Socioeconomic- and gender-based disparities in rates of hospitalization among HIV-infected patients in Ontario: a population-based study

Running head: Hospitalization of HIV-infected persons

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Abstract

Background

Because hospitalization of persons living with HIV-infection (PLWH) in the era of combination antiretroviral therapy (cART) may be an indicator of inadequate community-based care, population-based assessments of inpatient service utilization are a necessary component of the evaluation of the quality of HIV-related care.

Methods

Using a validated algorithm, we identified all PLWH in Ontario's administrative health-care databases aged 18 years and older between 1992 and 2008, and conducted a population-based study using ecologic and longitudinal individual-level analyses to quantify the immediate impact of cART on hospitalization rates and analyze recent trends (2002 to 2008) in rates of total and HIV-related hospitalizations.

Results

The introduction of cART in 1996/97 was associated with more pronounced reductions in rates of total (-94.8 vs. -63.3 per 1000 PLWH; p = 0.002) and HIV-related hospitalizations (- 59.5 vs. -37.1 per 1000 PLWH; p = 0.0002) among men relative to women. Between 2002 and 2008, higher rates of total hospitalization were associated with female sex [adjusted relative rate (aRR) 1.13; 95% CI: 1.02 to 1.24] and low socioeconomic status (aRR 1.22; 95% CI: 1.14 to 1.30). Higher rates of HIV-related hospitalizations were associated with low socioeconomic status (aRR 1.25; 95% CI: 1.12 to 1.40). Recent immigrants had lower rates of both total (aRR 0.70; 95% CI 0.61 to 0.80) and HIV-related hospitalizations (aRR 0.76; 95% CI 0.60 to 0.96).

Interpretation

Despite universal access to health care and overall declines in hospitalizations, we observed important gender- and socioeconomic-based disparities in hospitalization rates among PLWH living in Ontario, Canada.

Key words: HIV; hospitalization; trends; epidemiology; gender; socioeconomic status

Introduction

Patterns of health services utilization among patients infected with the human immunodeficiency virus (HIV) have been demonstrably altered by the introduction and widespread availability of combination antiretroviral therapy (cART) during the latter half of the 1990s.[1-5] Most notably, large declines in the rates of hospitalization for HIV-associated opportunistic infections were observed in the years immediately following the adoption of cART as the standard of care for

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HIV. However, more recent studies examining the utilization of inpatient services by persons living with HIV (PLWH) have described stabilizing or increasing rates of hospitalization, particularly among patients for whom the effects of HIV infection intersect with socially and structurally mediated barriers to care, such as women and ethnic minorities living with the disease.[6-10] These data are especially salient for the evaluation of hospitalization trends among PLWH residing in the province of Ontario, where important changes in the demographic composition of this population have been observed over the preceding decade. Specifically, the proportion of diagnoses comprised by women has increased from less than 3% in the early years of the epidemic to 22% in 2008.[11] Similarly, the prevalence of HIV among persons immigrating to Ontario from HIV-endemic countries has increased 62% since 2003.[11] In this context of pronounced change in both the treatment and demography of HIV infection, accurate population-based estimates of health services utilization are required by clinicians, researchers, and policy makers who are involved in the provision, evaluation and funding of HIV-related care. However, these data are presently lacking for Ontario, home to over 40% of Canada's population of PLWH and recipient of approximately half of all immigrants to Canada on an annual basis.[12]

Because hospitalization for HIV-related illness in the era of cART can be considered an indicator of inadequate community-based care, ongoing assessment of trends in inpatient service utilization is a necessary component of the evaluation of the quality of care for PLWH. We therefore conducted a population-based study of the temporal trends in hospitalization rates among PLWH in the province of Ontario. We hypothesized that, because of socially and structurally rooted challenges in accessing care among marginalized PLWH, rates of hospitalization in the modern era of cART (2002 to 2008) would be disproportionately higher among women, recent immigrants and PLWH living in low income neighborhoods.

Methods

Study Design

We used a validated case-finding algorithm derived from administrative data to identify all PLWH aged 18 years and older who were receiving care in the province of Ontario between April 1, 1992 and March 31, 2008. The development and test characteristics of the algorithm have been described in detail elsewhere.[13] Briefly, an algorithm of three physician claims with an International Classification of Diseases, Ninth Revision (ICD-9) code for HIV infection (042, 043, 044) within a three year period achieved a sensitivity and specificity of 96.2% (95% CI 95.2% - 97.9%) and 99.6% (95% CI 99.1% - 99.8%), respectively. We chose the end of the 2008 fiscal year for our analyses to meet the three-year 'look forward' criterion of the algorithm when assembling our cohort. We then conducted a retrospective, population-based study using both ecologic and individual level analyses to examine temporal trends in the rates of hospitalization among this cohort. Specifically, we used interrupted time series analysis to isolate and quantify the impact of the introduction of cART on hospitalization rates among PLWH in Ontario and methods of longitudinal data analysis to examine trends and predictors of hospitalization during the era of 'modern cART', defined as the period spanning April 1, 2002 to March 31, 2008. We selected this period for the longitudinal analyses because it corresponds to important changes in the demographic composition of PLWH in Ontario and to the availability of antiretrovirals with enhanced potency and ease of administration relative to earlier iterations of these drugs.[11,14]

Data Sources and Outcomes

We used the Canadian Institute for Health Information Discharge Abstract Database (CIHI-DAD) to determine the annual number of hospitalizations for each individual in our population-based cohort of PLWH. The CIHI-DAD contains information abstracted from all acute care hospital separations (i.e. discharge, sign-out, transfer to different facility) in the province of Ontario by trained health information professionals using standard diagnosis and procedure codes, including the dates of admission and discharge from the hospital, the diagnosis representing the condition that is accountable for the greatest portion of the length of stay or greatest use of resources during the hospitalization (i.e. the most responsible diagnosis) and secondary diagnoses and/or complications contributing to the admission. We calculated annual crude rates of total and HIV-related hospitalizations per 1000 population of PLWH aged 18 and over. HIV-related hospitalizations were defined as those admissions in which the most responsible diagnosis was coded as being attributable to HIV infection or an associated opportunistic infection using the relevant ICD-9 and 10th revision codes (ICD-10). We excluded obstetrical admissions and elective surgeries from our calculation of hospitalization rates.

We used the Ontario Registered Persons Database, a registry of all residents eligible for provincial health insurance, to identify individual demographic information such as age, sex, date of OHIP eligibility, and postal code. We determined patient SES at the neighborhood level for each year of follow-up using postal code information and Statistics Canada census data. We defined recent immigrants as all adults who were first issued an OHIP card within three years of becoming a prevalent member of our cohort. The use of date of issue of an OHIP card has been used as a proxy for the date of arriving in Ontario in other studies.[15]

Statistical analyses

In order to examine the impact of cART on hospitalization rates during the period spanning 1992 to 2008, we conducted an interrupted time series analysis using autoregressive integrated moving average (ARIMA) models with an indicator variable for the fiscal year 1996/1997, corresponding to the first full year that cART was widely available in Ontario.[16,17] We performed subgroup analyses to determine if the impact of cART on both total and HIV-related hospitalization rates varied according to sex and SES, and used the Ljung-Box χ^2 statistic to examine autocorrelation of the model residuals.[18]

For the longitudinal analyses, we evaluated temporal trends in the rates of hospitalization during the years 2002 to 2008 using multivariable generalized estimating equation (GEE) models with a log link function and autoregressive correlation structure.[19] Because GEE is not a likelihood based method, we used the quasilikelihood under the independence model information criterion measure (QIC and QICu) to ascertain both the appropriateness of the autoregressive correlation structure relative to other working correlation matrices and to assess the fit of our regression models.[20] We also evaluated the data for overdispersion by comparing the Poisson and negative binomial distributions.

We conducted separate analyses for total hospitalization rates and rates of HIV-related hospitalizations. All multivariable analyses included fiscal year as the main predictor, along with variables for sex, immigrant status and income quintile group (low vs. high), because of our a priori hypotheses that differences in access to care may contribute to an increased rate of hospitalizations among these groups. We estimated adjusted relative rates (aRR) from the model using calendar year as both a continuous variable and as a categorical variable. In the former case, trends are reported as percentages per year, while in the latter, aRRs were used to compare annual changes in the rate of hospitalization relative to the reference year of 2002. We

considered additional variables as confounders based on a plausible association with our outcomes of interest and if they changed the estimate for fiscal year by at least 10%.[21] Variables meeting this criterion included patient age, annual number of physician visits, geographic residence (urban versus rural), years with HIV infection and level of co-morbidity. We used the Johns Hopkins Adjusted Clinical Group case-mix assignment software (Sun Microsystems Inc., Santa Clara, CA) to determine the level of comorbidity for each patient based on diagnostic codes listed in hospitalization records and physicians' services claims from each year during the study period. This methodology is described in detail elsewhere.[22] We assessed the potential for collinearity between covariates using a threshold tolerance of > 0.4 and a variance inflation of $<$ 2.5. We also examined interactions between sex, SES and immigrant status with year in separate models. We included interaction terms in the final model if they were statistically significant and if their inclusion improved the goodness-of-fit of the model by at least 10%.

All statistical analyses were conducted using SAS statistical software, version 9.2 (SAS Institute Inc., Cary, NC).

Ethics approval

We obtained ethics approval for this study from the Research Ethics Board of Sunnybrook Health Sciences Centre and the Ethics Review Committee of the University of Toronto.

Results

Ecologic analyses

The sex- and SES-stratified temporal trends in both total and HIV-related hospitalization rates between 1992 and 2008 are shown in Figures 1 and 2. Over the sixteen year study period, crude

annual rates of total and HIV-related hospitalizations decreased from 388.6 to 112.4 per 1000 PLWH and 247.0 to 29.6 per 1000 PLWH, respectively. As expected, the introduction of cART was associated with significant reductions in rates of both total [- 87.9 per 1000 PLWH; 95% confidence intervals (CI): - 78.9 to - 96.8 per 1000 PLWH; $p < 0.001$] and HIV-related hospitalizations [- 57.2 per 1000 PLWH; 95% CI: - 51.9 to - 62.5 per 1000 PLWH; $p < 0.001$). In sub-group analyses, significant reductions in hospitalization rates were associated with the introduction of cART for both men and women living with HIV, as well as PLWH living in both high and low income neighborhoods. However, the impact of cART was more pronounced among men relative to women for both total (-94.8 vs. -63.3 per 1000 PLWH; $p = 0.002$) and HIV-related hospitalizations (- 59.5 vs. - 37.1 per 1000 PLWH; $p = 0.0002$). In contrast, no difference in the immediate impact of cART on total (-97.2 vs. -81.5 per 1000 PLWH; $p = 0.09$) or HIV-related hospitalization (-61.4 vs. -54.9 per 1000 PLWH; $p = 0.06$) rates was observed in low relative to high SES patients.

Multivariable Analysis of Hospitalization Trends

The demographic characteristics of the population of PLWH living in Ontario during the years 2002 to 2008 are presented in Table 1. For each year, most patients were male, lived in Ontario's large urban centres and were between the ages of 36 and 50 years old. The proportion of PLWH that were women increased from 17.0% in 2002 to 20.0% in 2008. Similarly, the numbers of individuals aged 50 and older increased longitudinally, accounting for 16.3% of PLWH in 2002 and 25.4% in 2008.

Crude and adjusted rates of total hospitalization among PLWH in Ontario decreased 2.7% (95% CI: 1.3% to 4.1%) and 2.3% (95% CI: 0.8% to 3.8%) per annum between the years 2002 and

2008. Over the six year study period, adjusted rates of total hospitalization were higher among women relative to men (aRR 1.13; 95% CI: 1.02 to 1.24) and PLWH living in low versus high income neighborhoods (aRR 1.22; 95% CI: 1.14 to 1.30). In contrast, recent immigrant status was associated with reduced rates of total hospitalization (aRR 0.70; 95% CI: 0.61 to 0.80) (Table 2).

Crude and adjusted rates of HIV-related hospitalizations remained relatively stable among PLWH in Ontario between 2002 and 2008, changing by - 0.8% (95% CI: -3.2% to 1.7%) and + 1.4% (95% CI: - 1.2% to + 4.1%) per annum, respectively. In contrast to total hospitalizations, an association with gender was not evident for this outcome. However, significant associations between HIV-related hospitalizations and both low SES and immigration status were observed (Table 2).

Interpretation

In our population-based study, we observed a striking reduction in the rates of total and HIV-related hospitalizations associated with the availability of cART between the years 1992 and 2008. Although these benefits were observed in all sub-groups examined, the effect of cART was attenuated among women relative to men. In the modern era of cART, sustained reductions in the rates of total hospitalization among PLWH were observed, while rates of HIV-related hospitalizations rates remained relatively unchanged during this six year period of follow-up. However, because numbers of HIV-related hospitalizations were relatively low, we cannot discount the possibility of a type II error when analyzing temporal trends in this outcome. We also identified several disparities in the risk of hospitalization among PLWH in Ontario following multivariable adjustment for sociodemographic variables, level of co-morbidity and

annual number of outpatient physician visits. Specifically, female sex and low SES were

significantly associated with higher rates of total hospitalization, with the latter variable also

being associated with a heightened risk of HIV-related hospitalization. In contrast to our initial

hypothesis, recent immigrants were less likely to be hospitalized in the era of modern cART

relative to the reference population of PLWH in Ontario.

Our findings of decreasing rates of hospitalization among PLWH in the era of modern cART are

similar to previous studies which have analyzed these trends in other regions.[10] In addition, our

work corroborates previous investigations highlighting inequity in hospitalization rates among

certain groups, most notably, women.[8,10] However, unlike other settings, our study was

conducted within a context of universal coverage for all medically necessary physician,

laboratory and inpatient services. Consequently, varying rates of hospitalization according to

gender, SES or immigration status should not be confounded by health insurance status, thereby

implying a role for other biological, social or structural factors in contributing to these

disparities. While the underlying basis of the observed differences cannot be discerned directly

from our administrative databases, several explanations are possible. With respect to women

living with HIV, a comprehensive body of literature exists describing various barriers impeding

access to regular HIV-related care, including lack of transportation, depression, a history of

physical and/or sexual abuse and the responsibility of caring for children and other family

members who may be living with the virus.[23-25] In addition, compared with men, women living

with HIV have been noted to be more likely to delay initiating cART and less likely overall to

begin treatment.[26,27] Furthermore, several antiretroviral toxicities are noted to occur at greater

frequency among women relative to men, including severe hypersensitivity reactions and

lipodystrophy.[28-30] As a result, women may be more likely to discontinue cART when compared

with men. While individuals living in low income neighborhoods undoubtedly share some of the obstacles to care faced by women, other structurally mediated inequities are important determinants of health among these patients. Specifically, instability with respect to housing status and food security have been both documented to undermine adherence to antiretroviral therapy and contribute to poor outcomes among PLWH.[31-34] Furthermore, despite the availability of various programs intended to mitigate the expense of cART for PLWH in Ontario who lack alternative sources of drug coverage, individuals who do not qualify for provincially-funded social assistance must assume a share of the cost of their treatment in the form of a co-payment that may be prohibitive when evaluated against competing demands for food and housing. Finally, reduced hospitalization rates among recent immigrants may be partially attributable to a health immigrant effect and/or policy changes in 2002 mandating HIV-antibody testing of all prospective applicants to Canada, thereby prompting these patients to seek care.

Several strengths and limitations of our work merit emphasis.   First, our study is truly population-based in nature, and therefore representative of all HIV-infected patients receiving care in the province of Ontario over the sixteen year study period. In addition, because we used administrative data, we were able to evaluate temporal trends and disparities in hospitalization rates among PLWH while considering variation in place of residence, outpatient health care utilization and extent of co-morbidity, important covariates that have not been traditionally considered in the study of this phenomenon. Nonetheless, our administrative databases are limited by their lack of clinical information, thereby precluding us from examining the role of variables such as stage of illness and adherence to cART in accounting for the observed disparities. However, this limitation is common among studies using administrative data for the conduct of health services research.[35] Furthermore, because our administrative databases lack

individual level measures of income, we used neighborhood income as a proxy for patient SES. However, this approach has been previously validated as a measure of household income and social deprivation.[36] In addition, residential neighborhood may exert effects on health and outcomes that are independent of those ascribed to individual income.[37] Finally, the potential for misclassification is always a consideration when using administrative data for health services research. To address this concern, we used a validated algorithm with excellent test characteristics for discriminating between HIV-infected and non-infected individuals to assemble our cohort of PLWH.[13] To our knowledge, this is the first population-based study using a validated case-finding algorithm to examine hospitalization trends in PLWH.

In summary, despite universal access to health care, we observed significant disparities in the rates of hospitalization among certain groups of PLWH living in Ontario. Our findings have important implications for researchers, clinicians and policy makers involved in the provision of HIV-related care. As HIV-related hospitalizations are largely preventable by the receipt of cART, these admissions should be considered indicators of failure to access appropriate medical care in the outpatient setting. In addition, persistent differences in rates of total hospitalization among specific groups of PLWH imply that gaps may exist within the existing complement of community-based health and social services that render the most marginalized HIV-infected patients vulnerable to poor health outcomes. Continued collaborations between the community of PLWH, researchers and policy makers will be essential to generate the qualitative and quantitative data required to elicit and address the social and structural factors that modify access to care among PLWH, and which may ultimately lead to greater parity in the quality of care received by all HIV-infected individuals.

Conflicts of Interest and Financial Disclosure

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Analysis and Interpretation of Data: Antoniou, Zagorski, Loutfy, Glazier, Strike

Acquisition of Data: Antoniou, Zagorski

Drafting of the manuscript: Antoniou

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Table 1: Characteristics of participants by years of follow-up (2002 to 2008)

Variables (%)	2002 (n = 9,985)	2003 (n = 10,561)	2004 (n = 11,183)	2005 (n = 11,803)	2006 (n = 12,411)	2007 (n = 12,986)	2008 (n = 13,607)
Age (years)							
18 to 35	2,667 (26.7%)	2,589 (24.5%)	2,546 (22.7%)	2,533 (21.5%)	2,561 (20.6%)	2,534 (19.5%)	2,557 (18.8%)
36 to 50	5,692 (57.0%)	6,114 (57.9%)	6,548 (58.6%)	6,898 (58.4%)	7,156 (57.7%)	7,406 (57.0%)	7,595 (55.8%)
51 to 66	1,428 (14.3%)	1,629 (15.4%)	1,835 (16.4%)	2,084 (17.7%)	2,363 (19.0%)	2,656 (20.5%)	2,990 (22.0%)
66+	198 (2.0%)	229 (2.2%)	254 (2.3%)	288 (2.4%)	331 (2.7%)	390 (3.0%)	465 (3.4%)
Sex							
Female	1,696 (17.0%)	1,870 (17.7%)	2,065 (18.5%)	2,242 (19.0%)	2,403 (19.4%)	2,572 (19.8%)	2,720 (20.0%)
Male	8,289 (83.0%)	8,691 (82.3%)	9,118 (81.5%)	9,561 (81.0%)	10,008 (80.6%)	10,414 (80.2%)	10,887 (80.0%)
Socioeconomic Status							
Low	5,442 (54.5%)	5,751 (54.5%)	5,924 (53.0%)	6,272 (53.1%)	6,641 (53.5%)	6,903 (53.2%)	7,233 (53.2%)
High	4,543 (45.5%)	4,810 (45.5%)	5,259 (47.0%)	5,531 (46.9%)	5,770 (46.5%)	6,083 (46.8%)	6,374 (46.8%)
Recent immigrant	534 (5.4%)	607 (5.7%)	684 (6.1%)	775 (6.6%)	848 (6.8%)	867 (6.7%)	864 (6.3%)
Urban residence	9,561 (95.8%)	10,121 (95.8%)	10,732 (96.0%)	11,324 (95.9%)	11,928 (96.1%)	12,451 (95.9%)	13,015 (96.0%)
No. outpatient visits							
0 to 2	3,635 (36.4%)	3,891 (36.8%)	4,177 (37.4%)	4,236 (35.9%)	4,572 (36.8%)	4,973 (38.3%)	5,485 (40.3%)
3 to 6	2,597 (26.0%)	2,801 (26.5%)	3,012 (26.9%)	3,146 (26.7%)	3,374 (27.2%)	3,706 (28.5%)	3,918 (28.8%)
7 to 10	1,545 (15.5%)	1,668 (15.8%)	1,770 (15.8%)	1,984 (16.8%)	2,008 (16.2%)	2,073 (16.0%)	2,057 (15.1%)
11+	2,208 (22.1%)	2,201 (20.8%)	2,224 (19.9%)	2,437 (20.6%)	2,457 (19.8%)	2,240 (17.2%)	2,147 (15.8%)

Table 2: Multivariable regression for hospitalization rates

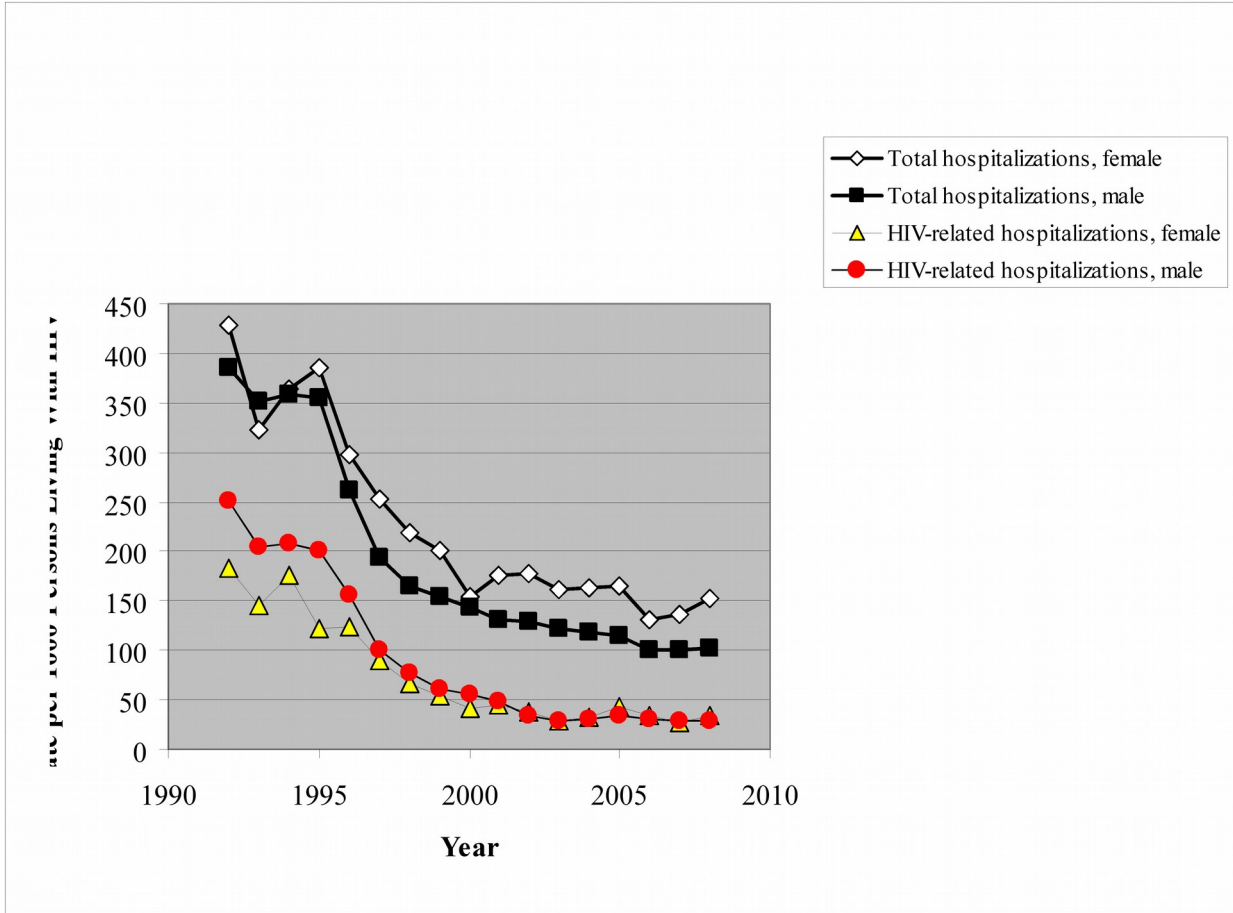| Variables	Total Hospitalization Rates	HIV-related Hospitalization Rates
	Adjusted Relative Rate (95% Confidence Interval)[*]	Adjusted Relative Rate (95% Confidence Interval)[*]
Year		
2002 (reference)	1.00	1.00
2003	0.89 (0.81 to 0.97)	0.84 (0.71 to 1.00)
2004	0.91 (0.83 to 1.00)	0.90 (0.76 to 1.08)
2005	0.91 (0.83 to 1.00)	1.11 (0.94 to 1.30)
2006	0.80 (0.73 to 0.88)	1.01 (0.85 to 1.20)
2007	0.83 (0.75 to 0.92)	0.92 (0.77 to 1.11)
2008	0.88 (0.79 to 0.97)	1.02 (0.85 to 1.21)
Gender		
Male (reference)	1.00	1.00
Female	1.13 (1.02 to 1.24)	0.91 (0.77 to 1.07)
Socioeconomic Status		
High (reference)	1.00	1.00
Low[†]	1.22 (1.14 to 1.30)	1.28 (1.15 to 1.43)
Recent Immigrant	0.70 (0.61 to 0.8)	0.76 (0.60 to 0.96)

[*]Models also adjusted for age, years HIV-positive, number of outpatient visits per annum, geographic residence (urban vs. rural) and level of co-morbidity using the Johns Hopkins Adjusted Clinical Group case-mix assignment software. Because number of outpatient visits may be on the causal pathway to the outcome, we repeated our analyses without this variable and attained similar estimates.

† Patients in lowest two lowest quintile groups.

Figure Legends

Figure 1: Hospitalization Rates among Persons Living with HIV in Ontario, 1992 -2008, stratified by sex

Figure 2: Hospitalization Rates among Persons Living with HIV in Ontario, 1992-2008, stratified by socioeconomic status (SES)

Legend:
- Total hospitalizations, high SES
- Total hospitalizations, low SES
- HIV-related hospitalizations, high SES
- HIV-related hospitalizations, low SES

X-axis: Year (1990, 1995, 2000, 2005, 2010)

Y-axis: 0, 50, 100, 150, 200, 250, 300, 350, 400, 450