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Human Herpesvirus 8 and Human Herpesvirus 2 Infections in Prison Population

L. Sarmati,[1] S. Babudieri,[2] B. Longo,[3] G. Starnini,[4] S. Carbonara,[5] R. Monarca,[6] A.R. Buonomini,[1] L. Dori,[1] G. Rezza,[3] and M. Andreoni[1]* Gruppo di Lavoro Infettivologi Penitenziari (GLIP)[†]

[1]*Clinic of Infectious Diseases, University of Tor Vergata, Rome, Italy*
[2]*Clinic of Infectious Diseases, University of Sassari, Italy*
[3]*Department of Infectious Disease, Istituto Superiore di Sanità, Roma, Italy*
[4]*Infectious Diseases Unit, Belcolle Hospital, Viterbo, Italy*
[5]*Clinic of Infectious Diseases, University of Bari, Italy*
[6]*Italian Prison of Viterbo, Viterbo, Italy*

Incarcerated persons have high rates of infectious diseases. Few data on the prevalence of sexually transmitted diseases in prisoners are available. This multi-center cross-sectional study enrolled 973 inmates from eight Italian prisons. Demographic and behavioral data were collected using an anonymous standardized questionnaire and antibodies to HIV, HCV, HBV, HSV-2, and HHV-8 were detected in a blood sample obtained from each person at the time of the enrollment in the study. Two hundred and two out of the 973 subjects (20.7%) had antibodies against HHV-8. HHV-8-seropositive subjects were more likely to be older than 30 years with a higher educational level. HHV-8 infection was associated significantly with HBV ($P < 0.001$) and HSV-2 ($P = 0.004$) seropositivity and with previous imprisonments. Multivariate analysis showed that HHV-8 infection in Italian inmates was associated with HBV ($P < 0.001$) and HSV-2 ($P = 0.002$) seropositivity otherwise among foreigners inmates HHV-8 was significantly associated with HBV infection ($P = 0.05$). One hundred and eighty-six (21.2%) prisoners had anti-HSV-2 antibodies. At multivariate analysis HSV-2-positivity was significantly associated with HIV ($P < 0.001$) and HHV-8 infections ($P = 0.003$), whereas it was inversely associated with HCV infection (0.004). A relatively high seroprevalence of HHV-8 and HSV-2 among Italian prison inmates was found. The association of HHV-8 and HSV-2 infections suggest sexual transmission of these viruses among Italian prison inmates. ***J. Med. Virol. 79:167–173, 2007.*** © 2006 Wiley-Liss, Inc.

KEY WORDS: human herpes virus 8; herpes simplex virus 2; Italian prisoners; sexual transmitted diseases

INTRODUCTION

Incarcerated persons have a disproportionate burden of infectious diseases, and present higher rates of disease morbidity and mortality than the general population [Hammett et al., 2002]. The prevalence of several infections such as hepatitis B, hepatitis C, HIV, and tuberculosis, is reported to be particularly elevated in the prison systems. The results of a study on infectious diseases in USA showed that, in 1997, from 20% to 26% of all people living with HIV, from 29% to 43% of those infected with hepatitis C virus, and 40% of those with tuberculosis had spent some time in a correctional facility [Hammett et al., 2003]. The overall prevalence of HBV infection among USA adult inmates ranges from 13% to 47%, whereas the prevalence of chronic HBV infection is approximately 1.0%–3.7%, which is two to six times higher than that reported among adults in the general US population [CDC, 2003]. Furthermore, outbreaks of tuberculosis among immunocompetent and immunosuppressed male prison inmates has also been reported [Centers for Disease

[†]The members of the GLIP(Gruppo di Lavoro Infettivologi Penitenziari) are: A. Sardu (Casa Circondariale Femminile (female jail), Pozzuoli, Napoli), G. Quercia (Casa di Reclusione (prison), Sulmona AQ), S. Vullo (Casa Circondariale (jail), Agrigento), A. Casti (Casa Circondariale and Casa di Reclusione, Cagliari), S. Novati (Casa di Reclusione, Milano Opera), G. Mazzarello (Casa Circondariale, Genova), M. Dierna (Casa Circondariale, Ragusa), A. Romano (Casa Circondariale, Lecce), V. Iovinella (Casa Circondariale and Casa di Reclusione, Napoli Poggioreale), G. Florenzano (Casa Circondariale, Sassari).

*Correspondence to: M. Andreoni, MD, Clinic of Infectious Diseases, Department of Public Health, Tor Vergata University, Rome Italy. E-mail: andreoni@uniroma2.it

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Control and Prevention, 2000; Mercer et al., 2003; Carbonara et al., 2005].

Several factors present before incarceration, such as low socioeconomic status, injection drug use, high risk sexual behavior, and poor access to health care, may influence the high rate of such infections. Inmates may also be exposed to infections during detention, and factors such as crowding, sharing contaminated items, injection drug use, sexual assault, may contribute to the acquisition of parenteral and sexual transmitted diseases during detention.

There is limited information on the impact of infections in Italian prisoners. However, a multi-center cross-sectional study conducted among prisoners from different Italian regions showed a disproportionate high prevalence of HIV, HCV, and HBV infection [Babudieri et al., 2005].

Other infections, such as HHV-8 and HVS-2, also merit investigation. Differently from HIV and HBV, which may be also transmitted through the blood (i.e., needle/syringe exchange, etc.), HSV-2 is an exclusive marker of sexual transmission; for this reason, it is worthwhile to assess its prevalence in a population considered at high risk of sexually transmitted infections. On the other hand, HHV-8 is transmitted mainly through the sexual route among gay men in the industrialized world but is highly prevalent in the general population in most developing countries, where it is probably transmitted through saliva. Thus is interesting to evaluate the extent of HHV-8 diffusion among prisoners, who live in close contact in an overcrowded environment, and to explore possible associations with exposure to other viral infections in order to identify similar routes of transmission.

The purpose of the present study was to assess the prevalence and correlates of HHV-8 and HSV-2 infections in Italian prison inmates with known HIV, HBV, and HCV serostatus.

METHODS

This multi-center cross-sectional study is part of a larger survey conducted on selected Italian correctional system facilities [Babudieri et al., 2005]. Briefly, the study was conducted on a sample of inmates from eight prisons sited in different areas representative of regions from north to south of Italy (Lombardy, Lazio, Apulia, Campania, Sicily, and Sardinia). Study participants were recruited between November 1, 2001 and February 20, 2002, by infectious-disease specialists acting as consultants to the prisons. A total of 1,181 inmates were asked to participate at the study (21.2% of the entire inmate population). Complete serological data were obtained from 973 out of the 1181 subjects enrolled in the study. The distribution of the Italian prisoners according to the regional origin was homogeneous with 46.6% (365/784) inmates from North-Center and 53.4%.(419/784) from South of Italy and isles. Relatively to the foreign inmates, 41% (78/189) comes from others European countries (mainly East/Central Europe), 36% (68/189) from North of Africa, 20% (37/189) from South of America, and 3% (6/189) from other countries (mainly China and other Asian countries).

Participating inmates were interviewed using an anonymous standardized questionnaire for collecting demographic data (i.e., age, place of birth and residence, and nationality) and behavioral data (i.e., use and modality of administration of illicit drugs and sexual behavior). A progressive numerical code, not including the name of the inmates, was used to link questionnaires and serum samples. Written informed consent was obtained from all participants, after having received complete information on the purpose of the study, in accordance with the ethical standards required by the Italian Ministry of Justice. The anonymity of the results was guaranteed.

Serological Evaluation

At the time of enrollment a blood sample was obtained from each person. Collected sera were stored at -20°C. All serological assays were carried out by a reference laboratory at the Infectious Disease Clinic of Tor Vergata University in Rome. HIV testing was performed using ELISA (EIAgen HIV-1 E HIV-2 Kit Clonesystems, Biochem Immunosystems Italia s.p.a., Casalecchio di Reno, Italy); reactive sera were confirmed by dot-blot (Chiron RIBA-HIV1/2 Strip Immunoblot Assay—SIA, distributed in Italy by Ortho Diagnostic Systems, Inc., Milan, Italy). HCV testing was performed using 3rd generation EIA (INNOTEST HCV Ab IV° EIA—Core-NS3-NS4-NS5 antigens, Innogenetics, Pomezia, Italy). HBsAg and HBcAb (IgG) were detected using the HBsAg Micro EIA Kit (Nuclear Laser Medicine, Settala, Italy) and the HBcAb One ELISA (Nuclear Laser Medicine, Settala, Italy), respectively. Antibodies to HSV-2 were detected by an enzyme-linked immunosorbent assay (ELISA) for qualitative detection of human immunoglobulin (Ig) G class antibody to HSV-2 (Herpe-Select 2 ELISA IgG Focus Technologies-Cypress, CA) with reported sensitivity of 98%–100% and specificity of 96%–99% [Ashley, 2001].

Antibodies to lytic antigens of HHV-8 were detected as described previously [Andreoni et al., 1999, 2002] using an immunofluorescence assay (IFA) based on BCBL-1 cell line (obtained through the AIDS Research and Reference Reagent Program, Division of AIDS, NIAID, NIH from Drs. M. McGrath and D. Ganem). Titrations were done with two-fold serial dilutions. Samples reactive at $>$1:20 dilution were considered positive. The sensitivity and specificity of the test at the serum dilution of 1:20 was demonstrated in a previous multicenter study [Schatz et al., 2001]. The titrations were done after twofold serial dilution of patient's sera.

Serological testing for HHV-8 was carried out on the coded samples in a blinded fashion.

Statistical Analysis

The statistical analysis was carried out using a standard statistical package (STATA/SE version 8). The seroprevalence of the different viral agents was calculated as the proportion of positive samples of the total number of tests. Odds ratios (OR) and their 95% confidence intervals (CI) were also calculated to assess associations with demographic and behavioral variables and with markers of other infections. Independent associations were evaluated by calculating the adjusted OR after accounting for putative confounding variables, using multiple logistic regression analysis. The level of significance for inclusion in the model as well as the final level of significance was set at $P < 0.05$. The variable "heterosexual" was used as reference for the calculation of the OR because it was assumed initially that non-intravenous drug using heterosexual contacts were at lower risk of sexually and blood-transmitted infections.

RESULTS

The characteristics of study participants are shown in Table I. The great majority (87%) of subjects were men, and 19.4% were foreigners.

About one third of the participants (30%) were intravenous drug users, whereas only a small proportion (0.6%) reported homosexual relationships. With regard to the frequency of other possible risks factors for parenteral or sexually transmitted infections, tattoos were very common (47.5%), followed by unprotected sex (23.3%), alcohol abuse (20.6%), and transfusions (4.8%). The majority of the study population (89.3%) had a history of previous imprisonment, and 63.9% of all inmates had a duration of current imprisonment longer than 1 year. Half of study population (52.6%) had antibodies against HBV, 38% were HCV-positive and 7.5% HIV-positive.

TABLE I. Characteristics of Inmates 973 Included in the Study

Variable	n	%
Male gender	847	87.0
Age (≥30 years)	741	76.2
Educational level (>8 years)	245	25.2
Area of origin other than Italy	189	19.4
Exposure category		
Heterosexual behavior	671	68.9
Use of intravenous drugs	296	30.4
Homosexual behavior	6	0.6
Other exposure		
Unprotected sex	227	23.3
Tattoos	463	47.5
Transfusions	76	4.8
Alcohol abuse	201	20.6
Previous imprisonment	588	89.3
Duration of current imprisonment		
≤1 year	283	36
>1 year	503	63.9
Viral infections		
HHV-8-positive	202	20.7
HSV-2-positive	186	21.2
HIV-positive	73	7.5
HCV-positive	370	38
Anti-HBc-positive	512	52.6

Two hundred and two out of the 973 subjects studied (20.7%) had antibodies against HHV-8. Using univariated analysis (Table II) HHV-8-seropositive subjects were more likely to be older than 30 years (cOR 2.1, 95% CI 1.3–3.3), and having a higher educational level (cOR 1.3, 95% CI 0.9–1.9). Foreigners were less likely to have anti-HHV-8 antibodies than Italian prisoners (cOR 0.6, 95% CI 0.4–1.03).

Geographical differences were observed in the distribution of HHV-8 seropositivity, with higher prevalence in Southern Italy and Islands compared to Central and Northern Italy (25.3% vs. 18.2%); the difference was statistically significant (OR: 1.55, 95% CI: 1.07–2.19; $P = 0.015$).

Among foreign inmates, the great majority of HHV-8 seropositivity was found among prisoners from South of America 34.3% (12/37) (mainly Brazilians), whereas similar results where obtain among subjects of European and African origin (18.3% and 17.9%, respectively) (data not shown).

No association was found between the presence of HHV-8 antibodies and the use of intravenous drugs, homosexual behavior, unprotected sex, tattoos, alcohol abuse, and have received blood transfusions. A significant association was found between having anti-HHV-8 antibodies and having been imprisoned in the past at least once (cOR 2.3, 95% CI 1.1–5.8). At last, no correlation was found between HHV-8 seropositive status and the duration or the number of imprisonments (data not shown).

HHV-8 infection was significantly associated with anti-HBC (cOR 2.2, CI 1.6–3.1) and HSV-2 (cOR 1.7, CI 1.1–2.5) seropositivity whereas a weak and non-statistically significant association was found with HIV and HCV.

One hundred and eighty-six prisoners had anti-HSV-2 antibodies (21.2%) (Table III). HSV-2 positive prisoners were more likely to be older than 30 years (cOR 2.2, CI 1.4–3.5). None of the evaluated risk factors was associated with HSV-2-seropositivity; however, a marginally significant association ($P = 0.06$) was found with homosexual behavior. HSV-2-positivity was associated significantly with HIV (cOR2.6, CI 1.4–4.7) and HHV-8 (cOR 1.7, CI 1.1–2.5) infection, whereas it was inversely associated with HCV infection (cOR 0.6, 95% CI 0.4–0.9).

No geographical differences were observed in the distribution of HSV-2 seropositivity with a prevalence of 20.5% (67/327) in Central and Northern Italy and 21.3% (79/371) in Southern Italy and Islands.

A multivariate model was undertaken to identify adjusted OR for correlates of HHV-8 and/or HSV-2 infection in the study population. With regard to HHV-8, this multivariate analysis was performed considering separately Italian and foreigner prisoners (Table IV). Among Italian inmates, HHV-8-positivity was associated, with HBV (aOR 2.7, CI 1.7–4.4) and HSV-2 seropositivity (aOR 1.8, CI 1.1–2.9). No association was

TABLE II. Risk Factors for HHV-8 Infection Among Inmates in Italy

Variable	HHV-8 positive/total (%)	cOR	95% CI
Total	202/973 (20.7)		
Male gender	178/847 (21.0)	0.8	0.5–1.4
Age			
<30 years	29/231 (12.5)	1	
≥30 years	173/741 (23.3)	2.1	1.3–3.3*
Educational level			
≤8 years	140/726 (19.3)	1	
>8 years	61/245 (24.9)	1.3	0.9–1.9***
Area of origin other than Italy	30/189 (15.8)	0.6	0.4–1.03**
Exposure category			
Heterosexuals	139/671 (20.7)	1	
Use of intravenous drugs	62/296 (20.9)	1.0	0.7–1.4
Homosexual behavior	1/6 (16.6)	0.7	0.08–6.6
Other exposure			
Unprotected sex	51/227 (22.4)	1.1	0.7–1.6
Tattoos	92/463 (19.8)	0.9	0.6–1.2
Transfusions	14/76 (18.4)	0.8	0.4–1.5
Alcohol abuse	36/201 (17.9)	0.8	0.5–1.2
Previous imprisonment			
None	8/70 (11.4)	1	
At least one	138/588 (23.4)	2.3	1.1–5.8†
Duration of imprisonment			
≤1 year	62/283 (21.9)	1	
>1 year	150/503 (20.8)	0.9	0.6–1.3
Viral infections			
HIV+	20/73 (27.4)	1.5	0.8–2.6
HCV+	88/370 (23.8)	1.3	0.9–1.8**
HBcAb+	137/512 (26.7)	2.2	1.6–3.1*
HSV-2+	53/186 (28.5)	1.7	1.1–2.5‡

Crude odds ratios and 95% confidence intervals.
*$P < 0.001$.
**$P = 0.06$.
***$P = 0.07$.
†$P = 0.02$.
‡$P = 0.004$.

found with previous imprisonments and with older age. Among foreigners, HHV-8 was significantly associated only with HBV (aOR 3.6, CI 0.9–13.5).With regard to HSV-2 (Table V), a significant association remained with HIV (aOR 3.1, CI 1.7–5.8) and HHV-8 (aOR 1.7, CI 1.2–2.6), while HCV-positivity could be considered "protective" (aOR 0.5, CI 0.3–0.8). Interestingly, an increased risk of HSV-2-positivity was found among participants with higher anti HHV-8 antibody titers (data not shown).

DISCUSSION

A high prevalence of HHV-8 infection (20.7%) among inmates of Italian prisons was found with an HHV-8 seroprevalence among inmates born in Italy of 21.9%.

HHV-8 infection is common in the Mediterranean areas [Gao et al., 1996; Perna et al., 2000]. In particular, although HHV-8 seroprevalence among Italian blood donors appears to be only slightly higher than that of USA blood donors (4% vs. 0%) [Gao et al., 1996], high prevalence rates have been detected in the South and in island regions of Italy. In Sicily, the seroprevalence in general population is 11.5% but varies significantly with age, from 6% under age of 16 to more than 20% after age 50, so mirrors the incidence of classical Kaposi's sarcoma tumor endemic in this geographical area [Perna et al., 2000]. This difference of HHV-8 seroprevalence between North and South of Italy, was similar in the population of Italian inmates relatively to the region of origin. However, also after stratifying by geographical origin, the prevalence of anti-HHV-8 antibodies found in Italian inmate population appears to be higher compared to the general population prevalence found in previous studies conducted in the same geographical areas. [Whitby et al., 1998; Rezza et al., 1999; Perna et al., 2000].

In European and other western countries, HHV-8 infection is usually acquired in adulthood, while in African countries was common in childhood and in adolescence [Mayama et al., 1998; Gessain et al., 1999]. These differences can be explained by different routes of HHV-8 transmission. Findings from countries where HHV-8 infection is endemic suggest that the virus can be transmitted among family members through saliva. In low prevalence areas and in high risk groups for HHV-8 infection, such as homosexual men, the major route of viral transmission seems to be sexual.

In this study the HSV-2 seroprevalence among Italian prison inmates of 21.2% was found. Very limited data are published on HSV-2 seroprevalence in inmates

TABLE III. Risk Factors for HSV-2 Infection Among Inmates in Italy

Variable	HSV-2 positive/total (%)	cOR	95% CI
Total	186/876 (21.2)		
Male gender	160/752 (21.3)	0.9	0.6–1.6
Age			
<30 years	28/221 (16.7)	1	
≥30 years	158/654 (24.2)	2.2	1.4–3.5*
Educational level			
≤8 years	135/661 (20.4)	1	
>8 years	51/213 (23.9)	1.2	0.8–1.8
Area of origin other than Italy	40/178 (22.5)	1.1	0.7–1.6
Exposure category			
Heterosexual	130/599 (21.7)	1	
Use of intravenous drugs	53/272 (19.5)	0.9	0.6–1.2
Homosexual behavior	3/5 (60.0)	5.4	0.9–32.7**
Other exposure			
Unprotected sex	43/188 (22.8)	1.1	0.7–1.7
Tattoos	83/415 (20.0)	0.9	0.6–1.2
Transfusions	16/67 (23.8)	1.2	0.6–2.1
Alcohol abuse	38/172 (22.1)	1.1	0.7–1.6
Previous imprisonment			
None	10/39 (25.6)	1	
At least one	112/522 (21.5)	0.8	0.4–1.8
Duration of imprisonment			
≤1 year	62/283 (21.9)	1	
>1 year	104/502 (20.7)	0.9	0.6–1.3
Viral infections			
HCV+	56/332 (16.9)	0.6	0.4–0.9***
HBcAb+	98/455 (21.5)	1.0	0.7–1.4
HIV+	22/56 (39.3)	2.6	1.4–4.7*
HHV8+	53/183 (28.9)	1.7	1.1–2.5†

Crude odds ratios and 95% confidence intervals.
*$P < 0.001$.
**$P = 0.06$.
***$P = 0.01$.
†$P = 0.004$.

population. High rate of HSV-2 antibodies (58%) was reported among female prisoners in Australia [Butler et al., 2000], and among inmates of a California correctional system (77.9%) [Ruiz et al., 1999], otherwise in a Danish male prisoner population HSV-2 seroprevalence resulted lower (19%) [Christensen et al., 2002].

HSV-2 seroprevalence in Italy is lower than that reported in other industrialized countries with a cumulative value of 5.5% in general population, and values of 7.6% among pregnant women [Suligoi et al., 2000, 2004].

Previous studies showed that in HIV-seropositive patients, HHV-8 infection was associated with HBV seropositivity but not with HCV infection [Rezza et al., 1998; Parisi et al., 2002]. In this study, HHV-8 infection in Italian inmates was associated with HSV-2, which is a sexually transmitted infection, and HBV, which is also transmitted in part by the sexual route. Previous studies in Northern Cameroon [Volpi et al., 2004] showed similar results, suggesting that HSV-2 may facilitate sexual transmission of HHV-8 infection. The association, among Italian prison inmates, between HSV-2,

TABLE IV. Risk Factors for HHV8 Infection Among Italian and Foreign Born Inmates

Variable	aOR	95% CI	*P*
Age (≥30 vs. <30 years)			
Italians	1.7	0.9–3.1	0.09
Foreigners	0.6	0.1–2.8	0.50
Previous imprisonments (yes vs. no)			
Italians	1.4	0.5–3.8	0.54
Foreigners	1.1	0.2–6.2	0.90
HBcAb-positive			
Italians	2.7	1.7–4.4	<0.001
Foreigners	3.6	0.9–13.5	0.05
HSV-2 positive			
Italians	1.8	1.1–2.9	0.022
Foreigners	1.5	0.3–6.2	0.57

Adjusted odds ratios and 95% confidence intervals.

TABLE V. Risk Factors for HSV-2 Infection Among Inmates in Italy

Variable	aOR	95% CI	*P*
Use of intravenous drugs (vs. Heterosexual)	1.0	0.6–1.6	0.65
Homosexual behavior (vs. Heterosexual)	3.3	0.5–21.2	0.21
HIV-positive	3.1	1.7–5.8	<0.001
HCV-positive	0.5	0.3–0.8	0.004
HHV8-positive	1.7	1.2–2.6	0.003

Adjusted odds ratios and 95% confidence intervals.

HHV-8, and HIV infections and the high seroprevalence of these three infections suggest the possibility that sexual relationships would be the most common way of transmission of these viruses in this population. The absence of correlation between HHV-8 and HIV and the inverse association between HSV-2 and HCV infections tend to exclude bloodstream transmission of HHV-8 in this study population.

Among foreign prison inmates, HHV-8 was associated with HBV but not with HSV-2-positivity. These findings suggest different ways of transmission for HHV-8 among foreign people, and are consistent with other studies showing that interfamilial transmission of HHV-8 and HBV through saliva and close contact may play an important role in developing countries [Dumpis et al., 2001; Hui et al., 2005; Van der Eijk et al., 2004].

The high prevalence of HHV-8 and HSV-2 infections in Italian inmates may suggests the transmission during imprisonment. However, although a significant association was found between having anti-HHV-8 antibodies and previous imprisonment, this result was not confirmed by multivariate analysis.

Before drawing conclusions some limitations will be discussed. Firstly, an association between HHV-8 seropositivity and homosexual behavior, one of the most common risk factor associated with HHV-8 infection, was found. However, self-report of homosexual behavior may be affected by stigma and lead to under-reporting and consequent misclassification. Secondly, the study participants were stratified in two groups, that is, Italians and foreigners, and the country origin of foreign prisoners was not taken into consideration. This may, to some extent, affect the results of some analyses, because of the large geographical variation of HHV-8 infection.

In conclusion, this study found a relatively high HHV-8 and HSV-2 seroprevalence among Italian prison inmates. Sexual relationships appear to represent an important way of transmission of HHV-8 virus in the inmates population of Italian origin, as suggested by the association of HHV-8 and other sexually transmitted viruses. Further studies are needed to investigate whether imprisonment in overcrowded environments may increase the risk of these infections, especially in low endemic areas.

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