

# Natural Pregnancies in HIV-Serodiscordant Couples Receiving Successful Antiretroviral Therapy

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**Summary:** Increasing numbers of HIV-serodiscordant heterosexual couples are concerned about the chances for pregnancy. We reviewed all natural pregnancies attained by HIV-serodiscordant couples seen in 3 clinics in Spain, in which the infected partner had undetectable plasma viremia while receiving highly active antiretroviral therapy (HAART). In the case of HIV-infected mothers, only those with undetectable viremia during pregnancy and at delivery were chosen. A total of 62 HIV-serodiscordant couples, 22 HIV-infected women (mean CD4 count of 522 cells/ $\mu$ L, 55% hepatitis C virus [HCV]-seropositive) and 40 HIV-infected men (mean CD4 count of 629 cells/ $\mu$ L, 75% HCV-seropositive), were recorded. Overall, 76 natural pregnancies occurred, and 68 children were born. There were 9 fetal deaths, 1 twin pregnancy, 6 couples with 2 consecutive babies, and 4 couples with 3 consecutive newborns. There were no cases of HIV seroconversion in uninfected sexual partners. One case of vertical HIV transmission occurred, however. Serodiscordant couples attaining natural pregnancy are exposed to a negligible risk of sexual transmission of HIV when the infected partner presents with complete suppression of plasma viremia while receiving HAART.

**Key Words:** antiretroviral therapy, HIV, sexual transmission, vertical transmission, viral load

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The availability of highly active antiretroviral therapy (HAART) has made HIV infection less of an obstacle to having children for HIV-infected subjects and their seronegative partners.<sup>1</sup> The dramatic reduction in the risk of sexual<sup>2</sup> and vertical<sup>3</sup> HIV transmission in patients receiving effective antiretroviral therapy gives support to these desires for having children. It is still unclear to what extent these findings represent a low risk of transmission of HIV in serodiscordant

couples who want to conceive by natural means, however. Here, we describe the rate of horizontal and vertical transmission of HIV in a group of serodiscordant couples who attained natural pregnancies, with the index case representing natural pregnancy during successful HAART.

## MATERIAL AND METHODS

All pregnancies attained by natural means in HIV-serodiscordant couples between January 1998 and December 2005 were retrospectively identified in 3 HIV reference clinics located in Spain. Only couples with the following characteristics were chosen: (1) HIV-1 infection in only 1 member, (2) plasma HIV RNA levels <500 copies/mL on HAART at the time of natural conception, and (3) prescription of effective HAART during pregnancy in HIV-infected women, and (4) viral load <50 HIV RNA copies/mL at delivery. All babies born to HIV-infected mothers received prophylaxis with zidovudine during delivery and after birth. The possibility of vertical HIV transmission was determined according to standard diagnostic protocols, including enzyme immunoassay (EIA) and polymerase chain reaction (PCR) for HIV at 1, 3, 6, and 12 months of age in the baby. The status of HIV infection in the seronegative partner was available before and more than 6 months after natural conception (in men) or delivery (in women) in all instances. Regarding statistical analysis, comparison of proportions was done using  $\chi^2$  and Fisher exact tests.

## RESULTS

A total of 62 HIV-discordant couples achieved natural pregnancies between 1998 and 2005 in the 3 institutions. The HIV-seropositive partner was the man in 40 cases (65%) and the woman in 22 cases (35%). Mean age was  $34 \pm 4$  years in the HIV-infected mothers and  $37 \pm 4$  years in the HIV-infected fathers. Median viral load at the time of conception was <500 HIV RNA copies/mL in male and female infected partners. All HIV-positive mothers had undetectable viremia (<50 copies/mL) at the time of delivery. In infected partners, the mean CD4 count was  $522 \pm 265$  cells/ $\mu$ L in women and  $629 \pm 271$  cells/ $\mu$ L in men.

All HIV-infected women were on HAART at the time of conception and throughout pregnancy. The nucleoside analogues most widely used in mothers during pregnancy

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were lamivudine (76%) and zidovudine (43%); no women received stavudine and didanosine in combination. There were 4 women (17%) who were treated with a triple-nucleoside analogue regimen (abacavir/lamivudine/zidovudine fixed-dose combination [Trizivir, GlaxoSmithKline, Rio de Janeiro, Brazil]). In 13 mothers (43%), the regimen was based on nonnucleoside analogues, nevirapine in all cases. In the 12 remaining pregnancies (40%), HAART contained protease inhibitors (PIs).

A total of 76 natural conceptions were recorded in the 62 HIV-discordant couples (Table 1). Fifty-two couples had a single pregnancy, and 6 and 4 couples had 2 and 3 consecutive pregnancies, respectively. There was 1 case of twin pregnancy and 9 spontaneous abortions. The rate of fetal death was higher in HIV-positive (7 [23%] of 30) women than in HIV-negative (2 [4.7%] of 42) women (odds ratio [OR] = 6.1, 95% confidence interval [CI]: 1.02 to 46.68; *P* = 0.02). Overall, 68 newborns were registered.

In all cases, the HIV-seronegative partner remained uninfected as shown repeatedly by lack of reactive EIA test results after natural conception and more than 6 months after delivery. There was 1 case of vertical HIV transmission in the 23 pregnancies from HIV-infected mothers, however. Briefly, a 37-year-old HIV-infected woman receiving long-term HAART got pregnant; her CD4 count was >500 cells/ $\mu$ L and her viremia was undetectable (<50 HIV-RNA copies/mL) at all 5 visits before delivery. No intrauterine invasive procedures were performed during pregnancy. Natural delivery was induced at approximately week 40, and zidovudine prophylaxis was applied. In the third week of life, the baby developed an acute respiratory syndrome and, unfortunately, died 3 days later. The virologic tests confirmed the diagnosis of HIV-1 infection, and the autopsy revealed *Pneumocystis jiroveci* pneumonia as the main cause of death.

## DISCUSSION

The issue of reproductive health in HIV-infected subjects is gaining importance, because most patients experiencing the benefit of HAART have returned to active life. Thus, HIV-infected patients are now considered for assisted

reproduction programs.<sup>4</sup> In the case of HIV-infected men (because of intense manipulation of the semen) and women receiving HAART, the reproductive efficacy of these techniques is limited, however.<sup>5,6</sup> Associated with these facts, the cost of assisted reproduction techniques and some ethical issues have prompted a significant number of couples to consider natural pregnancy.<sup>7</sup>

The first data on natural conception in HIV-discordant couples showed no cases of horizontal seroconversion within the first 6 months of pregnancy,<sup>8</sup> however, 4 women (3.8%) became infected with HIV thereafter. It is important to highlight the fact that only 21 HIV-infected men were receiving antiretroviral therapy, and no information is given in the report regarding levels of plasma viremia.

To our knowledge, ours is the first report describing the outcome of natural pregnancies in HIV-serodiscordant couples in which the HIV-infected partner is receiving maximally suppressive HAART. The fact that no horizontal HIV seroconversions occurred after unprotected sexual contact is in agreement with prior reports in other cohorts of HIV-discordant couples.<sup>2</sup>

In the developed world, the current overall rate of perinatal HIV infection is as low as 1% to 2% as a result of the widespread use of HAART in pregnant HIV-positive mothers.<sup>9</sup> There are still sporadic reports in the literature of pregnant women with undetectable plasma viremia giving birth to HIV-infected newborns,<sup>10</sup> as we unfortunately found in 1 case in our series. Transient episodes of viral replication and microtrauma in the placenta that might have gone unnoticed during the course of pregnancy are supposed to be the cause of these rare cases of fetal HIV infection.<sup>11</sup>

It seems that HIV infection itself does not alter the course of pregnancy.<sup>12</sup> Conflicting data exist regarding the influence of HAART on obstetric outcomes, however. A recent study has shown that the use of HAART in HIV-seropositive mothers is associated with a higher risk of fetal death.<sup>13</sup> In our series, the rate of intrauterine deaths was higher in HIV-positive women than in noninfected mothers, although the many potential factors associated with adverse pregnancy outcomes warrant a multivariate analysis to draw definite conclusions. Although the differences in fetal death risk by HIV status could have been attributable to ascertainment bias, HIV-discordant couples considering pregnancy should be informed that seropositive mothers on antiretroviral therapy, irrespective of pregnancy being attained by natural or artificial means, might potentially expose their newborns to a greater risk of spontaneous abortion and/or drug toxicity. They should also know that the benefit of HAART in preventing vertical HIV transmission clearly overcomes these concerns.

The retrospective nature of our study did not allow establishment of the overall risk of HIV transmission in serodiscordant couples attempting at natural conception because only those attaining pregnancy, and not all trying to get pregnant, were evaluated. The number of unprotected coital acts needed to attain pregnancy was not available. This information is important to validate natural conception as an acceptable option for HIV-discordant couples. The complete absence of sexual HIV transmission in our series is reassuring, however.

**TABLE 1.** Reproductive Outcome in 62 HIV-Discordant Couples in Which the HIV-Infected Partner Was Receiving Effective HAART

76 natural conceptions
52 couples with 1 pregnancy
6 couples with 2 consecutive pregnancies
4 couples with 3 consecutive pregnancies
1 twin pregnancy
9 fetal deaths
7 (23%) in 30 pregnancies among HIV-positive women
2 (4.7%) in 42 pregnancies among HIV-negative women
(OR = 6.1, 95% CI: 1.02 to 46.68; <i>P</i> = 0.02)
68 newborns
HIV transmission
Sexual: 0 cases in 76 pregnancies
Maternofetal: 1 case in 23 pregnancies among HIV-positive women

The main conclusion that we can draw from this study is that HIV-discordant couples seeking pregnancy should receive specialized medical counseling and evaluation. They should be informed of the risks of viral transmission through assisted or natural reproductive attempts. If the couple has opted for natural pregnancy, undetectable viremia under HAART is mandatory, and pregnancy is discouraged in patients with any level of HIV replication. Other transmissible infections (ie, viral hepatitis), cofactors that may increase the risk of HIV transmission or acquisition (ie, disruptions, inflammations, infections, dysplasias of the genital tract), and fertility potential (ie, through a spermogram in men and hormonal tests in women) should be evaluated within standard protocols. It is important to advise these couples to restrict overt sexual contacts to fertile days exclusively, for which the use of ovulation tests may be recommended. Pregnancy attempts should be limited in number, and couples should receive medical reassessment if conception does not occur in 3 to 6 months. As a future perspective that may offer new options to HIV-serodiscordant couples, the efficacy and safety of antiretrovirals in pre- and/or postexposure prophylaxis protocols warrant prospective evaluation.

#### REFERENCES

1. Chen J, Phillips K, Kanouse D, et al. Fertility desires and intentions of HIV-positive men and women. *Fam Plann Perspect*. 2001;33:144–152.
2. Castilla J, del Romero J, Hernando V, et al. Effectiveness of highly active antiretroviral therapy in reducing heterosexual transmission of HIV. *J Acquir Immune Defic Syndr*. 2005;40:96–101.
3. European Collaborative Study. Mother-to-child transmission of HIV-infection in the era of highly active antiretroviral therapy. *Clin Infect Dis*. 2005;40:458–465.
4. Englert Y, van Vooren J, Place I, et al. Assisted reproduction technology in HIV-infected couples. *Hum Reprod*. 2001;16:1309–1315.
5. Semprini A, Vucetich A, Hollander L. Sperm washing, use of HAART and role of elective caesarean section. *Curr Opin Obstet Gynecol*. 2004;16:465–470.
6. Coll O, Suy A, Figueras F, et al. Decreased pregnancy rate after in-vitro fertilization in HIV-infected women receiving HAART. *AIDS*. 2006;20:121–123.
7. Vernazza P, Hollander L, Semprini A, et al. HIV-discordant couples and parenthood: how are we dealing with the risk of transmission? *AIDS*. 2006;20:365–366.
8. Mandelbrot L, Heard I, Henrion-Geant E, et al. Natural conception in HIV-negative women with HIV-infected partners. *Lancet*. 1997;349:850–851.
9. Thorne C, Newell M. The safety of antiretroviral drugs in pregnancy. *Expert Opinion on Drug Safety*. 2005;4:323–335.
10. Burns D, Landesman S, Wright D, et al. Influence of other maternal variables on the relationship between maternal virus load and mother-to-infant transmission of HIV type 1. *J Infect Dis*. 1997;175:1206–1210.
11. Magder L, Mofenson L, Paul M, et al. Risk factors for in utero and intrapartum transmission of HIV. *J Acquir Immune Defic Syndr*. 2005;38:87–95.
12. Massad L, Springer G, Jacobson L, et al. Pregnancy rates and predictors of conception, miscarriage and abortion in US women with HIV. *AIDS*. 2004;18:281–286.
13. Suy A, Martinez E, Coll O, et al. Increased risk of pre-eclampsia and fetal death in HIV-infected pregnant women receiving highly active antiretroviral therapy. *AIDS*. 2006;20:59–66.