Human immunodeficiency virus serodiscordant couples on highly active antiretroviral therapies with undetectable viral load: conception by unprotected sexual intercourse or by assisted reproduction techniques?

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Until recently, only assisted reproduction was proposed to serodiscordant couples wishing to conceive. Nevertheless, recent publications have proposed unprotected sexual intercourse, targeting fertile days, for couples where antiretroviral treatment has lowered blood viral load to an undetectable level. Available data and the arguments for and against conception by safe sex versus the use of a strategy of unprotected sexual intercourse targeting fertile days are reviewed and analyzed. Although the rate of transmission of human immunodeficiency virus in serodiscordant couples in precise conditions (such as an undetectable viral load on treatment by highly active antiretroviral therapies and sexual intercourse limited to the fertile days) is very low, not zero, here we stress the various factors which can increase the risk of seroconversion in this particular population. In this context, it seems less cautious to abandon the recommendations of safe sex in serodiscordant couples desiring a child. The recourse to medically assisted procreation is advised, as long as evidence from further studies does not show that unprotected sexual intercourse, targeted to fertile days, does not have unexpected harmful consequences.

Key words: human immunodeficiency virus / assisted reproduction / safe sex / child wish / unprotected intercourse

Introduction

Human immunodeficiency virus (HIV) affects more than 30 million people worldwide, with most cases located in sub-Saharan Africa (UNAIDS, 2007; Cohen et al., 2008). In 2007, 2.5 million individuals were infected (UNAIDS, 2007). The epidemic is still progressing but the desire for children is still real in HIV positive patients independent of their clinical status (Paiva et al., 2003; Heard et al., 2007; Nóbrega et al., 2007). Fortunately, over the last decade, considerable progress has been made in multidrug highly active antiretroviral therapies (HAARTs), thus dramatically modifying the life expectancy and the quality of life of affected patients and reducing the number of new cases of acquired immune deficiency syndrome and mortality resulting from this pathology (Nieuwkerk et al., 2001; Parsons et al., 2006). Consequently, the seroconcordant or serodiscordant couples’ wish to conceive a child has increased among HIV carriers (Englert et al., 2001). The recourse to medically assisted procreation (i.e. assisted reproduction techniques: ARTs) has developed substantially in the last decade, thus allowing great security for couples to conceive, protecting the HIV negative partner as well as the future child (Englert et al., 2004; Bujan et al., 2007a, b; Savasi et al., 2007). These methods follow a growing consensus about the legitimacy to medically assist pregnancy-willing couples (Englert et al., 2001). In this context, Barreiro et al. (2007) published a paper in favor of conception by unprotected sexual intercourse during fertile days for HIV serodiscordant couples treated by HAART with an undetectable viral load. More recently, the Swiss HIV commission stated in its guidelines that: ‘The risk of sexual transmission of HIV is negligibly low if three conditions are met: (1) the HIV-infected patient is receiving antiretroviral therapy with excellent adherence; (2) blood viral load has consistently been undetectable (<40 copies per ml) for more than 6 months; and (3) no STDs are present in either of the partners’ (Vernazza et al., 2007).
2008). This point of view has been criticized by Wilson et al. (2008) who showed, using a theoretical model, that abandoning condom use could quadruple the number of contaminations and have, therefore, a significant negative effect in terms of public health. Nevertheless, 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, centered optimally around ovulation, in order to conceive. In that perspective, sexual intercourse represents, therefore, a potential alternative to ART.

The present article emphasizes this debate, analyzing available data and reviewing arguments about conception by ART versus the use of a strategy of unprotected sexual intercourse, targeting fertile days.

**The risks of HIV contamination during unprotected sexual intercourse**

Heterosexual intercourse is today the major vector of infection transmission of HIV. Nevertheless, many factors modulate the frequency of viral contamination of a partner.

When the male partner is infected, the rate of transmission of HIV seems to be five to eight times higher than when the female partner is infected (European Study Group on Heterosexual Transmission of HIV, 1992; Padian et al., 1997; Baeten and Overbaugh, 2003). According to Quinn et al. (2000), this risk however is similar. Using a mathematical model, Wilson et al. (2008) estimated the cumulative annual risk of transmission of HIV from woman to man to be 0.0022 and from man to woman to be 0.0043 considering an average of 100 acts of sexual intercourse per year. Atia’s review concludes that no transmission in patients treated with antiretroviral treatment and with viral load below 400 c/ml was observed: the data are compatible with one transmission per 79 person-years (Attia et al., 2009).

If the HIV-unaffected partner presents vaginal infection, the risk of seroconversion is higher with a relative risk (RR) of 1.51 (RR 1.89 in the case of severe vaginal bacteriosis) (Sewankambo et al., 1997). Prevalent herpes simplex virus (HSV)-2 infection is associated with a 3-fold increase in the risk of HIV acquisition among both men and women in the general population (Brown et al., 2006; Freeman et al., 2006).

Numerous studies have proved that the risk of transmission of HIV to an uninfected partner increases with an increase in the plasma viral load. This risk varies between 0.0011 (unadjusted) and 0.0001 per unprotected sexual intercourse if the viral load is less than 1700 c/ml (Gray et al., 2001; Wawer et al., 2005; Shapiro and Ray, 2007). Achieving a viral load under the assay detection limit considerably reduces this risk. Other factors can modify the infectivity of the HIV-affected partner.

It is well-documented that the existence of associated genital lesions increase the risk of contamination: often, HIV-infected patients show co-infections, as shown by Taha et al. (1999), Sangani et al. (2004) and Sewankambo et al. (1997), reporting a rate of 55% of bacterial vaginosis in symptomatic and asymptomatic HIV patients. These co-infections increase the viral RNA in secretions, multiplying the risk of seroconversion of the healthy partner by 10–300 times per unprotected sexual intercourse (Rotchford et al., 2000; Shapiro and Ray, 2007).

The presence of genital ulcerations in the HIV-positive partner [mainly due to HSV, H. Ducreyi et T. Pallidium (Risbud et al., 1999)] increases the RR of transmission [RR: 2.04 (Wawer et al., 2005); RR = 5.3 (Boily et al., 2009); RR = 10 to 50 for male to female transmission and 50 to 300 for female to male transmission per sexual intercourse (Hayes et al., 1995)]. Prevalence of these ulcerations should nevertheless be taken into account. In sub-Saharan African countries where a large proportion of the population is contaminated with HIV, genital ulceration prevalence can be as high as 68% (O’Farrell, 2001). HSV seroprevalence is also very high (80%, Weiss 2004) in contrast with developed countries where seroprevalence ranges from 8% to 33%. It is worth noting that in developed countries HSV seroprevalence is rising (Malkin, 2004; LeGoff et al., 2007).

The presence of a distinct genital reservoir which is contaminated by the virus and where the viral strain and the viral load can be different from the plasma strain and load should also be taken into account. The spermatic compartment has a certain peripheral autonomy with a local viral replication (DNA and RNA found in the genital tract) comparable to plasma measures. The viral concentrations are sometimes superior or inferior to the plasma concentration and the virus strains can sometimes have different resistance characters. Studies diverge on whether this situation can be clinically significant for patients on HAART and with undetectable viral load:

1. The semen: according to Vernazza et al. (2000), patients on antiretroviral treatment whose plasma viral load is undetectable have less than a 4% probability of having HIV DNA in spermatic secretions. The possibility of spermatic positive viral load when the plasma viral load is negative has been shown by Coombs et al. (1998), Tachet et al. (1999), Bujan et al. (2004) and Englert et al. (2004). The literature review by Van leeuwen et al. (2007) illustrates the discordance between viral loads in these two body fluids. Zhang et al. (1998) detected proviral HIV DNA in seminal cells in men with long-term suppression of HIV RNA in the plasma, with no genotypic mutations. Pasquier et al. (2008) described a case of persistent and increasing HIV RNA in semen despite an effective control of HIV viral load in the blood for several months (no mutation was shown). Byrn et al. (1997) and Eron et al. (1998) showed the presence of different genotypic variants in these two compartments, possibly altering the efficiency of treatment at a genital level.

2. Vaginal secretions: Kovacs et al. (2001) found that 20% of women with an undetectable plasma viral load under antiretroviral treatment (especially protease inhibitor) have HIV RNA in vaginal secretions. According to Coombs et al. (2003), although there is a correlation between blood viral load and the detection of virus in genital secretions, one-third of women and 4% of men with undetectable viral load have detectable viral RNA in their genital secretions.

As in all chronic diseases, the compliance to long-term therapy is far from perfect (Murphy et al., 2001; Murri et al., 2001; Cauldbeck et al., 2009; Rudy et al., 2009). The authors report their personal experiences (unpublished data) of the discovery, while running routine pre-insemination control tests in the cadre of a HIV-infected
patients’ program of the fertility clinic of the Erasme Hospital, of a highly contaminated sperm sample from a man known, however, to have undetectable plasma viral load under HAART: previously, his checked sperm samples had shown no detectable viral load. It was later found that the patient had stopped his therapy since his last medical check and had omitted to inform anyone.

It should also be kept in mind that the reported rates of seroconversion of the unaffected partner are those observed in stable couples having unprotected sexual intercourse (0.1–0.5%; De Vincenzi, 1994; Gray et al., 2001), a risk inferior to rates of seroconversion reported for occasional sexual contacts (3.1–8.2% for occasional intercourse, as for example, in prostitution; Cameron et al., 1989; Mastro et al., 1994; Baeten and Overbaugh, 2003). This could be explained by the acquired immunity, of T-cytotoxic lymphocytes, against the virus of the infected-partner (Bienzle et al., 2000) or by a ‘natural’ selection of couples with a low risk of transmission, as these observations have been reported among couples initially discovered as being serodiscordant.

The spread of the virus in the population leads to couples forming even when the seropositivity is already known. If the condom has always been used in these stable couples, a first unprotected sexual intercourse in order to conceive could correspond to an occasional intercourse (no immunity), and the risk of seroconversion could then be that of an occasional couple.

### Number of acts of unprotected intercourse to obtain conception

The number of acts of sexual intercourse necessary to obtain conception should also be considered. In the general population, the probability of conception per sexual intercourse varies from 0.10 to 0.33 according to the day of intercourse in the fertile period (Wilcox et al., 1995), as shown in a study where 80% of the tested women were aged between 26 and 35 years.

The average number of acts of sexual intercourse necessary to achieve pregnancy at 26–35 years of age for a normally fertile couple is hence 3–10. For a risk of HIV transmission of 0.0001 per unprotected sexual intercourse, the risk of seroconversion would then be 0.001 per pregnancy.

Nowadays, the desire to have a child in many countries is expressed increasingly later in life, and this factor should be considered: the more the age of the woman deviates from the optimal conception age (25 years), the higher the average number of cycles necessary to obtain conception. Also, the rate of HIV transmission (per sexual act and adjusted to viral load) differs according to the age of patients, with a higher rate of transmission among the 15–29-year-olds compared with those above 30 (RR 2.38) (Wawer et al., 2005), which could partly compensate for the higher number of cycles necessary to conceive.

Unfortunately, many data from the literature suggest that HIV carriers on HAART have a reduced fertility compared with HIV-negative individuals. Reports suggest an altered ovarian function in affected women and a pregnancy rate inferior to that of the control population both for natural reproduction and ART (Zaba and Gregson, 1998; Clark et al., 2001; Lo and Schambelan, 2001; Yaro et al., 2001; Englert et al., 2004; Coll et al., 2006; Martinet et al., 2006; Van Leeuwen et al., 2007).

According to Lo and Schambelan’s review (2001), it seems that when the male patient with HIV is asymptomatic, the spermatic and fertility parameters are more or less normal. These data are disputed in several papers which demonstrate sperm anomalies in HIV-1 infected patients (Dulouest et al., 2002; Englert et al., 2004; Nicopoullos et al., 2004; Bujan et al., 2007a; b; La Sala et al., 2007). Taking all these parameters into consideration, it is very likely that the required numbers of cycles necessary to conceive are higher in asymptomatic HIV patients than the generally accepted observations for an average population of a comparable age. More acts of unprotected sexual intercourse would be necessary, increasing the risk of seroconversion of the partner and leading, in a number of cases, to the need for ART.

### Pregnancy and the risk of seroconversion

If the infected partner is a man, the seroconversion of the future mother following unprotected sexual intercourse at the time of conception leads to a higher risk of maternofetal HIV transmission, the viral load being particularly high during primo-infection (Leynaert et al., 1998; Patterson et al., 2007). Besides, according to the same authors, the search for seroconversion in the pregnant woman can be at first falsely negative, owing to the latency of appearance of antibodies, therefore leading to delays in the initiation of antiretroviral treatment. Distress of the couple facing such an event at the initiation of a pregnancy, after having deliberately taken this risk, should not be underestimated.

The actual recommendations stress the need for protected sexual intercourse, the cornerstone of prevention. Epidemiologic data show that, in this field, the improved results are far from evolving at the same speed as that of therapies. The education of the youth is a laborious task and demands multidisciplinary programs in order to spread the message. Despite those sustained campaigns, a large proportion of the population remains insensitive to these recommendations. Stable and serodiscordant couples are barely concerned by these prevention programs and the use of condoms is hardly followed (26% of men and 34% of women in heterosexual HIV-serodiscordant couples, formed for more than 12 months, have unprotected sexual intercourse (Bouhnik et al., 2007); 45% of serodiscordant couples have had unprotected sex during the last 6 months (Wolf et al., 2003; Shapiro and Ray, 2007)). In the population of serodiscordant couples requesting assisted reproduction in Erasme, Brussels, 14.5% (32 of 221) do not systematically have protected intercourse (unpublished data).

The difficulty of spreading the prevention message across the general population might be greater if unprotected sex is allowed at certain times.

For concerned couples, if conception by unprotected sexual intercourse is encouraged during the fertile period, what would be the impact on the practice of safe sex outside of these periods?

Would this temporary consent weaken the prevention policies against HIV and would it not encourage couples who received this permission, or rather this paradoxical message, to continue to practice unprotected sex, which could be particularly risky during a pregnancy when the immunity defenses of the pregnant woman are diminished, particularly in the genital tract (Beigi et al., 2007) and when the RR of being infected by HIV is 2.16 compared with non-pregnant women.
It is very comforting to observe that the rate of transmission of HIV in serodiscordant couples, in precise conditions, such as an undetectable viral load on treatment by HAART and sexual intercourse limited to the fertile days, is very low, even if it is not zero (Wilson et al., 2008). 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. Nevertheless, if unprotected sexual intercourse is encouraged for conception without any preliminary studies, the aforementioned different aspects could be neglected.

It is absolutely true that natural conception would reduce the costs of treatments such as ART and that it would contribute in increasing autonomy and the quality of life of couples living with HIV. Besides, it has been reported that half of HIV-infected serodiscordant couples, who have had no success with ART, ultimately have resorted to natural conception and human immunodeficiency virus type 1 (HIV-1) transmission in HIV-1-discordant partners. J Infect Dis 2000; 182:123–132.


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