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# Seroprevalence of Herpes Simplex Virus Type 2 in Adult HIV-Infected Patients and Blood Donors in Croatia

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## ABSTRACT

*The present study estimates herpes simplex virus type 2 (HSV-2) seroprevalence and evaluates its association with age, sex, human herpesvirus type 8 (HHV-8) and human immunodeficiency virus (HIV) among adults in Croatia. A cross-sectional survey included 166 HIV-infected patients and 219 blood donors. Antibodies against HSV-2 were determined by enzyme immunoassays based on gG2 recombinant glycoprotein. HSV-2 seroprevalence was 45.8% in HIV-infected patients and 8.7% in blood donors ( $p < 0.0001$ ; OR 8.8; 95% CI 5.05–15.49). Independent predictors of HSV-2 seropositivity were HIV infection (OR 11.0; 95% CI 5.93–20.41), female gender (OR 2.28; 95% CI 1.22–4.26), older age (OR 3.93; 95% CI 2.74–7.11), and HHV-8 seropositivity (OR 2.72; 95% CI 1.09–6.75). Understanding the epidemiology of HSV-2 is a critical first step in designing interventions to decrease HSV-2 and HIV transmission. The association of HSV-2 with HIV infection and HHV-8 antibodies suggests a similar transmission route.*

**Key words:** HSV-2, Croatia, HIV, blood donors, HHV-8, seroprevalence

## Introduction

Herpes simplex virus type 2 (HSV-2) is one of the most common causes of genital ulceration<sup>1–3</sup>. Genital herpes is a lifelong incurable infection that causes medical, psychological and social concerns. There is a synergistic interaction between HSV-2 and HIV<sup>1–4</sup>. HSV-2 increases risk of HIV acquisition and transmission while HIV increases clinical and subclinical HSV-2 reactivation<sup>4</sup>. Further, HSV-2 reactivation increases HIV viral load in secretions obtained from genital herpes lesions as well as in plasma<sup>1–4</sup>. Accurate type specific HSV serological methods facilitate HSV diagnostics, and allow a better understanding of the burden of infection<sup>3,4</sup>. The prevalence of HSV-2 varies in different populations<sup>5–10</sup>. HSV-2 antibodies are found more frequently at older age, in females, in populations with risky sexual behaviour and in HIV-infected patients<sup>1–10</sup>.

Human herpesvirus type 8 (HHV-8) seems to share similar transmission routes as HSV-2, and shows various prevalences in different populations<sup>11,12</sup>. Low prevalence of HIV infection in Croatia has been reported so far<sup>13,14</sup>.

The seroprevalence of herpes simplex virus type 2 (HSV-2) antibodies in adults in Croatia has as yet not been described. The aim of the present study is to report the HSV-2 antibody prevalence in adult HIV-infected patients compared to blood donors.

## Methods

### *Study population*

A cross-sectional study was conducted at the University Hospital for Infectious Diseases, Zagreb, Croatia between May 1999 and August 2001. The study included 385 participants: 166 HIV-infected patients and 219 blood donors. Age and gender was reported in all subjects as well as the risk groups in HIV-infected patients.

### *Serological testing*

We analyzed serum samples for antibodies against HSV-2 and HHV-8. All sera were frozen and stored at

–20 °C till testing. Antibodies to HSV-2 were determined by enzyme-linked immunosorbent assays (ELISA) based on gG2 recombinant HSV-2 specific glycoprotein (ETI-HSVK-G 2, DiaSorin, Italy). Equivocal HSV-2 EIA results led to confirmatory immunoblot (HerpesSelect 1 and 2 Immunoblot IgG, Focus, USA). HHV-8 antibodies were analyzed with commercially available ELISA (HHV-8 IgG Antibody, ABI, Columbia, USA). All tests were performed and interpreted according to the manufacturer’s guidelines.

*Statistical analysis*

Bivariate associations were evaluated by odds ratio (OR) and corresponding 95% confidence intervals (CI). The association of gender, age (dichotomized at 40 years), and HIV and HHV-8 status with HSV-2 seropositivity was examined in a multivariable logistic regression model. Statistical analysis was performed with STATA software version 8.0.

**Results**

HSV-2 antibodies were analyzed in 166 HIV-infected patients (males, 74.1%) and 219 blood donors (males, 79.0%). The median age for both study groups was 39 years (ranges 19–74 for HIV-infected patients and 18–64 for blood donors). Seventy-three (44.0%) HIV-infected patients and 116 (53.0%) blood donors were older than 40 years.

The seroprevalence of HSV-2 was 45.8% in HIV-infected patients and 8.7% in blood donors ( $p < 0.0001$ ; OR 8.84; 95% CI 5.05–15.49). Among HIV-infected patients and blood donors older than 40 years HSV-2 seroprevalence was 61.6% and 13.9% respectively ( $p < 0.001$ ; OR 9.94; 95% CI 4.89–20.18). Among subjects younger than 40 years 33.3% HIV-infected patients and 2.9% blood donors had HSV-2 antibodies ( $p < 0.001$ ; OR 16.67; 95% CI 4.89–56.83). We found HSV-2 antibodies in 43.9% male and 51.2% female HIV-infected patients ( $p = 0.48$ ), and 7.5% male and 13.0% female blood donors ( $p = 0.25$ ). Among HIV-infected men who had sex with men (MSM)

HSV-2 seroprevalence was similar to other risk groups (52.1% in MSM vs. 43.2% in non-MSM;  $p = 0.31$ ). The data on HHV-8 has been previously reported (12). Briefly, the seroprevalence of HHV-8 was 13.3% (22 of 166 subjects) in HIV-infected patients and 4.1% (9 of 219 subjects) in blood donors<sup>12</sup>.

In our analysis HSV-2-antibodies were associated with HIV-infection, female gender, older age and HHV-8 seropositivity (Table 1).

**Discussion**

We found that HSV-2 antibodies were more common in HIV-infected patients than in blood donors. HSV-2 seroprevalence of 45.8% in HIV-infected patients was similar to one found in Germany, but lower than in Coventry, United Kingdom<sup>8,9</sup>. Higher HSV-2 seroprevalence rates in HIV-infected patients have been reported from Africa (up to 90%) or in clinics where many HIV patients of African origin are treated<sup>9,10</sup>. HSV-2 seroprevalence in Croatian blood donors (8.7%) was similar to the 4 to 24% range reported by Peabody et al. in the general population of different European countries<sup>5</sup>. However, direct comparison of seroprevalence studies is difficult because study populations varied and different serological tests were used.

HSV-2 antibody status is stated as a surrogate marker of sexual behaviour. This could explain the higher seroprevalence rate in older age. Women generally had a higher HSV-2 seroprevalence compared to men<sup>1–10</sup>. In our study females were 2.33 more likely to have HSV-2 antibodies than males on multivariable analysis. Peabody et al.<sup>3,5</sup> reported that women were 1.26 to 1.64 more likely to have HSV-2 antibodies than men in different European countries.

There is epidemiological and biological evidence of an interaction between HSV-2 and HIV<sup>1–4</sup>. The HIV infectiousness is increased in persons coinfecting with HSV-2. HSV-2 reactivation and shedding are more frequent among those with higher HIV plasma viral load and lower CD4<sup>+</sup> T-cells count. HSV-2 increases HIV susceptibility by pro-

**TABLE 1**  
FACTORS ASSOCIATED WITH THE PRESENCE OF HSV-2 ANTIBODIES AMONG 385 CROATIAN ADULTS:  
166 HIV-INFECTED PATIENTS AND 219 BLOOD DONORS

	Univariable (OR; 95% CI)	p value	Multivariable* (OR; 95% CI)	p value
HIV infection (yes vs. no)	8.84 (5.05–15.49)	<0.0001	11.00 (6.92–20.41)	<0.0001
HHV-8 antibodies (yes vs. no)	4.28 (2.02–9.07)	<0.0001	2.72 (1.09–6.75)	0.031
Gender (male vs. female)	0.64 (0.38–1.08)	0.09	0.43 (0.23–0.82)	0.01
Age (>40 vs. ≤40 years)	2.29 (1.47–3.70)	0.001	3.93 (2.17–7.11)	<0.0001

OR – odds ratio; CI – confidence interval

\* The odds ratio for each variable was adjusted for all other variables in the table

viding a portal of entry, at which more activated CD4<sup>+</sup> T-cells as the target for HIV can be found<sup>2-4</sup>. Recognition, diagnostics and treatment of genital herpes might prevent transmission of HIV<sup>1-4</sup>.

HSV-2 is a well known sexually transmitted agent that is related with HHV-8, and vice versa<sup>11</sup>. HSV-2 and HHV-8 might share similar acquisition modes, although the exact routes of HHV-8 transmission are still controversial<sup>11,12</sup>. Mediterranean countries such as Croatia were labelled as areas with high HHV-8 prevalence<sup>11</sup>, but we found that the seroprevalence of HHV-8 in our country was low (4.1% in blood donors and 13.3% in HIV-infected patients)<sup>12</sup>.

Limitations of our study should be noted. We used a convenience sample; however, we studied 166 out of around 300 HIV-infected patients registered in Croatia from 1985 till 2001<sup>13,14</sup>. Our subjects demographically resembled the HIV population in Croatia (13,14). Hence, our results might be generalized for the HIV-infected population in Croatia.

In conclusion, we found a relatively high HSV-2 seroprevalence in HIV-infected patients. HIV infection was the strongest predictor of HSV-2 seropositivity. Other factors associated with HSV-2 seroprevalence were age more than 40 years, female gender and HHV-8 seropositivity.

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## SEROPREVALENCIJA VIRUSA HERPES SIMPLEX TIP 2 U ODRASLIH OSOBA ZARAŽENIH HIV-OM I DOBROVOLJNIH DAROVATELJA KRVI U HRVATSKOJ

### SAŽETAK

Prikazani su rezultati istraživanja seroprevalencije virusa herpes simplex tipa 2 (HSV-2) u odraslih osoba u Hrvatskoj te povezanost HSV-2 s dobi, spolom, humanim herpesvirusom tipa 8 (HHV-8) i virusom humane imunodeficijencije (HIV). U presječnu studiju je uključeno 166 HIV-inficiranih pacijenata i 219 dobrovoljnih darovatelja krvi. Protutijela na HSV-2 su određena imunoenzimskim testom koji se temeljio na gG2 rekombinantnim glikoproteinima. Seroprevalencija HSV-2 u HIV-inficiranih pacijenata bila je 45,8%, a u dobrovoljnih darovatelja krvi 8,7% ( $p < 0.0001$ ; OR 8,8; 95% CI 5,05–15,49). Nezavisni prediktori za HSV-2 bili su HIV-infekcija (OR 11,0; 95% CI 5,93–20,41), ženski spol (OR 2,28; 95% CI 1,22–4,26), starija dob (OR 3,93; 95% CI 2,74–7,11) i seropozitivnost HHV-8 (OR 2,72; 95% CI 1,09–6,75). Poznavanje epidemiologije HSV-2 je prvi korak u kreiranju mjera za smanjivanje prijenosa HSV-2 i HIV-a. Povezanost HSV-2 s HIV-infekcijom i protutijelima na HHV-8 upućuje na sličan put prijenosa.