

Seroprevalence of cytomegalovirus, *Toxoplasma gondii*, syphilis, and hepatitis B and C virus infections in a regional population seropositive for HIV infection

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OBJECTIVE: To determine the prevalence of exposure to cytomegalovirus (CMV), *Toxoplasma gondii*, syphilis, hepatitis B virus (HBV) and hepatitis C virus (HCV) in a large, well characterized, regional population presenting for human immunodeficiency virus (HIV) care.

DESIGN: Demographic and serological data compiled prospectively in a relational database used for routine patient care. Results were analyzed for statistically significant trends within demographic subpopulations known to be at risk of such infections.

PATIENTS AND SETTING: A total of 1274 persons with documented HIV infection in southern Alberta have sought medical care since 1985. Serological status to CMV, *T gondii*, syphilis, HBV and HCV infections were routinely requested as part of the initial assessment. All patients with serological results available were included in the analysis.

RESULTS: CMV infection was found in 84.1% of patients. A lower prevalence of CMV infection in those under 30 years old ($P < 0.001$), intravenous drug users (IVDUs) ($P = 0.001$) and in patients with transfusion-acquired HIV ($P < 0.001$) was seen. *T gondii* seropositivity was found in 10.6% of patients, with an increased risk of seropositivity in those born outside of Canada ($P < 0.001$). Syphilis seropositivity was present in 5.1% of patients, with a higher prevalence in gay males ($P = 0.1$). HBV carrier status was noted in 8.0% of patients, with males having an increased risk ($P = 0.025$). Since 1990, there has been a 17.6% prevalence of HCV, predominantly in IVDUs ($P < 0.001$).

CONCLUSION: Seroprevalence to common pathogens in HIV disease varies significantly among subpopulations, necessitating individual testing.

Key Words: Education, Epidemiology, Opportunistic infections, Prevention, Risk factors

Pour le résumé, voir page 210

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Séroprévalence de l'infection au cytomégalovirus, à *Toxoplasma gondii*, de la syphilis, de l'hépatite B et de l'hépatite C dans une population régionale séropositive à l'égard du VIH

OBJECTIF : Déterminer la prévalence de l'exposition au cytomégalovirus (CMV), à *Toxoplasma gondii*, à la syphilis, à l'hépatite B et à l'hépatite C dans une population régionale bien caractérisée et nombreuse, nécessitant des soins pour l'infection au virus de l'immunodéficience humaine.

MODÈLE : Des données démographiques et sérologiques ont été compilées de façon prospective dans une base de données relationnelle utilisée pour la prestation des soins standard. Les résultats ont été analysés pour déceler les tendances statistiquement significatives à l'intérieur d'une sous-population démographique exposée à un risque à l'égard de ce type d'infection.

PATIENTS ET CONTEXTE : En tout, 1 274 personnes vivant dans le Sud de l'Alberta et présentant une infection au VIH documentée ont consulté depuis 1985. Le statut sérologique à l'égard du CMV, de *T. gondii*, de la syphilis, du HBV et du HCV a été demandé d'emblée dans le cadre de l'évaluation initiale. Tous les patients dont les résultats sérologiques étaient disponibles ont été inclus dans l'analyse.

RÉSULTATS : On a identifié l'infection à CMV chez 84,1 % des patients, avec une prévalence moindre de l'infection à CMV chez ceux de moins de 30 ans ($P < 0,001$), chez les toxicomanes ($P = 0,001$) et chez les patients ayant contracté le VIH lors d'une transfusion ($P < 0,001$). La séropositivité à l'égard de *T. gondii* a été observée chez 12,6 % des patients, avec risque accru de séropositivité chez les sujets nés à l'extérieur du Canada ($P < 0,001$). La séropositivité à l'égard de la syphilis a été observée chez 5,1 % des patients, avec une prévalence plus forte chez les hommes gais ($P = 0,1$). Le statut de porteur du HBV a été noté chez 8,0 % des patients, les hommes présentant un risque accru ($P = 0,025$). Depuis 1990, on a observé une prévalence de 17,6 % des cas de HCV surtout chez les toxicomanes ($P < 0,001$).

CONCLUSION : La séroprévalence à l'égard d'organismes pathogènes courants dans la maladie au VIH varie significativement selon les sous-populations, ce qui nécessite l'application de tests individuels.

Aggressive attempts to prevent reactivation of latent opportunistic infections, treat concurrent infections and reduce susceptibility to new infections are the cornerstones in the comprehensive care for the individual infected with human immunodeficiency virus (HIV) (1). Despite this approach, there is limited information published on the prevalence of, or susceptibility to, many of the common infections in newly diagnosed HIV-infected patients. Many social, medical and geographic variables may determine the exposure to major pathogens such as cytomegalovirus (CMV), *Toxoplasma gondii*, *Treponema pallidum* (syphilis), hepatitis B virus (HBV) and hepatitis C virus (HCV) (2-5). For the community, data on the prevalence of such infections are important in guiding public health policies and interventions. For the individual with HIV infection and his or her clinician, these data are critical to optimizing care. The purpose of this study was to determine the prevalence of previous exposure to these five pathogens in a large, well-defined, regional, HIV-infected population presenting for care over a 12-year period.

PATIENTS AND METHODS

Study population: The Southern Alberta HIV Clinic has provided care to 1274 patients residing in southern Alberta with documented HIV infection from November 1985 to May 1997. As part of the initial assessment of all HIV-infected patients, serological testing for CMV infection, *T. gondii* infection, syphilis, HBV and, since 1990, HCV infection is routinely ordered. The results of these tests were entered into a computerized relational database that is used to facilitate routine care as well as for administrative and epidemiological purposes. Patients missing either certain serological results or specific demographic information were considered unevaluable and excluded from the statistical analysis of that group.

Serology: CMV serology was determined to be positive on the basis of the presence of immunoglobulin (Ig) G antibodies to CMV with the Enzygnost Enzyme Immunoassay (EIA, Behring

Diagnostics Inc, California). Until 1994, toxoplasma serology was determined to be positive if IgG antibodies to *T. gondii* were present at a titre greater than 1/64 using the Organon Teknika EIA Kit (North Carolina) and, after 1994, using the EIA Platella kit (Sanofi, Paris, France). Syphilis serology was determined to be positive on the basis of a positive rapid plasma reagin test confirmed by a positive micro hemagglutination assay or a positive FTAb test (Miles Laboratories, Indiana). Hepatitis B serology was deemed to be positive by the presence of hepatitis B surface antigen (HBsAg) in the blood using an enzyme immunoassay (EIA) test up to 1989 (Abbott Laboratories) and the Uniform Two kit enzyme linked immunoassay since 1989 (ELISA, Organon Teknika). Hepatitis C serology was deemed to be positive by the presence of IgG to hepatitis C in blood as determined by the Ortho-Chiron recombinant immunoblot antibody assay, first generation from 1990 to 1992, second generation 1993 to 1994 and third generation from 1995 onwards (RIBA, Chiron Corporation, California). Where patients had more than one test result available, the serological report obtained at the time of initial assessment was included in the study.

Statistical methods: Seroprevalence of each of the five pathogens was determined for the entire population and then compared among sex, country of birth, ethnicity, year of first visit, age at first visit and risk factor for acquisition of HIV. The relationship between seropositivity and the group being analyzed was determined using a one-tailed test, or Fisher's exact *t* test where applicable with small sample sizes, and a statistical significance level of 0.05.

RESULTS

CMV: For 1058 of 1274 patients, CMV serology results were available (Table 1). Eight hundred and ninety of 1058 patients (84.1%) had positive serology to CMV infection. There was no temporal change in seropositivity between patients with HIV diagnosed between 1985 and 1990 and those diagnosed in

TABLE 1
Seroprevalence of cytomegalovirus in a regional human immunodeficiency virus seropositive population

Category	Number (%) tested negative	Number (%) tested positive	P
Total population	168 (15.9)	890 (84.1)	
Sex			
Male	150 (15.3)	828 (84.7)	0.10
Female	18 (22.5)	62 (77.5)	
Country of birth			
Canada	126 (17.3)	602 (82.7)	0.001
Outside Canada	8 (6.2)	121 (93.8)	
Unknown	34	167	
Ethnicity			
Caucasian	149 (17.0)	729 (83.0)	0.01
Other	12 (8.6)	128 (91.4)	
Unknown	7	33	
First visit			
1985 to 1990	57 (15.2)	319 (84.8)	0.60
1991 to 1996	111 (16.3)	571 (83.7)	
Age (years)			
Younger than 30	87 (23.4)	285 (76.6)	<0.001
30 to 45	72 (12.7)	493 (87.3)	0.10
Older than 45	9 (7.4)	112 (92.6)	0.01
Risk factor			
Men who have sex with men	98 (11.8)	736 (88.2)	0.001
Intravenous drug users	23 (28.0)	59 (72.0)	0.001
Blood product recipients	16 (53.3)	14 (46.7)	<0.001
Other	31 (27.2)	83 (72.8)	0.001

1991 or later. There was no statistically significant difference in seroprevalence between the sexes. Non-Caucasians had a slightly higher risk of being seropositive than Caucasians ($P=0.01$). Patients born outside of Canada showed a statistically significant increased risk of being seropositive for CMV infection compared with those born within Canada ($P=0.001$). Patients who acquired HIV through receipt of blood or blood products had the lowest serological prevalence to CMV infection, with 46.7% being serologically positive; in comparison, 88.2% of homosexual males were serologically positive ($P<0.001$). Intravenous drug users (IVDUs) and patients with other risk factors for the acquisition of HIV infection also showed a statistically significant decrease in risk for CMV seropositivity ($P=0.001$). The likelihood of being serologically positive to CMV infection increased with age at first visit, in that 76.6% of patients with HIV infection younger than 30 years of age were positive in contrast with 92.6% of patients aged 45 years or older ($P<0.001$).

T. gondii: For 1074 of 1274 patients, toxoplasma serology results were available (Table 2). One hundred and fourteen of 1074 patients (10.6%) showed serological evidence for *T. gondii* infection. Year of presentation, sex, ethnic background and risks for HIV acquisition did not show statistically significant differences among the groups analyzed. Country of birth was

TABLE 2
Seroprevalence of *Toxoplasma gondii* in a regional human immunodeficiency virus seropositive population

Category	Number (%) tested negative	Number (%) tested positive	P
Total population	960 (89.4)	114 (10.6)	
Sex			
Male	887 (89.4)	105 (10.6)	0.99
Female	73 (89.0)	9 (11.0)	
Country of birth			
Canada	683 (92.2)	58 (7.8)	<0.001
Outside Canada	94 (74.6)	32 (25.4)	
Unknown	183	24	
Ethnicity			
Caucasian	809 (90.0)	90 (10.0)	0.06
Other	113 (85.0)	20 (15.0)	
Unknown	37	4	
First visit			
1985 to 1990	362 (88.1)	49 (11.9)	0.30
1991 to 1996	598 (90.2)	65 (9.8)	
Age (years)			
Younger than 30	337 (91.3)	32 (8.7)	0.25
30 to 45	523 (90.2)	57 (9.8)	0.70
Older than 45	100 (80.0)	25 (20.0)	0.001
Risk factor			
Men who have sex with men	756 (89.4)	90 (10.6)	0.99
Intravenous drug users	78 (95.1)	4 (4.9)	0.06
Blood product recipients	30 (90.9)	3 (9.1)	0.99
Other	96 (93.2)	7 (6.8)	0.25

statistically significant; 25.4% of patients born outside Canada were serologically positive to *T. gondii* infection in contrast with 7.8% of those born within Canada ($P<0.001$). The probability of being seropositive to *T. gondii* was significantly higher for patients over the age of 45 years ($P=0.001$).

Syphilis: Syphilis serology was available for 1092 of 1274 patients (Table 3). Positive results were obtained in 56 of 1092 (5.1%) of those tested. There was no statistically significant difference in group analysis by ethnicity, country of birth or in year of presentation for care. Females had a slightly lower risk of being seropositive to syphilis than males ($P=0.05$). Seroprevalence was higher in patients whose risk factor for acquiring HIV infection was homosexuality (6.3%) compared with intravenous drug use (3.8%), but these numbers failed to reach statistical significance ($P=0.1$). Patients younger than age 30 years had a significantly lower rate of seropositivity (2.4%, $P=0.01$) than patients over age 45 years (8.7%, $P=0.025$).

HBV: HBSAg serology results, signifying HBV carrier status, were available for 1031 of 1274 patients at the clinic, of which 82 (8.0%) were positive (Table 4). Male patients had a significantly higher incidence of seropositivity than females ($P=0.025$). There was no difference in seropositivity by year of presentation, patient age, country of birth, ethnicity or risk for HIV acquisition obtained through group analysis.

TABLE 3
Seroprevalence of syphilis in a regional human immunodeficiency virus seropositive population

Category	Number (%) tested negative	Number (%) tested positive	P
Total population	1036 (94.9)	56 (5.1)	
Sex			
Male	957 (94.6)	55 (5.4)	0.05
Female	79 (98.8)	1 (1.2)	
Country of birth			
Canada	702 (95.6)	32 (4.4)	0.25
Outside Canada	119 (93.0)	9 (7.0)	
Unknown	115	15	
Ethnicity			
Caucasian	871 (93.7)	49 (6.3)	0.75
Other	129 (94.9)	7 (5.1)	
Unknown	36	0	
First visit			
1985 to 1990	385 (94.8)	21 (5.2)	0.99
1991 to 1996	651 (94.9)	35 (5.1)	
Age (years)			
Younger than 30	369 (97.6)	9 (2.4)	0.025
30 to 45	552 (93.9)	36 (6.1)	0.25
Older than 45	115 (91.3)	11 (8.7)	0.03
Risk factor			
Men who have sex with men	814 (93.7)	55 (6.3)	0.10
Intravenous drug users	75 (96.2)	3 (3.8)	0.80
Blood product recipients	26 (92.9)	2 (7.1)	0.30
Other	115 (98.3)	2 (1.7)	0.10

HCV: Two hundred and fifty-six patients received hepatitis C serology testing since its introduction in 1990 (Table 5). Of these, 45 (17.6%) were positive. Risk factor for acquiring HIV infection was highly significant. Only 10 patients (6.0%) whose risk factor was homosexuality had positive hepatitis C serology compared with 31 IVDUs (70.5%) ($P < 0.001$). Patients born outside of Canada showed a statistically significant lower risk for positive hepatitis C serology compared with those born in Canada ($P = 0.025$), although the small numbers of patients born outside Canada suggest interpreting this result with caution. Patients whose ethnicity was not Caucasian showed a statistically significant higher risk of positive serology than Caucasians ($P = 0.005$). A highly significant increase in risk for positive hepatitis C serology was seen in patients younger than 30 year (27.7%) compared with those above 45 years of age (6.3%, $P = 0.03$). There was no significant difference between sex.

DISCUSSION

Knowledge of the prevalence of exposure to various pathogens in an HIV-positive population is important for both the individual and the community (1). For the individual, it allows appropriate preventative, prophylactic and therapeutic regimens to be implemented. For the community, it allows for the overlap

TABLE 4
Seroprevalence of hepatitis B in a regional human immunodeficiency virus seropositive population

Category	Number (%) tested negative	Number (%) tested positive	P
Total population	949 (92.0)	82 (8.0)	
Sex			
Male	878 (90.6)	81 (9.4)	0.025
Female	71 (98.6)	1 (1.4)	
Country of birth			
Canada	614 (91.9)	54 (8.1)	0.90
Outside Canada	112 (91.8)	10 (8.2)	
Unknown	223	18	
Ethnicity			
Caucasian	800 (91.4)	75 (8.6)	0.75
Other	107 (93.9)	7 (6.1)	
Unknown	42	0	
First visit			
1985 to 1990	401 (91.6)	37 (8.4)	0.80
1991 to 1996	548 (92.4)	45 (7.6)	
Age (years)			
Younger than 30	348 (92.8)	27 (7.2)	0.60
30 to 45	492 (90.9)	49 (9.1)	0.75
Older than 45	109 (94.8)	6 (5.2)	0.30
Risk factor			
Men who have sex with men	762 (91.3)	73 (8.7)	0.50
Intravenous drug users	56 (93.3)	4 (6.7)	0.60
Blood product recipients	29 (96.7)	1 (3.3)	0.50
Other	102 (96.2)	4 (3.8)	0.10

of different diseases to be monitored, thus opening the opportunity for prevention of exposure in susceptible populations.

CMV is a ubiquitous and endemic pathogen transmitted by close physical contact with body fluid from an infected person (2). Its prevalence is related to socioeconomic status and geographical location, ranging from 13% to 60% in areas of the United States, to 40% in Canada and Europe, and nearly 100% in Africa and the far east (6). The rate of infection within our HIV seropositive population is high at 84.1%. We did not see a difference between males and females, which contradicts the findings of some previous studies. Previous studies support our findings in that ethnic background and country of birth were found to influence the seroprevalence of CMV (7,8). We also saw the frequency of positive serology for CMV increase with age. IVDUs, and blood and blood product recipients also showed a relatively decreased risk of being seropositive for CMV, which has not been previously noted in HIV-infected populations. Homosexual males have a high prevalence of CMV, and made up the majority of the population studied. HIV-infected individuals within low risk groupings should receive advice on how to reduce their risk of CMV acquisition, while individuals in the high risk groups might consider prophylaxis against reactivation of the pathogen.

Seroprevalence of *T gondii*, which is most commonly acquired by ingestion of oocytes or viable cysts from feces or food, is influenced by geographic, climatic, ethnic and socioeconomic factors (3). The prevalence of positive *T gondii* serology in the general population varies from 13% to 40% among regions in Canada (9,10). In Canada, there is a documented increase in positivity of 2.5 times for those born outside of the country (9). Age, but not sex, has been identified as a significant risk factor, but it has recently been suggested that being a non-Caucasian male may also be a risk factor (3,11,12). The prevalence of positive *T gondii* serology among HIV-infected patients also varies greatly worldwide at 16% and higher in the United States, 27% in the United Kingdom, 59% in France and up to 96% in areas of western Europe and Africa (11-14). We found a low overall prevalence of 10.6%, not related to sex or risk of HIV acquisition. We saw a statistically significant high prevalence in patients born outside of Canada. An increase in positivity as age increased, that reached statistically significant values for patients over age 45 years, was observed. The low prevalence of infection and the use of prophylactic regimens explains the very low incidence of *T gondii* disease in our patient population, with only 14 cases seen in 1274 patients over 12 years.

Homosexual males have accounted for 46% to 58% of all syphilis cases in North America since 1990 (4,15,16). The seroprevalence of syphilis in HIV-infected patients (28% to 31%) has been reported to be as high as five to seven times that of HIV-negative individuals (4% to 6%) in some parts of the United States (4,15,16). The rate of positive syphilis serology in our HIV-infected population was found to be low (5.1%) and similar to the documented seroprevalence of HIV-negative individuals. This suggests that other factors besides HIV infection contribute to syphilis exposure. Positivity was lower in patients under age 30 years, and higher in patients over age 45 years, supporting the previous belief that the chance of exposure to this pathogen increases with age. No temporal change in the seroprevalence of syphilis over the past 12 years was noted in our population.

Transmission of HBV commonly occurs through sexual contact and intravenous drug use, and rarely through blood transfusion (17,5). An increase in prevalence is seen with increasing age, although overall prevalence varies within different socioeconomic and geographic groupings (5). One of the main risk factors identified for acquisition of HBV is the endemic rate of HBV within one's country of origin (17). We found no difference in seropositivity among country of birth; however most of our patients born outside of Canada came from countries with a low prevalence or prevalence equivalent to that in Canada. Some studies have shown that while the seroprevalence of HBV may be around 20% for HIV-negative patients, for the HIV-positive population it could be as high as 70% (5). This is much higher than our results demonstrated, with an overall positive serology rate within our population of only 8%. No group in our analysis had a significantly increased risk of positive serology over the total population, although a significantly lower percentage of females had positive serology than males.

TABLE 5
Seroprevalence of hepatitis C in a regional human immunodeficiency virus seropositive population

Category	Number (%) tested negative	Number (%) tested positive	P
Total population	211 (82.4)	45 (17.6)	
Sex			
Male	192 (83.8)	37 (16.2)	0.10
Female	19 (70.4)	8 (29.6)	
Country of birth			
Canada	173 (79.7)	44 (20.3)	0.025
Outside Canada	38 (95.0)	2 (5.0)	
Ethnicity			
Caucasian	180 (85.3)	31 (14.7)	0.01
Other	31 (68.9)	14 (31.1)	
First visit			
1985 to 1990	27 (100)	0 (0)	0.01
1991 to 1996	184 (81.1)	43 (18.9)	
Age (years)			
Younger than 30	47 (72.3)	18 (27.7)	0.03
30 to 45	128 (83.7)	25 (16.3)	0.75
Older than 45	36 (93.7)	2 (6.3)	0.03
Risk factor			
Men who have sex with men	157 (94.0)	10 (6.0)	<0.001
Intravenous drug users	13 (29.5)	31 (70.5)	<0.001
Blood product recipients	6 (85.7)	1 (14.3)	0.99
Other	35 (92.1)	3 (7.9)	0.10

Intravenous needle sharing and blood transfusions have been identified as important vehicles for HCV transmission, with seropositivity as high as 95% in these groups (5,18,19). The seroprevalence in frequent recipients of blood or blood products has been measured as high as 87% (18,20). Our study demonstrated a low seroprevalence in this group (14.3%) not significantly different from our whole population. IVDUs were identified as the largest proportion of seropositive patients in our study (70%). Sexual spread of HCV does occur infrequently, with negligible incidence among spouses of HCV seropositive individuals (18). Our results support other published results in that gay males had a low seroprevalence of infection (6.0%). Positive HCV serology has been measured at 8% in persons attending sexually transmitted disease clinics in the United States (18). The prevalence and trends of HCV infection in the general population has been documented as being similar between HIV-positive (9.2%) and HIV-negative (7.9%) people (5). The results obtained for our population follows these general trends.

CONCLUSIONS

The results obtained from our study provide a detailed serological profile of our past and present clinic population, and explain the spectrum of opportunistic infections seen in our population over the past 12 years. General trends in prevalence that were previously reported in non-HIV-infected popu-

lations were demonstrated with some unique characteristics. This knowledge aids the development of strategies to reduce the frequency of opportunistic infections in the future and suggests possible interventions when serology results are unavailable.

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