordant couples, little is known about the possible role of HIV virus or HAART on their fertility, especially of the negative influence on oocyte quality. Insufficient

data are available about reproductive assistance. Only nine retrieved articles evaluated the outcome of IVF-ICSI in HIV-serodiscordant couples with HIV-infected females from 2003 to 2011 with a total of 306 couples and 399 cycles. The majority of HIV-infected women wishing to become mothers tries to achieve pregnancy without help, and asks for assistance only if they do not conceive. In the future, efforts to design a multicentric study, in order to create larger cohorts, should be strengthened.

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## Authors' roles

V.S. conceived the manuscript, participated in the research and in the writing of the article and critically revised the manuscript for important intellectual content. L.M. and A.L. contributed to study conception, participated in the research and in the writing of the manuscript and tables and contributed to the analysis and interpretation of the data. I.C. contributed to study conception, participated in the writing of the article and critically revised the manuscript. All the authors have seen and approved the final version.

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