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Sexually Transmitted Diseases and Risk of HIV Infection

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We have analyzed the association between sexually transmitted diseases (STD) and HIV infection, using data from a cross-sectional survey of subjects attending STD clinics in Northern Italy conducted since 1988. A total of 1,711 subjects (1,259 males, 452 females), who had referred themselves to three STD clinics in Northern Italy for suspected STD or STD treatment, were included for the study. Out of these, 145 subjects (113 males and 32 females) were HIV-positive. A total of 58 HIV-positive and 368 HIV-negative subjects reported a history of STD; the corresponding odds ratio (OR) was 2.3 (95% confidence interval (CI) 1.5–3.6) for subjects reporting a history of STD. Considering various STD in details, the estimated OR was 1.8 (95% CI 0.8–3.8) for a history of gonorrhoea and 1.5 (95% CI 0.8–2.7) of syphilis, and the OR was 1.8 (95% CI 1.0–3.2) and 2.2 (95% CI 1.3–3.8), respectively, for a positive TPHA and VDRL test. The results of the test for HbsAg were available in 50 HIV-positive and 1,028 HIV-negative subjects; the OR of HIV infection in subjects with HbSAg was 3.9 (95% CI 1.7–9.0). Presence of genital ulcers at clinical examination was not significantly associated with the risk of HIV infection (OR yes vs no genital ulcers 1.5, 95% CI 0.6–2.8).

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The relationship between sexually transmitted diseases (STD) and risk of HIV infection has been an object of increasing interest (1–4). Biological considerations and epidemiological data suggest that STD may favour HIV transmission (5–7). Available data, however, are not completely consistent. For instance, it has been suggested that ulcerative and non-ulcerative STD may affect the risk of HIV infection differently, ulcerative diseases being at higher risk (8, 9). The role of STD in HIV infection risk may differ for males and females and in heterosexual or homosexual relationships (7, 9, 10). Most of the available evidence is based on studies conducted in developing countries or in homosexual populations, and few data are available from European countries.

We analyzed the association between STD and HIV infection, using data from a cross-sectional survey of subjects attending STD clinics in Northern Italy.

MATERIALS AND METHODS

This cross-sectional study has been conducted since September 1988 in three STD clinics in Bergamo, Verona and Brescia, in Northern Italy. The design of the study has previously been described (11). Eligible for the study were subjects who had referred themselves for the first time to these collaborating centres for suspected STD or for treatment. To obtain estimates of the prevalence of HIV infection in patients attending STD clinics for problems or counselling, we excluded from the investigation all subjects who attended the clinics for HIV antibody testing only or for clinical counselling related to known HIV infection.

At clinical registration patients were given an anonymous identification code and were asked to give informed consent to the study. A total of 1,259 men (median age 30 years, range 16–70) and 452 women (median age 28 years, range 16–61) agreed to participate. Less than 3% of eligible subjects refused to enter the study. This report is based on data collected till March 1993.

All subjects were asked to complete a standard questionnaire giving information on their general characteristics, lifestyle, sexual habits and history of drug use and STD (herpes simplex virus, condylomas, urethritis, gonorrhoea, syphilis, vaginal infection in women and balanitis in men) and any blood transfusions they had received. Physical examination was carried out and a blood sample was taken to establish HIV status. A subject was considered HIV-antibody-positive if a positive competitive enzyme-linked immunosorbent assay (ELISA) was confirmed by a Western blot analysis. If specifically requested by the patient, the identification code was broken and the result was revealed. The VDRL and TPHA tests were routinely performed by standard methods to assess serological evidence of syphilis. Hepatitis B virus (HBV) surface antigen (Hbs Ag) has been routinely assayed since March 1989, so this was available for only 1,078 subjects.

Data analysis

The association between STDs and HIV serological status was estimated using odds ratio (OR) and their 95% confidence intervals (CI) (12). Unconditional logistic regression with maximum likelihood fitting was used. Included in the regression equations were terms for age, sex, intravenous drug use and in turn various indicators of STD (13).

RESULTS

The distribution of 145 HIV-positive and 1,566 HIV-negative subjects according to sex, age and marital status is presented in Table I. HIV-positive subjects were more frequently males (OR 0.7, 95% CI 0.4–1.0) and aged 25–34 years.

Intravenous drug use markedly increased the risk of HIV infection: in comparison with non-users, the OR for HIV infection was 10.2 (95% CI 5.3–22.4) and 20.8 (95% CI 13.4–32.2), respectively, in occasional and regular users (Table II).

Male homosexuality was more frequently reported by HIV-positive than HIV-negative subjects (OR 2.3, 95% CI 1.2–4.3, for always vs never homosexual intercourse) (Table II).

The relation between STD and HIV status is shown in Table II. The risk of HIV-positive status was 2.3 (95% CI 1.5–3.6) in subjects reporting a history of STD; considering separately subjects reporting one or two or more STD, the respective OR estimates were 2.2 and 2.3.

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Table I. *Distribution of 145 HIV-positive and 1,566* HIV-negative subjects according to sex, age, marital status and indicators of HIV infection risk, Italy 1988–1993*

	HIV status	
	Positive No. (%)	Negative No. (%)
Sex		
Males	113 (78)	1146 (73)
Females	32 (22)	420 (27)
Age		
≤24	35 (24)	381 (24)
25–34	89 (61)	650 (42)
≥35	21 (15)	535 (34)
Marital status		
Married	55 (39)	664 (43)
Never married	86 (61)	867 (57)

* In some cases the sum does not represent the total because of missing values.

No association emerged between number of sexual partners over the 3 years before the interview and risk of HIV infection (data not shown in Table). The association between number of sexual partners and risk of HIV infection was also analysed in strata of intravenous drug use and homosexuality in men. In comparison with subjects reporting no or one sexual partner over the 3 years before the interview, the estimated OR of HIV serum positivity was 1.1 in subjects reporting 2–3, 4–5 and ≥6 sexual partners, 0.6 and 0.7 when the analysis considered heterosexual men and 0.5, 0.7 and 0.4 when the analysis considered homosexual men. The corresponding values were 1.5, 1.4 and 1.0 and 0.8, 0.5 and 1.0, respectively, for never intravenous drug use and always intravenous drug use.

DISCUSSION

These results support the finding of an association between a history of selected STD and risk of HIV infection. Some caution is necessary, however, in their interpretation. Despite the sensitive nature of the questionnaire, responses were generally satisfactory, with the exception of information on number of sexual partners (11). In fact, the percentage of subjects not giving information on number of sexual partners was not negligible (about 15%). However, the frequency of missing values was comparable in HIV-positive and HIV-negative subjects (e.g. the number of sexual partners was missing for 17% of HIV-positive and 12% of HIV-negative subjects), and the corresponding figures were 16% and 14% for men reporting homosexual intercourse or not. The information on general characteristics, sexual habits and medical history considered in this study was self-reported, and some mis-reporting is likely. However, it is unlikely that information bias was different for HIV-antibody-positive or -negative patients, since the blood-test was taken after data collection. Furthermore, consistent evidence emerged after checking self-reported information and data collected during the clinical examination. Similarly, a consistent relationship was observed between self-reported history and serological evidence of syphilis. HIV infection is associated with the presence of anticardiolipin antibodies and consequently with false-positive VDRL tests (14). This might explain the positive association between the VDRL test and risk of HIV infection, but we found a positive relationship with TPHA, too.

Table II. *Distribution$^{\Phi}$ and corresponding odds ratios of HIV-positive and HIV-negative subjects according to indicators of selected sexually transmitted diseases, Italy 1988–1993*

	HIV status		Odds ratio (95% CI)*
	Negative	Positive	
Intravenous drug use (times/week)			
Never	1368	53	1+
≤1 (occasional)	37	16	10.2 (5.3–22.4)
>1 (regular)	75	68	20.8 (13.4–32.2)
Homosexuality in men			
Never	882	68	1+
Always	217	39	2.3 (1.2–4.3)
History of STD			
No	1079	74	1+
Yes			
one disease	121	20	2.2 (1.3–4.0)
two or more diseases	247	38	2.3 (1.1–4.4)
History of syphilis			
No	1273	111	1+
Yes	125	17	1.5 (0.8–2.7)
History of gonorrhea			
No	1299	113	1+
Yes	96	12	1.8 (0.8–3.8)
Genital ulcers at study entry			
No	1515	121	1+
Yes	71	12	1.5 (0.6–2.8)
TPHA			
Negative	1379	85	1+
Positive	209	22	1.8 (1.0–3.2)
VDRL			
Negative	1418	82	1+
Positive	170	25	2.2 (1.3–3.8)
HbsAg			
Negative	976	38	1+
Positive	52	12	3.9 (1.7–9.0)

$^{\Phi}$ In some cases the sum does not represent the total because of missing values.
* Multivariate estimates including terms for age, sex, intravenous drug use, homosexuality and in turn the above listed variables.
+ Reference category.

The association between STD and HIV infection may partly be explained by common risk factors for both conditions (15, 16), but in this series the association was confirmed after taking into account potential confounding factors such as indicators of sexual habits.

This is a cross-sectional study and, as such, it is open to bias and limitations. HIV infection may alter the natural history of STD (17) and further facilitate the risk of STD infection. The cross-sectional design does not allow for analysis of the timing of HIV and various STDs. Further, the data collection lasted 5 years; however, during this study period

the prevalence of HIV infection in the study population did not markedly change (18), and inclusion in the multivariate analysis of information for year of data collection did not change the estimated OR (data not shown). There is, however, consistent evidence from different populations of an association between various STDs and HIV (8, 9). For example, the risk of HIV infection was about double in prostitutes with a history of syphilis in a study conducted in Africa, and in American homosexuals (3, 10).

STD may facilitate HIV infection in different ways. First of all, STD may facilitate the HIV contact with blood, for example through genital ulcers. Some follow-up studies have shown a time relation between the presence of genital ulcer and HIV infection (9, 19). In this series we found no significant association between the presence of genital ulcers at trial entry and risk of HIV infection, but the finding was based on few subjects.

STD may activate macrophages and stimulate T-lymphocytes (20–22) (which *in vitro* are more susceptible to HIV infection than unstimulated cells) (23), and antigenic stimulation of latent HIV-infected T-lymphocytes could result in activation of the virus and increased viral shedding (24).

We also observed a strong relation between HbsAg positivity and HIV infection. This persisted after taking into account the role of intravenous drug use, suggesting similar conditions facilitating the HIV and HVB infection. The lack of association between number of sexual partners over the 3 years before the interview and risk of HIV infection must be considered cautiously, in view of the low statistical power in male nonusers of intravenous drugs and potential biases.

In conclusion this study offers further data on the importance of STD in the risk of HIV infection and underlines the need for populations attending STD clinics to undergo HIV infection screening and prevention campaigns.

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