

BACKGROUND: There is indirect evidence that HIV-1 exposure does not inevitably lead to persistent infection. Heterogeneity in susceptibility to infection could be due to protective immunity. The objective of this study was to find out whether in highly HIV-1-exposed populations some individuals are resistant to infection. **METHODS:** We did an observational cohort study of incident HIV-1 infection-among 424 initially HIV-1-seronegative prostitutes in Nairobi, Kenya, between 1985 and 1994. 239 women seroconverted to HIV-1 during the study period. Exponential, Weibull, and mixture survival models were used to examine the effect of the duration of follow-up on incidence of HIV-1 infection. The influence of the duration of exposure to HIV-1 through prostitution on seroconversion risk was examined by Cox proportional hazards modelling, with control for other known or suspected risk factors for incident HIV-1 infection. HIV-1 PCR with env, nef, and vif gene primers was done on 43 persistently seronegative prostitutes who remained seronegative after 3 or more years of follow-up. **FINDINGS:** Modelling of the time to HIV-1 seroconversion showed that the incidence of HIV-1 seroconversion decreased with increasing duration of exposure, which indicates that there is heterogeneity in HIV-1 susceptibility or acquired immunity to HIV-1. Each weighted year of exposure through prostitution resulted in a 1.2-fold reduction in HIV-1 seroconversion risk (hazard ratio 0.83 [95% CI 0.79-0.88], $p < 0.0001$). Analyses of epidemiological and laboratory data, show that persistent seronegativity is not explained by seronegative HIV-1 infection or by differences in risk factors for HIV-1 infection such as safer sexual behaviours or the incidence of other sexually transmitted infections. **Interpretation:** We conclude that a small proportion of highly exposed individuals, who may have natural protective immunity to HIV-1, are resistant to HIV-1. **PIP:** A cohort study conducted in 1985-94 among 424 prostitutes from Nairobi, Kenya, who were initially human immunodeficiency virus (HIV)-1 seronegative, tended to provide support for the observation that some individuals in highly exposed populations may be resistant to infection. During the 10-year study period, 239 of these women seroconverted. The overall HIV-1 incidence was 42/100 person-years. After the first 2 years of follow up, in which the majority of seroconversions occurred, HIV-1 prevalence reached a plateau and then began a steep decline. To determine whether the risk of HIV-1 infection declined over time as a result of the selection of resistance, incidence rates among women with less than 3 years' versus more than 3 years' duration of prostitution were compared for 1989-93. An increasing protective effect for each seronegative year of exposure was observed. The estimated cumulative protective effect for women practicing prostitution from 1984-93 and remaining seronegative, compared to women who entered prostitution in 1994, was over 100-fold. To rule out the possibility that the decrease in seroconversion with duration of exposure reflected differences in sexual behavior or immunity to sexually transmitted diseases that facilitate HIV transmission, Cox proportional hazards modelling was performed. The weighted duration of prostitution was independently associated with a decreased risk of seroconversion. Each weighted year of exposure resulted in a 1.2-fold decrease in risk. Women who seroconverted were more likely to report 1 or more regular partners and to use condoms with these partners than their counterparts who remained seronegative. Elucidation of the protective mechanisms and the factors mediating the development of immunity against HIV-1 could be important to HIV-1 vaccine research.