Increases in HIV incidence among men who have sex with men undergoing repeat diagnostic HIV testing in Ontario, Canada

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Objective: To estimate HIV incidence density for different exposure categories among people undergoing repeat testing in Ontario, Canada.

Methods: Persons using voluntary, diagnostic HIV testing at least twice were identified by computerized and manual record linkage. In the 1992–2000 period, 980 seroconverters and 340 994 repeat negative testers contributed 936 145 person years (PY) of observation. Incidence density (ID) was calculated according to Kitayaporn *et al.*. Poisson regression was used to evaluate differences in incidence.

Results: Among men who have sex with men (MSM), ID declined between 1992–1996, from 1.23 per 100 PY in 1992 to 0.79 per 100 PY in 1996 [relative risk (RR), 0.86 per year; 95% confidence interval (CI), 0.77–0.96]. Subsequently, ID increased to 1.39 per 100 PY in 1999 (RR, 1.18 per year; 95% CI, 1.05–1.34). In 2000, ID was 1.16 per 100 PY but this decrease was not statistically significantly different from 1999. MSM in their twenties had the highest ID in 1992–1996, but in 1996–2000 MSM in their thirties had the highest risk of infection. Among injecting drug users (IDU), ID decreased from 0.64 per 100 PY in 1992 to 0.14 per 100 PY in 2000 (RR, 0.87 per year; 95% CI, 0.80–0.94). Among heterosexuals, annual incidence remained constant at about 0.03 per 100 PY in 1992–2000.

Conclusions: Increases in ID were identified among MSM from 1996 to 1999. These findings are consistent with other research. Continued vigilance and improved surveillance are needed to better understand and control the epidemic.

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Keywords: Drug users; epidemiology; heterosexual transmission; HIV diagnostic tests; homosexual men; surveillance

Introduction

To monitor trends in the HIV epidemic, it is essential to determine the rate of spread of infection and which populations are affected. Repeated cross-sectional studies may be used to compare HIV prevalence over time and indirectly impute incidence. This approach can be useful to monitor change but its validity to determine HIV incidence is questionable even when the population under study is stable and randomly sampled [1].

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A prospective, observational cohort study is the preferable method to measure HIV incidence. However, large numbers of participants must be followed to observe sufficient numbers of new HIV infections. The ability to identify changes in rates of new infection can be limited by the small number of infections that occur in any one study. As an alternative approach, we used existing data from the HIV-testing database at the Ontario Ministry of Health and Long Term Care to monitor and characterize incident cases of HIV. The objective of this analysis was to estimate incidence density according to exposure category among people undergoing repeat testing.

Materials and methods

Data source

We undertook secondary data analysis of the HIV-testing database of the Central Public Health Laboratory (CPHL). This database includes information on all voluntary, diagnostic tests done in Ontario. HIV tests are available at no cost and are prescribed through a physician or anonymous testing centre. Blood specimens are submitted with a test requisition form to the nearest of six regional Public Health Laboratories. All screen test positives are confirmed by Western blot at the CPHL. The computerized database operates from a single server at the CPHL and is connected in real-time with the regional laboratories. Test submissions for the same patient are linked to create a patient-based record using name and date of birth, where possible, or with specific codes when information regarding previous sample numbers is provided.

Repeat testers with two or more linked tests, whose first test was HIV-negative, were used to form a retrospective cohort for analysis of incidence density. Tests from 1 January 1 1992 to 31 October 2001 were used; 1992 was the first complete year for which both positive and negative HIV tests were computerized. Seroconversions were documented when persons with previous negative serology tested HIV-positive.

The assignment of the HIV exposure category was based on a hierarchy of decreasing epidemiologic risk of transmission, and accumulated risk factor information from all tests for a given repeat tester. Categories included men who have sex with men (MSM), MSM who were also injection drug users (MSM-IDU), injection drug users (IDU), and heterosexuals. Heterosexuals were further divided into two groups: 'high-risk' heterosexuals reported sexual contact with an HIV-positive person or a person at risk, whereas 'low-risk' heterosexuals did not. Age was estimated as the midpoint of the age at a tester's first and last test. The geographic region was based on the Public Health Unit of the HIV test provider for the last HIV test, as information on tester's residence is not collected.

Calculation of incidence density

Incidence density among repeat HIV testers was calculated for each HIV exposure category for each year from 1992 to 2000, the last complete calendar year, using the method described by Kitayaporn and colleagues [2]. Only repeat testers whose first HIV-negative test was in 1992–2000 were included. Incidence density is expressed as the number of new infections per 100 person-years (PY), and is the ratio of the numerator and the denominator, as defined below.

Numerator

Since actual dates of infection were unknown, the probability of seroconversion was assumed to be uniformly distributed over the seroconversion interval (SI) from the last negative test to the first positive test. If the SI fell completely within the calendar year of interest, a count of 1 was assigned. If the SI was not entirely within the calendar year of interest, then a fractional count was assigned for that calendar year equal to the duration of the SI within the calendar year divided by the total duration of the SI.

Denominator

For persistently negative testers, the amount of time within the calendar year of interest was assigned. For seroconverters, the time allocated for each day within the calendar year of interest was equal to the time between that day and the date of the positive test divided by the duration of the SI. For example, consider a seroconverter who tested HIV negative on January 1 and HIV positive on December 31 of the same year. This person would contribute 1 person-day to the denominator on 1 January (365/365), 0.5 person-days on July 1 (181/365), and zero person-days on December 31 (0/365).

Statistical analysis

Ninety-five per cent confidence intervals (CI) for incidence density estimates were calculated based on the assumption that the count of apportioned seroconverters is a Poisson variable whose square root is the standard error [3]. Poisson regression was used to evaluate changes in incidence density over time within each exposure category [4] using PROC GENMOD in SAS [5]. The dependent variable was the log count of the apportioned seroconverters rounded to the nearest whole number. Unequal person-time across categories was adjusted through inclusion of a term for the PY of observation [4]. The traditional 0.05 critical *P*-value was used to determine significant effects. Results of Poisson regressions are reported as relative

risks. Further Poisson regression analysis, stratified by exposure category, was done to determine the effects of gender, age and geographic region.

Results

Between January 1992 and October 2001, a total of 2 593 903 HIV tests were performed by the HIV Laboratory, excluding repeat positive tests. Record linkage identified 341 974 testers with two or more tests and who had their first HIV negative test in 1992–2000. Of these, 980 seroconverted and the remainder were negative at their last test. Together, repeat testers formed a retrospective cohort with 936 145 PY of observation in 1992–2000. The mean inter-test interval was 2.0 years for persistently HIV-negative testers and 1.6 years for seroconverters. The mean number of tests linked was 2.6 for HIV-negative repeat testers and 3.6 for seroconverters.

Exposure category information was available for 76% of seroconverters and 57% of negative testers. Among the 730 seroconverters with exposure information, 425 (58.2%) were MSM, 18 were MSM-IDU (2.5%), 123 were IDU (16.8%), two received clotting factor (0.2%), five received blood transfusions (0.7%), three were from HIV-endemic regions (0.4%), 39 were high-risk heterosexual (5.3%), 70 were low-risk heterosexual (9.6%), 29 had 'no identifiable risk' (4.0%), and 16 had 'other' exposures (2.2%). The categories for which there were sufficient PY for analysis were MSM (n = 37 314 PY), IDU (n = 38 167 PY), high-risk heterosexuals (n = 35 179 PY), and low-risk heterosexuals (n = 265 135 PY).

MSM

In the 1992–1996 period, a decreasing trend in incidence density was observed (see Fig. 1 and Tables 1 and 2.) Incidence density declined from 1.23 per 100 PY in 1992 to 0.79 per 100 PY in 1996 [relative risk (RR), 0.86 per year; $P = 0.007$]. Subsequently, incidence density increased to 1.39 per 100 PY in 1999 and was 1.78 times higher than that of 1996 ($P = 0.004$). In 2000, incidence density decreased to 1.16 per 100 PY, but was not significantly different from 1999.

Trends in incidence differed by age (see Table 2). In 1992–1996, the risk of infection declined with age. Conversely, in 1996–2000, MSM in their thirties had the highest risk of infection. Within age categories, the increase in new infections in 1996–1999 was statistically significant among MSM aged 30–39 years (RR, 1.27 per year; 95% CI, 1.07–1.51; $P = 0.006$) but was not among those aged 20–29 years (RR, 1.09 per year), 40–49 years (RR, 1.14 per year), or those 50 years and older (RR, 0.71 per year).

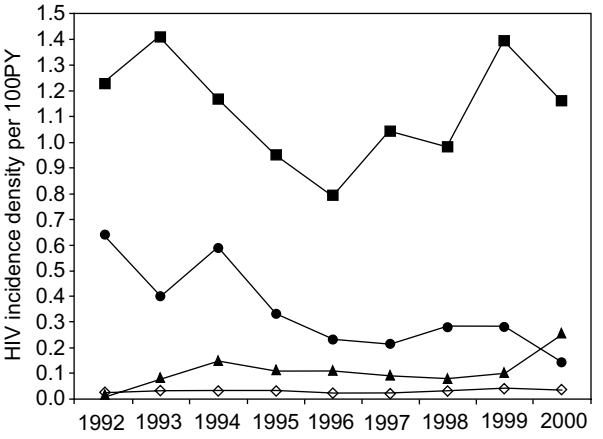

Fig. 1. HIV incidence density per 100 PY among repeat HIV testers in Ontario, Canada, 1992–2000, by exposure category. ■, MSM (n = 37 314 PY); ●, IDU (n = 38 167 PY); ▲, High-risk heterosexuals (n = 35 179 PY); ◇, Low-risk heterosexuals (n = 265 135 PY).

Incidence density was significantly higher in Toronto and Ottawa compared to the rest of Ontario (see Table 2). In both centres, incidence density increased in 1996–1999 (Toronto: RR, 1.11 per year; 95% CI, 1.06–1.41; $P = 0.006$; Ottawa: RR, 1.49 per year; 95% CI, 1.05–2.12; $P = 0.02$).

IDU

Time trends were observed among IDU (see Fig. 1 and Tables 1 and 3.), such that incidence declined over the 1992–2000 period. Gender and age effects were not statistically significant in Poisson regression analysis. The risk of infection was highest in the city of Ottawa and in northern Ontario. Temporal changes in 1992–2000 within each region were examined, but none were significant (data not shown).

Heterosexuals

Among high- and low-risk heterosexuals combined, Poisson regression found no significant change over time in the period from 1992 to 2000 (see Fig. 1 and Tables 1 and 4.). Those at greatest risk of infection were male, aged 50 years and older, and at 'high risk'. Among high-risk heterosexuals, males were at significantly greater risk of infection (RR, 2.03; 95% CI, 1.07–3.83; $P = 0.03$). Changes over time among male and female low-risk heterosexuals and male high-risk heterosexuals were not significant (data not shown). Among high-risk heterosexual females, incidence density rose to 0.23 per 100 PY in 2000, and was 3.12 times greater than incidence in 1992–1999 combined (95% CI, 1.18–8.27; $P = 0.02$).

Table 1. HIV incidence density per 100 person-years (PY) (95% confidence interval) among repeat HIV testers in Ontario, Canada, 1992–2000.

Exposure category	PY (n)	SC (n)	1992	1993	1994	1995	1996	1997	1998	1999	2000
MSM	37 314	406	1.23 (0.63–1.82)	1.41 (1.00–1.81)	1.17 (0.85–1.48)	0.95 (0.69–1.22)	0.79 (0.56–1.03)	1.04 (0.76–1.31)	0.98 (0.70–1.27)	1.39 (1.04–1.75)	1.16 (0.79–1.53)
IDU	38 167	119	0.64 (0.18–1.10)	0.40 (0.17–0.62)	0.59 (0.36–0.82)	0.33 (0.17–0.49)	0.23 (0.1–0.36)	0.21 (0.09–0.33)	0.28 (0.14–0.42)	0.28 (0.13–0.43)	0.14 (0.02–0.27)
All heterosexuals	300 314	106	0.02 (0–0.05)	0.03 (0.01–0.06)	0.04 (0.02–0.07)	0.04 (0.02–0.05)	0.03 (0.01–0.04)	0.03 (0.01–0.04)	0.03 (0.02–0.05)	0.04 (0.02–0.06)	0.05 (0.02–0.08)
High-risk heterosexuals	35 179	39	0.01 (0–0.08)	0.08 (0–0.18)	0.15 (0.03–0.26)	0.11 (0.02–0.20)	0.11 (0.02–0.20)	0.09 (0.01–0.16)	0.08 (0–0.16)	0.10 (0–0.19)	0.25 (0.05–0.44)
Low-risk heterosexuals	265 135	68	0.02 (0–0.05)	0.03 (0–0.05)	0.03 (0.01–0.05)	0.03 (0.01–0.04)	0.02 (0–0.03)	0.02 (0.01–0.03)	0.03 (0.01–0.04)	0.04 (0.02–0.06)	0.03 (0.01–0.05)

SC, Seroconversions; MSM, men who have sex with men; IDU, injecting drug users.

Discussion

The results suggest that incidence declined among MSM in 1992–1996, then increased in 1996–1999 in the two largest urban centres in the province, Toronto and Ottawa. In 2000, incidence among MSM appears to have stablized. In 1992–2000, incidence decreased among IDU. Among heterosexuals, incidence remained generally constant, although rates among high-risk heterosexual females appear to have increased in 2000.

Limitations in the analytical approach may have biased the incidence density estimates. Record linkage of repeat testers depends on the quality of identifying information provided on test requisition forms. A substantial number may not have been linked. Linkage of anonymous testers is difficult and their exclusion may have resulted in an under-estimate of incidence. Four per cent of HIV tests in Ontario are anonymous [6] but they are known to be at highest risk for HIV infection [7]. Also, information on exposure category was more complete among seroconverters than repeat HIV-negative testers; this difference may have resulted in over-estimates of incidence.

The data were limited to those who sought testing and were re-tested, though available information suggests that the majority of MSM and IDU have tested for HIV and often repeatedly [8,9]. People who seek HIV testing or seek testing more frequently tend to have greater risk for HIV transmission [8,9]. This would lead to over-estimates of HIV incidence. Also, persons who become infected may have an increased likelihood of testing in the subsequent few months as a result of specific high-risk exposures and symptoms of seroconversion illness [10]. This would lead to an upward bias in estimated HIV incidence for recent periods. We examined the estimated HIV incidence among repeat testers for a given year calculated in subsequent years. For MSM, IDU and high-risk heterosexuals, measured incidence was substantially lower with 1 to 2 years of additional data but then stabilized. Our experience indicates that to interpret estimates for a given year with confidence, at least one additional year of testing data is needed.

The validity of the repeat-tester technique can be evaluated through comparison with other measures of incidence, and rates of sexually transmitted infections and risk behaviour. Remis and colleages estimated incidence using the detuned assay among HIV testers using the same data source as our repeat-tester analysis, and found results consistent with ours [11,12]. Further, reported cases of rectal and pharyngeal gonorrhea, a marker of transmission in the MSM population, suggest an increase among Ontario males between 1995 and 2000 [13]. Elsewhere in Canada, a Vancouver cohort observed increases in new infections among young

Table 2. Relative risks (RR) and 95% confidence interval (CI) for seroconversion among men who have sex with men repeat HIV testers in Ontario, Canada, 1992–2000. Results of Poisson regressions.

Characteristic	Person-years (n)	Seroconversions (n)	RR (95% CI)	*P*
Calendar year, 1992–1996[a]	19 813	208	0.86 (0.77–0.96)	0.007
Calendar year, 1996–1999[a]	19 685	203	1.18 (1.05–1.34)	0.008
Calendar year, 1996–2000[a]	22 952	241	1.12 (1.02–1.23)	0.01
Age group, 1992–1996				
30–39 years	8099	89	0.72 (0.53–0.98)	0.04
40–49 years	4079	27	0.42 (0.26–0.64)	0.0001
⩾ 50 years	2281	11	0.32 (0.16–0.57)	0.0004
(referent = 20–29 years)	4848	74	–	–
Age group, 1996–2000				
30–39 years	9329	123	1.35 (0.98–1.86)	0.06
40–49 years	4671	41	0.94 (0.63–1.40)	NS
⩾ 50 years	2627	11	0.43 (0.22–0.82)	0.01
(referent = 20–29 years)	5497	54	–	–
Geographic region[b]				
Toronto	23 341	298	2.76 (2.02–3.76)	< 0.0001
Ottawa	3664	42	2.48 (1.63–3.79)	< 0.0001
(referent = Ontario, other)	9976	46	–	–

[a]Relative risk per year. [b]Adjusted for calendar year. RR, Relative risk; CI, confidence interval; NS, not statistically significant.

Table 3. Relative risks (RR) and 95% confidence interval (CI) for seroconversion among injecting drug user repeat HIV testers in Ontario, Canada, 1992–2000. Results of Poisson regressions.

Characteristic	Person-years (n)	Seroconversions (n)	RR (95% CI)	*P*
Calendar year, 1992–2000[a]	38 167	119	0.87 (0.80–0.94)	0.0006
Male sex[b]	24 787	74	0.90 (0.62–1.31)	NS
(referent = female)	13 197	45	–	
Age group				
30–39 years	17 399	68	1.47 (0.94–2.28)	0.08
40–49 years	7633	18	0.90 (0.50–1.63)	NS
⩾ 50 years	991	2	0.79 (0.19–3.30)	NS
(referent = 20–29 years)	10 628	28	–	–
Geographic region				
Ottawa	2397	33	9.27 (5.05–17.0)	< 0.0001
Northern Ontario	3768	15	2.26 (1.07–4.74)	0.03
Other Ontario	21 814	34	1.05 (0.57–1.92)	NS
(referent = Toronto)	9807	16	–	–

[a]Relative risk per year. [b]Adjusted for calendar year. RR, Relative risk; CI, confidence interval; NS, not statistically significant.

MSM [14]. Internationally, there is evidence of increasing incidence among MSM in San Francisco [15,16]. There are no Ontario data on rates of high-risk behaviour among MSM in 1996–1999, but internationally, increasing rates have been reported in Sydney, Australia [17], in cities in the USA including San Francisco [16,18–20], and in Amsterdam [21]. There is also evidence to suggest increasing unprotected anal sex in Vancouver, Canada [22].

Despite the limitations of the repeat-tester technique, we are confident that the increase in HIV incidence observed among MSM undergoing repeat testing in 1996–1999 was real. The advent of widespread use of highly active anti-retroviral therapies (HAART) in 1996 may have lead to a belief that HIV is easily treated, which could result in riskier sexual behaviour [17,23]. Additionally, HAART has decreased the incidence of AIDS and AIDS-related mortality [24]. With improved quality of life, more HIV-positive people would be sexually active, which increases the likelihood of encountering an infected sex partner. Other potential explanations include adaptation, desensitization or safer-sex 'fatigue' or 'burnout' [25,26].

We observed a decrease in HIV incidence among IDU in the 1992–2000 period. Rates were highest in Ottawa. Ottawa is the second largest urban centre in

Table 4. Relative risks (RR) and 95% confidence interval (CI) for seroconversion among heterosexual repeat HIV testers in Ontario, Canada, 1992–2000. Results of Poisson regressions.

Characteristic	Person-years (n)	Seroconversions (n)	RR (95% CI)	*P*
Calendar year, 1992–2000[a]	300 314	106	1.05 (0.96–1.15)	NS
Male sex	142 461	78	1.58 (1.14–2.19)	0.006
(referent = female)	193 033	67	–	–
Age group				
30–39 years	90 201	34	1.33 (0.85–2.10)	NS
40–49 years	35 669	15	1.35 (0.73–2.48)	NS
⩾ 50 years	12 054	7	2.28 (1.08–4.87)	0.03
(referent = 20–29 years)	137 379	39	–	–
Geographic region				
Toronto	102 821	42	1.62 (1.06–2.47)	0.02
Ottawa	27 757	11	1.39 (0.70–2.77)	NS
(referent = other Ontario)	166 477	43	–	–
High risk heterosexual	35 179	39	4.39 (2.95–6.51)	< 0.0001
(referent = low-risk heterosexual)	265 135	68	–	–

[a]Relative risk per year. RR, Relative risk. CI, confidence interval. NS, not statistically significant.

Ontario, and is geographically close to the city of Montreal, Quebec, which has high HIV prevalence among IDU [27]. Our findings and those of others [27] suggest that incidence among IDU in Ottawa is unacceptably high. Incidence was also higher among IDU in northern Ontario, which is comprised of predominantly rural and small urban centres, than in Toronto. In the north, more IDU prefer cocaine and crack cocaine as their drug of choice than in Toronto (Millson, personal communication, 2001). The regional difference in incidence may be due to more cocaine use in Ottawa and the north, and its associations with binge injection and use of shared needles and drug paraphernalia [28].

Among heterosexuals, incidence remained generally stable in 1992–2000. However, rates were significantly higher in 2000 among heterosexual females reporting sex with an HIV-positive partner or a partner at risk for HIV (i.e. 'high risk'). Due to the instability of estimates in the final year of analysis, this finding should be interpreted with caution. *Chlamydia* and gonorrhea cases have increased from 1999 to 2000 among females and males (Wallace, Ontario Ministry of Health, personal communication, 2001). Such increases, if real, could be due to improved screening and test-seeking among those at risk. Alternatively, they could be a result of increases in risk behaviour, or increasing incidence among MSM, and subsequent transmission from MSM who also had female partners.

We also found that heterosexuals who were male or aged 50 years or older were significantly more likely to become infected in 1992–2000. Given the epidemiology of HIV in Ontario, we think this is unlikely [6]. Rather, the difference may be due to misclassification of exposure category, as some men, particularly older men, may not admit same-sex behaviour to their health care provider. Higher rates among older heterosexuals also may have occurred if only those at extreme risk of infection were tested.

Although the repeat-tester technique may overestimate the true incidence of HIV, it is useful in identifying relative changes in rates over time when testing patterns are well understood. The technique is low cost because it uses existing testing data. This is especially useful in jurisdictions where cohort studies are not economically viable. Data from this technique and other sources in Ontario indicate that infections increased among MSM in 1996–1999. The recent rise was temporally associated with the advent and wider use of HAART. HAART may have changed the epidemiological balance of HIV such that the net effect was a rise in transmission. In light of the increase, prevention programmes and strategies should be revisited.

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Appendix

The Polaris HIV Seroconversion Study team

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