

Pre-exposure prophylaxis and timed intercourse for HIV-discordant couples willing to conceive a child

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Many HIV discordant couples express a strong wish to conceive a child. Insemination with processed semen is offered to these couples in many countries. Given the very low level of transmission risk during fully suppressive antiretroviral therapy, we offered timed intercourse combined with pre-exposure prophylaxis to further reduce the transmission risk. In 53 cases natural conception was attempted using the proposed method. Pregnancy rates were high reaching a plateau of 75% after 6 cycles. Advanced age in the female partner was a predictor for infertility in these couples.

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Introduction

Physicians caring for patients with HIV-infection are frequently confronted with the wish of conception. Since its introduction by Semprini et al. in 1992 [1], several European clinics have adopted the approach of intra-uterine insemination (IUI) with processed semen [2] to minimize the risk of HIV transmission in discordant couples with infected male partners. Current practice in Europe indicates that artificial insemination with processed semen is the only method that most physicians propose to their patients, although the method is cumbersome, costly and its pregnancy rate is only 15% after a single intra-uterine insemination (IUI) [3]. Of note, the effect on risk reduction of the IUI practice cannot be determined given the very low a-priori risk in patients treated with HAART [4]. Still, for a significant number of couples, the wish of parenthood remained unaccomplished due to the technical and financial hurdles associated with the proposed unique mode to conceive a child. Notably, the majority of these couples are only confronted with functional infertility due to the potential

risk of transmission during conception. Highly potent antiretroviral therapy (HAART) has not only improved life expectancy dramatically, it has – according to some experts – virtually eliminated the risk of sexual transmission of HIV [5]. In fact, since the introduction of HAART not a single fully documented case of transmission under stable HAART has been published [6,7].

In our counseling service for HIV-discordant couples interested in artificial insemination with processed semen it became obvious, that couples themselves strongly overestimate the risk of transmission. Contrary to this high fear of contamination, we did not find a single man with detectable HIV-RNA in the semen prior to processing (detection level 40 cp/ml) among all our couples (n = 104) who attended the insemination clinic when the male partner was already on suppressive HAART for more than 6 months. Given the theoretically low risk of HIV-transmission in this setting [5], we started to openly discuss the residual risk of transmission and offered an alternative method for risk reduction using

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timed intercourse and pre-exposure prophylaxis [8]. We describe the clinical setting and the pregnancy rates in this counseling service.

Methods

The program started in February 2004. Serodiscordant couples (male HIV+) who attended the counseling service for artificial insemination with processed semen at the Kantonsspital St. Gallen, Switzerland, received an update regarding our current knowledge on HIV-transmission under HAART. The ethical review board was approached but did not consider this counseling service as a study requiring signed consent. Based on the observation of a substantial number of unprotected sexual intercourse in couples willing to conceive a child (not receiving further counseling) our service was considered as an important support to reduce the potential risk of transmission [8]. It was therefore considered as a standard procedure to inform the couples about all potential options to reduce transmission risk. Couples did, however, receive a written information that also informed them about the off-label use of antiretroviral drugs as pre-exposure prophylaxis. During the first three years of the program, couples received information about two alternative methods to conceive a child: insemination with processed semen at our clinic or timed intercourse with pre-exposure prophylaxis (PrEP). We determined the preference of the couples for either method. Starting in 2007, the method of timed intercourse and PrEP became the principal method proposed. After the counseling visit, couples were followed by telephone interview or E-mail. They were asked about their decision regarding conception method and about the number of attempts of unprotected intercourse with or without PrEP, results of pregnancy and (4th generation) HIV-tests performed in the female partner. In 2007, additional centers (see authors affiliation) adopted the counseling method according to a standardized procedure.

Counseling was guided by a structured guideline covering history of previous conception attempts and risk behavior, discussion of transmission risks under HAART, methods to reduce transmission risks including artificial insemination, antiretroviral therapy and the theoretical considerations from animal studies [9] supporting the use of pre-exposure prophylaxis.

The following guidelines were proposed to the couples as a reasonable mean to reduce the risk of transmission by natural conception with timed intercourse:

- (1) male partner being successfully treated with undetectable HIV-RNA in plasma (<50 cp/ml) without the need of HIV-RNA testing in semen
- (2) no current symptoms of genital infections, no unprotected sex with other partners

- (3) use of an LH-test in the urine to determine the optimal time of conception (36 h after LH-peak)
- (4) pre-exposure prophylaxis with tenofovir, first dose at LH-peak and second dose 24 h later
- (5) after 6 unsuccessful attempts a fertility evaluation was suggested.

The program was only discussed with couples, where the male partner was under a fully suppressed HIV therapy (HIV-RNA < 50 cp/ml) for at least 6 months. Timed intercourse with PrEP consisted of daily determination of LH-peak in urine to optimize timing of sexual intercourse, and two doses of tenofovir (300 mg). The first dose of tenofovir was taken by the female partner in the morning of the LH-peak and a second dose the next morning. Intercourse was timed at the evening after the second dose of tenofovir. The couples were informed using written information about the nature of the off-label use of tenofovir in the HIV-negative partner.

A previous evaluation of fertility was not required for this program but most male partners had performed a sperm evaluation. Couples with indication for fertility problems (e.g. poor sperm motility) were not discouraged but re-evaluation proposed after 5 unsuccessful attempts. Women, whose male partners were treated with a co-formulated tenofovir and emtricitabine (Truvada®) did use the partner's Truvada (n=11) instead of tenofovir with the same dosing interval as described above.

Pregnancy rates were calculated for each cycle and reported as cumulative pregnancy rates per couple. Second conception attempts of couples who had already conceived once and restarted the procedure for a second pregnancy were included in the analysis. Differences in age as a predictor of fertility were evaluated using Mann-Whitney U test.

Results

A total number of 46 couples opted for the proposed method of timed intercourse with PrEP. After 2007, nine (of 46) women decided against the use of PrEP and just performed timed intercourse, mostly since they considered the risk of transmission too low to justify additional drug exposure to the offspring. Among the 21 couples who attended our counseling service during the first three years and who decided to conceive a child by either method, only one couple opted for the insemination method with processed semen (not included in this analysis). Among the 45 couples 7 had a second attempt after a successful natural conception (6 of 7 women experienced spontaneous abortion). Thus, the calculation for the pregnancy rates was based on 53 situations of couples deciding to become pregnant.

The median age at the time of conception the first conception attempt was 38 years for the male and 33 years for the female partner. During the observation time, the 53 couples had a total number of 244 documented unprotected events of vaginal intercourse. None of the female partner had seroconverted for HIV.

The pregnancy rates after natural conception in these 53 couples was 26% for the first attempt and increased up to 66% after five attempts to reach a plateau of 75% after 12 attempts (see Fig. 1). Including only the 45 first attempts, the respective percentages were 29%, 62% and 71%. Six women were 40 years or older, only one of them conceived but experienced a miscarriage. The median age of women who had not successfully conceived by natural intercourse was 37 years, as opposed to 32 years in women with successful conception ($p < 0.001$).

Discussion

The program presented in this case series offers an easier method to reduce the very low residual risk of transmission. It originated from a counseling service after realizing the absence of any transmission events in couples having unprotected intercourse during HAART [8]. The additional risk reduction offered to these couples in these series was based on biological evidence and animal studies [10].

After open discussion of the transmission risk under fully suppressive HAART, the vast majority of counseled couples opted for the alternative self-controlled method using timed intercourse and PrEP. It is noteworthy, that

these selected couples attending a special counseling service did not opt to have unprotected sex despite the open discussion of the risk situation and despite the fact that many other HIV-discordant couples in Switzerland did have sex without condoms regularly [11]. In this report, strong adherence to safer sex recommendations was also associated with being afraid of infecting the HIV-negative partner. The lack of an open debate about the low level of transmission risks for many years has probably helped to maintain this high degree of anxiety [8].

The pregnancy rates in this case series was much higher than previously reported for IUI with processed semen [2]. The plateau of the pregnancy rate curve after a few unsuccessful attempts indicates primary fertility problems in approximately one fourth of HIV-discordant couples. Advanced age appeared to be the most likely predictor of infertility. In couples (male under HAART) who wish to use timed intercourse with or without PrEP to further reduce the very low risk of transmission, it appears reasonable to counsel them to try natural conception for 5–6 cycles. After six unsuccessful attempts fertility evaluation should be encouraged.

The method proposed here to reduce the theoretically very low residual risk of transmission by timed intercourse and PREP can be considered as a psychological means to support the couples to cope with their anxiety. However, we and others [12,13] believe it is time for the medical professionals to openly discuss our knowledge regarding transmission risks and to reduce the exaggerated degree of anxiety often present in our patients.

During the preparation of this manuscript, the first successful trial of pre-exposure prophylaxis in men having

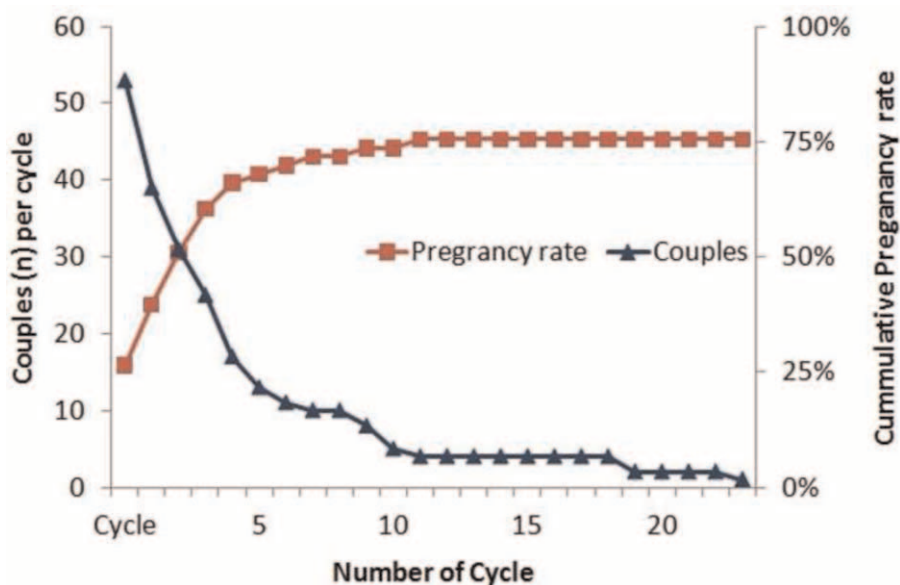


Fig. 1. Pregnancy rate per menstrual cycle. The cumulative pregnancy rate (squares) is plotted against the number of menstrual cycles. The number of women having attempted to become pregnant per cycle is shown (diamonds).

sex with men was published [11]. Based on animal models, PrEP is also likely to prevent male-to-female transmission of HIV [10]. However, the recently announced closure of a PrEP-study in women (FEM-PrEP) reduces the enthusiasm for this strategy as a main preventive effort [14]. But we would like to stress the difference between PrEP trials and the methods proposed here: PrEP described here was used as a theoretical risk reduction strategy in a situation where the a-priori risk is considered to be extremely low [5]. In addition, PrEP was only given 36 and 12 h prior to timed vaginal intercourse. Given the strong social pressure to conceive children in many resource-limited regions, the proposed method of timed intercourse coupled with PrEP might, however, warrant further development. Whether timed intercourse coupled with PrEP for conception might result in improved adherence and hence better efficacy to prevent transmission remains therefore to be shown in settings where the male partner is not treated. The role of timed-intercourse coupled with PrEP might help women at risk to significantly reduce their risk of HIV acquisition during conception. Further studies are urgently needed in resource-limited regions to evaluate the potential timed intercourse and PrEP for this population.

Contribution of authors

The majority of couples (45/53) was counseled at the Cantonal Hospital St. Gallen. All co-authors participated in the setup of the remaining The remaining couples were contributed by the Munich or Linz site. All authors have participated in the counseling of couples presented in this case series. PV has written the manuscript. All authors have participated in the finalization of the manuscript and seen the final version.

None of the authors declares a conflict of interest pertinent to the subject.

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