Editorial

HIV-infected women in Europe: gender-specific needs and challenges

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In collaboration with the Strong, HIV positive, Empowered Women (SHE) programme, an industry-funded initiative aimed at improving the quality of life of HIV-positive women, *Antiviral Therapy* has taken the excellent step to dedicate a Supplement Issue addressing the needs and challenges related to the care of women living in Europe. Included articles present the multiple facets of gender-specific issues and research gaps, ranging from HIV testing strategies to antiretroviral combination therapy, including long-term challenges associated with chronic HIV infection.

If HIV was regarded as a disease predominantly affecting young males at the beginning of the epidemic, this is no longer true. According to UNAIDS latest global estimates, women comprise >50% of individuals living with HIV [1]. Their background, mode of infection, or origin make them a very heterogeneous population whose voice is barely heard. Most studies in the early antiretroviral therapy (ART) era have addressed gender-specific issues based only on motherhood or mother-to-child transmission. However, there are still surprisingly high rates of late HIV diagnosis among women in Europe. Johnson *et al*. [2] discuss the many reasons for missed opportunities for HIV testing and suggest that women are more affected than men by the prospect of negative consequences, including the fear of disclosure and the effect on their reproductive choices. Even testing during pregnancy, listed as the standard of care [3], is not universally applied in Europe. In the prenatal setting, a universal opt-out strategy would indeed be a step towards an increased HIV testing rate.

Miralles *et al*. [4] show that many HIV-positive women in Europe are in vulnerable social situations, especially migrants. Data from the Swiss HIV Cohort Study have not demonstrated an increased risk of mortality in patients originating from sub-Saharan Africa, but more virological failures [5]. Sexuality empowerment is also addressed by Miralles *et al*. [4] as an important asset to curb new HIV infections in Russia.

HIV-positive women now have the option of motherhood. Data on the safety of most antiretroviral agents in pregnancy are accumulating, and no signal for teratogenicity has been found for newer drugs. The efavirenz saga illustrates how important pregnancy registries are, especially where drug options are limited, and passive reporting is failing to adequately address this urgent need for data. Efavirenz was banned for the treatment of pregnant women and, by extension, to women of childbearing age. As a consequence, access to a widely used, convenient and efficient regimen became difficult for a large part of the female population. A meta-analysis and systematic review [6] and the joint efforts of international stakeholders, such as the World Health Organization (WHO) or the International Aids Society, all concur to change the practice. As a result, efavirenz is now the preferred first-line option in the WHO 2013 recommendations [7]. A very recent report from France presented at the *20th Conference on Retroviruses and Opportunistic Infections* in 2013 concluded that there was evidence for an elevated risk of congenital abnormalities associated with efavirenz compared with other ART, although importantly no neural tube defects were reported [8]. While these data are worrisome, the risk remains low when considered in context as part of the overall evidence. Further studies on the safety of ART in pregnancy should be strongly encouraged.

Approximately 90% of European women living with HIV are of childbearing age. Together with the 'Swiss Statement' [9] and the results of HPTN 052 [10], a randomized trial to determine the effectiveness of two treatment initiation strategies in preventing the sexual transmission of HIV in HIV-serodiscordant couples, the use of non-barrier contraceptives is now standard practice for many HIV-positive, ART-treated women who do not want to get pregnant. Haberl *et al*. [11] convincingly show that the efficacy of the contraceptive pill may be lowered because of drug–drug interactions with some components of ART. Recent studies assessing the high number of unintended pregnancies in ART-treated women in the USA [12] demonstrate the crucial role of the coordination of HIV management with sexual and reproductive healthcare delivery.

Drug recommendations address women's needs regarding contraceptive use (sometimes) or motherhood (with the aim of not transmitting the virus), but rarely when it comes to specific pharmacokinetics or dosage. Do antiretrovirals have a similar effect on men and women?

Clinical trials to assess the efficacy and safety of investigational drugs rarely include women of childbearing age as the need for multiple methods of contraception, often required, limits their access to the testing of new innovative drugs [13]. The low inclusion of women in trials can have additional reasons, such as insufficient community advocacy or low flexibility in clinic attendance requirements [13]. Therefore, most treating physicians have no other choice than to extrapolate data from clinical trials conducted mainly in men. For example, rilpivirine was tested in two large international Phase III trials accounting for <25% of women [14,15]. d'Arminio Monforte *et al*. [16] nicely demonstrate in their report that these retrospective analyses from randomized clinical trials are not powered to detect gender differences. As shown in the CASTLE study, differences are mainly attributable to the higher discontinuation rate of female participants [17]. In the Swiss HIV Cohort study, gender inequalities in the response to combination ART are mainly explained by the different prevalence of socioeconomic characteristics and by the slower implementation of new combination ART regimens in women compared with men [18,19].

Researchers should ensure the proportional representation of women in early phase studies. Large clinical trials including only women should be conducted and the complete chain of European research, from clinical trial sponsors to scientific journal editors or ethics committees – to name but a few – should ensure that female data are conducted, analysed and published in a timely manner.

Female HIV patients live longer than their male counterparts [20]. However, as shown by Dominguez *et al*. [21], data on ageing in HIV-positive women are scarce, and in many cohorts the number of ageing females is too small to draw meaningful conclusions. The US Food and Drug Administration conducted a recent analysis and demonstrated that immunological and virological outcomes are not inferior in women aged ≥50 years compared with those aged ≥35 years. However, although reassuring, these data should be verified in other contexts [22].

Despite many shortcomings related to knowledge on the care of HIV-infected women, some highly relevant new data have been reported in recent years. Women can be empowered to control their sexuality-associated risk of HIV acquisition, and the Caprisa trial has shown that vaginally-applied tenofovir can reduce the rate of HIV infection in exposed women by 39% [23]. Microbicide efficacy is still limited and the application a challenge [23], but it is a step forward to partner-independent protection. Pre-exposure prophylaxis (PreP) – administration of an antiretroviral drug in HIV-uninfected men or women – can prevent HIV acquisition. PreP studies have demonstrated the efficiency of this strategy, mostly in serodiscordant couples. However, results in general female populations have been disappointing. In a recent conference report, none of three PreP and microbicide interventions tested in the VOICE study provided additional protection against HIV acquisition, most likely because few of the female participants used the products as instructed [24].

Of note, the HPTN 052 trial [10], with its reinforcement of the 'Swiss Statement' [9] message, helps both HIV-infected and HIV-exposed women to find a way back to normalization in discordant partnerships. Importantly, 50% of HPTN 052 index cases were women and this increases the generalizability of the study results.

In low/middle-income countries, ART coverage is higher among women than men [25]. Cohort studies from resource-limited settings indicated a 37% increase in the risk of death for men compared with women [26]. In Africa, men also suffer major obstacles to access effective care and efforts should be made to create male-friendly health structures in these settings [27,28]. To better account for gender inequalities that are well known to drive the HIV epidemic in Africa, UNAIDS encourage the collection and use of sex- and age-disaggregated data to monitor and evaluate the effect of programmes on different populations.

Even if there are parts of the world with very promising developments in HIV care for women, we would like to emphasize the need for the early identification of research gaps in this population and a linkage with reproductive health structures. All measures directed

towards the empowerment of HIV-infected women concerning their sexuality, health and beyond, will affect their quality of life and long-term outcome. Finally, systematic gender-based analyses should assess the challenges to accessing care for both women and men to ensure that the needs of all individuals living with HIV/AIDS are adequately addressed.

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