HAART improves quality of life: should we care about the quality of spermatozoa?

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Improvement in quality of life (QOL) under HAART has been extensively reported in the past few years [1]. Complete suppression of viral replication in blood not only results in an improvement of the cell-mediated immune system, it also dramatically improves life expectancy for most patients with no co-morbidity such as hepatitis C or substance abuse [2]. As a result of this development, an increasing proportion of couples living in an HIV-discordant partnership express the desire to conceive a child [3]. Consequently, several clinics in Europe specialized in artificial reproduction techniques are now offering artificial insemination with processed semen and even more specialized in-vitro techniques [4].

In order to limit the risk of transmission during a medical procedure, most European programmes of artificial insemination in HIV-discordant couples request or at least suggest that the HIV-infected partner is under treatment with a fully suppressive HAART. Unfortunately, information about the effect of HAART on semen quality and male fertility is limited. A number of cross-sectional studies have examined alterations in sperm quality, including sperm motility in HIV-infected individuals, but the results still remain controversial [5–11]. More importantly, the cross-sectional nature of such studies precludes conclusions about the cause of the observed changes in sperm quality. Theoretically, the mitochondrial toxicity associated with some nucleoside analogue reverse transcriptase inhibitors (NRTI), could have a negative impact on sperm mitochondria, and thus on energy production and the motility of mature spermatozoa [12]. In a small cross-sectional study ($n = 31$) [13], we found a weak association between the exposure to d-drugs and mitochondrial DNA content in spermatozoa, but no significant association with reduced sperm motility. The two largest cross-sectional studies found a reduction in sperm motility in HIV-infected male patients (mostly under HAART) compared with fertile, HIV-negative individuals [5,10]. None of those studies could, however, dissect the role of HIV infection from the effects of treatment.

In this issue of the journal *AIDS*, Van Leeuwen *et al.* [14] describe for the first time a longitudinal analysis of qualitative aspects of semen after the initiation of HAART. Almost all of the 34 male patients studied had never been exposed to an antiretroviral therapy when they were included in the 48-week observational study. At inclusion, the authors carefully evaluated potential co-factors such as sexually transmissible infections, follicle-stimulating hormone levels and CD4 cell counts. As a result of the multiple semen collection visits over the period of one year, the authors were able to apply a repeated measurements procedure using mixed-effects models. All possible confounders that might have influenced the results were carefully ruled out. As a result of the longitudinal design and the sophisticated statistical methodology, the authors have been able to demonstrate clearly that antiretroviral treatment resulted in a significant effect on sperm motility. Surprisingly, this effect was demonstrated despite the use of drugs that are generally considered to be less toxic to mitochondria. None of the 34 patients was taking stavudine and only one was taking didanosine, whereas five were on a

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zidovudine-based regimen and another five were on a nucleotide-sparing regimen.

The results of the trial are indeed remarkable. If confirmed, semen motility would be one of the most sensitive indicators of the toxicity of antiretroviral drugs. Future comparative studies should therefore evaluate the relative effect of different drugs on sperm motility, and the role of mtDNA depletion as a potential biological mechanism should be further evaluated.

What also remains to be shown is the long-term treatment effect on sperm motility. More importantly, the extent to which reduced sperm motility translates into reduced male fertility is also unclear. In our small series of 22 couples having unprotected intercourse with a short preexposure prophylaxis for the woman while the male partner was under completely suppressive HAART, pregnancy rates were still surprisingly high [15]. After three timed intercourses, more than 50% of the women were pregnant but six women remained non-pregnant despite more than six timed intercourses.

In our experience, an increasing number of couples testify that they have unprotected sex with or without the desire to conceive a child. The concept of a very limited infectivity under HAART, especially in a steady partnership, is increasingly adopted by HIV-discordant couples. It is therefore likely that more and more couples will try on their own, with or without timed intercourse or preexposure prophylaxis, to conceive by natural intercourse. If HAART results in reduced male fertility, progressively more sterile couples will seek professional advice. It therefore remains crucial that infertility clinics specialize in the treatment of HIV-infected patients and offer artificial reproductive assistance to these couples.

Conflicts of interest: None.

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