COMMENTARY

Genital shedding of HIV-1 despite successful antiretroviral therapy

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HIV-1 is most commonly transmitted by sexual intercourse but the exact mechanism of such transmission remains unclear. A prerequisite for sexual transmission is the presence of the virus at the site of the mucosal contact. There have been several investigations of genital shedding in semen but, partly because of the methodological complexities of the study of female genital secretions, only small studies have been conducted in women. In this issue of *The Lancet*, Andrea Kovacs and colleagues describe a large cross-sectional study among women of the systemic and local genital factors associated with the genital shedding of HIV-1.

How will studies of female genital shedding of HIV-1 help in the management of patients with HIV-infection? Almost certainly, the likelihood of sexual transmission depends on the presence of HIV in the genital tract (the inoculum). The concentration of HIV-1 at the mucosal site is conceivably a major risk factor for sexual transmission.[1] However, the association of concentration of HIV-1 in genital secretions with risk of transmission has not been investigated. Instead, large epidemiological studies have shown that the HIV-RNA concentration in blood is the main factor that influences transmission.[2] In keeping with findings in HIV-infected men and in smaller studies in women, Kovacs and colleagues' study showed a significant correlation between the HIV-RNA concentrations in the blood and in the genital tract. However, this correlation is weak, as is the case between blood and semen concentrations in several studies.[1] Thus, other biological or methodological factors must contribute to the variability of the genital shedding of HIV.

Kovacs and colleagues examined the role of peripheral blood mononuclear-cell cultures, lymphocyte subpopulations, and antiviral therapy as cofactors in genital HIV shedding. None of these factors remained significantly associated after adjustment for blood viral load. Methodological limitations might also play a part. The investigators used a very sensitive method (HIV-PCR) to measure cell-free virus but a very insensitive method (culture, 6% positives) to detect cell-associated HIV-1 in the genital tract. Thus, the effect of a factor, such as a genital infection, that results in an increase predominantly of cell-associated HIV is likely to be underestimated by this method. Use of an HIV-DNA detection method in future studies might help in the further investigation of these issues.

Two important findings emerge from Kovacs and colleagues' study. In general, HIV-RNA concentration in the genital tract was about one log below the value in blood, but HIV-RNA was higher in the genital tract than in the blood in 3·6% of the women. Similar "hypersecretors" have been found among men.[3] Thus active local HIV replication probably occurs in the genital compartment in these people.

The other surprising finding was the detection of HIV-RNA in the genital tract in a third (27) of the women with HIV-RNA below 500 copies/mL, most of whom received antiviral treatment. Of these 27 women, six (three of whom were on treatment) had a genital viral load of 10^4–10^5 copies/mL. This finding differs from that among a Swiss cohort of HIV-infected men being treated with highly active antiretroviral therapy (HAART),[4] but it is in keeping with previous findings of HIV-1 replication being confined essentially to the male genital tract, and supports recent findings of local HIV-1 replication in the female genital tract.[5] However, these extremely high concentrations of HIV-RNA in the genital tract of treated individuals need to be confirmed in a larger series of women treated with HAART.

According to the study by Quinn and colleagues[2] transmission risk is very low in patients with a blood viral load of below 1500 copies/mL. The finding of high genital viral load in the absence of detectable blood viral load suggests that blood viral load measurements might strongly underestimate transmission risk in some individuals. Genital viral load might serve as a better estimate for the transmission, and such a model has been described for HIV-1 in semen.[6]

What Kovacs and colleagues' study indicates is that women in whom HAART has suppressed HIV-1 concentrations in the blood might still have high concentrations of HIV-1 in the genital tract. The lack of an association between genital inflammation and viral shedding in multivariate analysis does not rule out the possibility that genital inflammation might account for the unusually high genital HIV-RNA concentrations in a few selected cases. Thus patients will have to continue to be warned about the consequences of unprotected sex even if blood tests indicate that they have responded to antiretroviral therapy.

Pietro L Vernazza

Division of Infectious Diseases, Department of Medicine, Cantonal Hospital, 9007 St Gallen, Switzerland
(e-mail: Pietro.Vernazza@kssg.ch)

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