Incidence of chronic obstructive pulmonary disease in people with HIV in Ontario, 1996–2015: a retrospective population-based cohort study

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Abstract

Background: Because of high smoking rates and HIV-related factors, people with HIV may be at high risk for chronic obstructive pulmonary disease (COPD); however, population-based estimates of the incidence of COPD among people with HIV are lacking, particularly for women. We compared the incidence of COPD among Ontario adults aged 35 years or more with and without HIV between Jan. 1, 1996, and Dec. 31, 2015.

Methods: We conducted a population-based study using Ontario's health administrative databases. We compared the incidence of COPD between people with and without HIV using standardized incidence ratios and generalized estimating equations with a log link function.

Results: We identified 1849 people with HIV and 1 168 727 HIV-negative people who were newly diagnosed with COPD between 1996 and 2015. People with HIV were younger than HIV-negative people (mean age 49.7 [standard deviation 10.4] yr v. 62.2 [standard deviation 14.8] yr; standardized difference 0.98). Rates of COPD were higher among people with HIV than among HIV-negative people (10.4 v. 9.0 cases per 1000 person-years; standardized incidence ratio 1.16, 95% confidence interval [CI] 1.10 to 1.21; adjusted rate ratio 1.34, 95% CI 1.27 to 1.41). In sex-stratified analyses, rates of COPD were higher among men with HIV (adjusted rate ratio 1.32, 95% CI 1.24 to 1.40) and women with HIV (adjusted rate ratio 1.54, 95% CI 1.37 to 1.72) than among men and women without HIV. In a sensitivity analysis, smoking explained observed differences in COPD incidence.

Interpretation: People with HIV had higher rates of incident COPD than HIV-negative people. This may reflect the disproportionately higher prevalence of smoking among the former.

Improvements in care have reduced HIV-related morbidity and mortality, such that noninfectious comorbid diseases now account for an increasing proportion of deaths among people with HIV.[1–6] In the context of an aging population with rates of smoking and alcohol use that exceed those of the general population,[7,8] studies characterizing the burden of comorbid disease in people with HIV are required to optimize their care.

Chronic obstructive pulmonary disease (COPD) is a debilitating illness that affects more than 380 million people worldwide and is projected to become the fourth-leading global cause of death by 2030.[9,10] A recent meta-analysis showed that the prevalence of COPD among people with HIV was greater than that among HIV-negative control populations (pooled odds ratio 1.14, 95% confidence interval [CI] 1.05 to 1.25).[11] Although smoking is the most well recognized risk factor for COPD,[12] several studies have shown higher rates of COPD in people with HIV than in HIV-negative people after adjustment for smoking, which suggests that

immune and infectious factors may be involved in the pathogenesis of COPD in people with HIV.[13–18] However, inferences from existing studies exploring the burden of COPD in people with HIV are limited by samples that were small and not population-based.[13,14,19–21] In addition, studies characterizing the incidence of COPD in women with HIV are lacking, despite the increasing representation of women among global populations of people with HIV.[22]

Accordingly, we compared the incidence of COPD in people with and without HIV in Ontario, home to over 40% of Canadians with HIV.[23] We hypothesized that, because of

HIV-related immune and inflammatory factors and a high prevalence of smoking, people with HIV would have a higher incidence of COPD than the general population.

Methods

Setting

We conducted a population-based study comparing the incidence of COPD among Ontario adults aged 35 years or more with and without HIV between Jan. 1, 1996, and Dec. 31, 2015. We selected this period because it corresponds with the advent of highly active antiretroviral therapy, the availability of modern, potent antiretrovirals and the ensuing reduction in HIV-related morbidity and mortality. We restricted our analyses to people more than age 35 because our COPD case-finding definition was validated in this population and COPD is less common in younger people, and to align with COPD surveillance reports.[24]

Data sources

We used Ontario's health administrative databases, which are linked securely by means of unique encoded identifiers and analyzed at ICES (www.ices.on.ca). We identified adults with HIV using the Ontario HIV Database, an administrative registry of Ontario residents with diagnosed HIV that was generated with a validated case-finding algorithm.[25] We obtained hospital admission and emergency department data from the Canadian Institute for Health Information's Discharge Abstract Database and National Ambulatory Care Reporting System, respectively. We used the Ontario Health Insurance Plan database to identify claims for physician services, and obtained basic demographic and date of death data from the Registered Persons Database, a registry of all Ontario residents eligible for health insurance.

Study population

For each year of the study, we used the Registered Persons Database to identify all adults in Ontario aged 35 years or more who were alive and eligible for health insurance and did not have a diagnosis of COPD. From within this cohort, we identified people who had been diagnosed with HIV using the Ontario HIV Database. Human immunodeficiency virus status was a time-varying covariate, so that people could potentially contribute time to both the HIV-negative cohort and the HIV-positive cohort. People could enter the analysis in any year from 1996 to 2015.

Outcomes

Our primary outcome was the incidence of COPD, and our exposure of primary interest was HIV infection. We calculated COPD incidence rates per 1000 person-years of observation for people aged 35 years or more as the collective number of newly diagnosed cases annually for the overall analysis period (1996–2015). Because COPD incidence did not increase linearly over time, we also treated year as a categoric variable by dividing our study period into 5-year intervals (1996–2000, 2001–2005, 2006–2010, 2011–2015). We used

an offset term to adjust for varying durations of follow-up during the calendar year period of interest. For people who died or lost health insurance eligibility during follow-up, we truncated their observation at the pertinent date.

We defined COPD using a previously validated case finding algorithm of 1 or more physician billing claims, or 1 or more hospital discharges, or both, with a diagnosis of COPD (*International Classification of Diseases, 9th Revision* codes 491, 492, 496; *International Statistical Classification of Diseases and Related Health Problems, 10th Revision* codes J41, J42, J43, J44).[26] This case definition was found to have a sensitivity and specificity of 85.0% and 78.4%, respectively, for identifying COPD with Ontario's health administrative records and has been used extensively to study outcomes among people with COPD.[27,28]

Statistical analysis

We computed standardized differences to compare characteristics of people with and without HIV with a new diagnosis of COPD during the study period. Standardized differences of less than 0.1 indicate good balance between groups for a given covariate.[29]

We calculated expected numbers of COPD cases in people with HIV by applying incidence rates from the HIV-negative population to the person-time accrued by people with HIV. We compared rates of COPD between people with and without HIV in 2 ways. First, we calculated standardized incidence ratios (SIRs) as the ratio of observed to expected number of COPD cases in people with HIV and derived 95% confidence intervals (CIs) around SIRs using an exact method.[30] We evaluated average annual percent changes in SIRs using joinpoint regression analysis (Joinpoint Regression Program, Version 4.0.4, Statistical Methodology and Applications Branch, Surveillance Research Program, National Cancer Institute). Next, we compared rates of incident COPD between people with HIV and a 1% random sample of people without HIV using generalized estimating equations Poisson regression analysis.

We adjusted models for fixed and time-varying covariates that could influence the risk of being diagnosed with COPD, including age, year (5-year intervals), sex, urban versus rural residence, socioeconomic status and comorbidity. Specifically, we included age and sex in our models to adjust for differences in the population structure between people with and without HIV. We adjusted for socioeconomic status and rural residence because people with HIV were disproportionately represented in low-income neighbourhoods and urban centres, and prior research has associated these variables with COPD.[31] We adjusted for comorbidity burden to account for differences in the underlying health of people with and without HIV.

We determined patient socioeconomic status at the neighbourhood level using postal code information and Statistics Canada census data. We used the Charlson Comorbidity Index score to adjust for annual differences in comorbidity burden. We stratified analyses by sex to explore heterogeneity in the risk of COPD by HIV status among women and men. We used the quasi-likelihood under the independence model

criterion to compare the fit of various models, with the smallest criterion value chosen as the best-fitting model.[32] We conducted all analyses using SAS version 9.3 (SAS Institute).

Because the health administrative databases do not include reliable information on smoking, we conducted a simple bias analysis to explore whether differences in rates of COPD could be explained by variations in smoking prevalence between people with and without HIV.[33] Specifically, we explored the impact of smoking on adjusted relative rates using published estimates of the prevalence of smoking in Ontario residents with and without HIV[34,35] and published estimates of the association between smoking and COPD[12] (Appendix 1, available at www.cmajopen.ca/content/8/1/E83/suppl/DC1).

Ethics approval

The use of data in this project was authorized under section 45 of Ontario's *Personal Health Information Protection Act*, which does not require review by a research ethics board.

Results

We identified 10 480 538 people aged 35 or more with a valid Ontario health card, of whom 1 432 584 died and 810 819 lost health insurance eligibility during the study period. Among the remaining 8 237 135 people, we identified 1849 people with HIV and 1 168 727 HIV-negative people who were newly diagnosed with COPD between 1996 and 2015.

Compared to HIV-negative people, those with HIV were younger (mean age 49.7 [standard deviation 10.4] v. 62.2 [standard deviation 14.8]; standardized difference 0.98], and less likely to be female (18.6% v. 49.2%; standardized difference 0.68) and rural residents (4.8% v. 16.4%; standardized difference 0.39) (Table 1). In addition, people with HIV had a greater comorbidity burden and were disproportionately represented in the lowest neighbourhood income quintile.

During the study period, we observed a higher incidence of COPD among people with HIV than among HIV-negative people (10.4 v. 9.0 cases per 1000 person-years; SIR 1.16, 95% CI 1.10 to 1.21) (Table 2). Similar results were obtained on multivariable regression (adjusted rate ratio 1.34, 95% CI 1.27 to 1.41).

The average annual percent change in the incidence of COPD did not change significantly over the study period among people with HIV (–1.5%, 95% CI –5.8% to 2.9%), whereas it declined among HIV-negative people (–2.0%, 95% CI –2.6% to –1.3%). Trends in SIRs for COPD showed an average annual percent increase of 1.2% (95% CI –0.1% to 2.4%) (Figure 1). When examined according to 5-year intervals, standardized incidence ratios were significantly higher for people with HIV than for HIV-negative people in 2006–2010 (SIR 1.35, 95% CI 1.25 to 1.46) and 2011–2015 (SIR 1.16, 95% CI 1.07 to 1.26) only (Table 2). However, on multivariable regression, people with HIV had higher rates of COPD than HIV-negative people in all 5-year periods. We observed similar results when we stratified results by sex (Table 2).

Using a conservative estimate of a nearly fourfold increased risk of COPD among current smokers and a prevalence of smoking among Ontario residents with and without HIV of 32.7% and 11.3%, respectively, we found that people with HIV were no longer at higher risk for COPD than HIV-negative people (adjusted rate ratio 0.92) (Appendix 1). Similar results were obtained for sex-stratified analyses using sex-specific estimates of the prevalence of smoking, with adjusted relative rates of COPD among men and women with HIV of 0.89 and 1.02, respectively.

Interpretation

In our population-based study, we observed higher standardized and adjusted incidence rates of COPD among women and men with HIV than in HIV-negative people. Although a simple bias analysis showed that our results were sensitive to adjustment for smoking, this finding should be considered hypothesis generating given that we were unable to account for this variable directly using our databases.

Our findings build on those of other large studies examining the burden of COPD in people with HIV. Specifically, a study of 33 420 people with HIV (98% male) receiving care through the US Veterans Affairs Health Care System showed higher rates of COPD relative to HIV-negative veterans less than (rate ratio 1.17, 95% CI 1.11 to 1.24) and more than (rate ratio 1.08, 95% CI 1.01 to 1.15) 50 years of age.[21] Our study adds to these findings by being population-based in nature, thereby allowing us to study all people with HIV who were diagnosed with COPD over a 20-year study period. We also found that people with HIV were diagnosed with COPD almost a decade younger than HIV-negative people. Furthermore, we found an increasing trend in the SIR, which may be explained by sustained higher rates of smoking in people with HIV relative to the general population and an increasing proportion of people with HIV aged 55 years or more (7.4% in 2000 to 30.0% in 2015).[36] Finally, we derived population-based estimates of COPD in women with HIV.

Our study has important implications for the management of people with HIV. First, although population-level screening for COPD is currently not supported by evidence, a recently published guideline from the Global Initiative for Chronic Obstructive Lung Disease endorses spirometry for active case finding in patients with risk factors and symptoms.[9] Because people with HIV may include a higher than average risk group of people at risk for COPD, screening spirometry may be appropriate for this population. Early diagnosis and intervention aimed at preventing loss of lung function may be particularly important for people with HIV and COPD, as several studies suggest that hospital admissions and emergency department use related to COPD are more common in this population relative to HIV-negative people with COPD.[37,38] Second, efforts to identify and implement smoking cessation strategies acceptable to people with HIV are required. Prior research has shown that smoking now accounts for more years of lost life among people with HIV who smoke than HIV infection itself.[39] Yet comparatively few studies exist evaluating

Table 1: Characteristics of Ontario adults with chronic obstructive pulmonary disease by HIV status, 1996–2015

Characteristic	No. (%) of people*		Standardized difference
	HIV-positive n = 1849	HIV-negative n = 1 168 727	
Age at COPD diagnosis, yr, mean ± SD	49.7 ± 10.4	62.2 ± 14.8	0.98
35–50	1109 (60.0)	295 145 (25.2)	0.75
51–65	581 (31.4)	372 349 (31.9)	0.01
66–80	138 (7.5)	354 952 (30.4)	0.61
> 81	21 (1.1)	146 281 (12.5)	0.46
Sex			
Female	343 (18.6)	574 911 (49.2)	0.68
Male	1506 (81.4)	593 816 (50.8)	
Neighbourhood income quintile			
5 (highest)	226 (12.2)	194 214 (16.6)	0.13
4	232 (12.5)	211 964 (18.1)	0.16
3	276 (14.9)	229 285 (19.6)	0.12
2	395 (21.4)	255 273 (21.8)	0.01
1 (lowest)	705 (38.1)	273 384 (23.4)	0.32
Missing	15 (0.8)	4607 (0.4)	0.05
Rural residence	88 (4.8)	191 541 (16.4)	0.39
No. of hospital admissions for COPD in 24 mo after diagnosis			
Mean ± SD	1.8 ± 1.8	1.4 ± 1.0	0.24
Median (IQR)	1 (1–2)	1 (1–2)	0.16
Charlson Comorbidity Index score			
No hospital admissions	779 (42.1)	583 870 (50.0)	0.16
0	376 (20.3)	351 901 (30.1)	0.23
1	76 (4.1)	93 203 (8.0)	0.16
≥ 2	618 (33.4)	139 753 (12.0)	0.53
Diagnosis of asthma	533 (28.8)	306 935 (26.3)	0.06
Died during follow-up	512 (27.7)	392 758 (33.6)	0.13
Diagnosed with *Pneumocystis jirovecii* pneumonia before COPD diagnosis	187 (10.1)	NA	–
No. of years between HIV diagnosis and COPD diagnosis, mean ± SD	9.1 ± 6.0	NA	–

Note: COPD = chronic obstructive pulmonary disease, IQR = interquartile range, NA = not applicable, SD = standard deviation.
*Except where noted otherwise.

strategies for smoking cessation in this population, and the success of interventions appears modest.[40,41]

Limitations

Our findings are strengthened by the population-based nature of our data, which allowed us to examine all Ontario residents with HIV who have entered care. However, our study has some limitations. We used administrative databases and did not have access to past or present smoking prevalence, information quantifying smoking history, duration and amount, marijuana use, injection drug use and laboratory data, including viral load and CD4 cell count. Similarly, we did not have reliable data on antiretroviral use. Although use of antiretroviral therapy has been associated with a lower risk of COPD in the

Table 2: Standardized incidence ratios and adjusted rate ratios of chronic obstructive pulmonary disease

Group/period	Rate per 1000 person-years (95% CI)		Standardized incidence ratio (95% CI)	Adjusted rate ratio (95% CI)*
	HIV	No HIV		
Overall	10.4 (9.9 to 10.9)	9.0 (9.0 to 9.0)	1.16 (1.10 to 1.21)	1.34 (1.27 to 1.41)
1996–2000	11.3 (10.0 to 12.7)	10.7 (10.7 to 10.8)	1.06 (0.94 to 1.19)	1.25 (1.10 to 1.42)
2001–2005	9.1 (8.2 to 10.1)	8.5 (8.5 to 8.5)	1.07 (0.96 to 1.19)	1.23 (1.10 to 1.37)
2006–2010	11.8 (10.9 to 12.8)	8.7 (8.7 to 8.8)	1.35 (1.25 to 1.46)	1.55 (1.42 to 1.70)
2011–2015	9.8 (9.0 to 10.6)	8.4 (8.4 to 8.4)	1.16 (1.07 to 1.26)	1.26 (1.16 to 1.38)
Women				
Overall	12.1 (10.9 to 13.4)	8.5 (8.5 to 8.6)	1.42 (1.27 to 1.57)	1.54 (1.37 to 1.72)
1996–2000	17.5 (12.8 to 23.4)	10.1 (10.1 to 10.2)	1.73 (1.28 to 2.28)	1.80 (1.34 to 2.43)
2001–2005	12.2 (9.4 to 15.6)	8.2 (8.2 to 8.3)	1.48 (1.15 to 1.88)	1.48 (1.15 to 1.91)
2006–2010	13.0 (10.6 to 15.6)	8.3 (8.3 to 8.4)	1.56 (1.29 to 1.87)	1.64 (1.35 to 1.99)
2011–2015	10.3 (8.6 to 12.3)	7.8 (7.7 to 7.8)	1.33 (1.11 to 1.58)	1.41 (1.17 to 1.69)
Men				
Overall	10.1 (9.6 to 10.6)	9.5 (9.5 to 9.5)	1.06 (1.01 to 1.12)	1.32 (1.24 to 1.40)
1996–2000	10.6 (9.2 to 12.0)	11.3 (11.3 to 11.4)	0.93 (0.82 to 1.06)	1.21 (1.04 to 1.40)
2001–2005	8.6 (7.7 to 9.7)	8.8 (8.8 to 8.9)	0.98 (0.87 to 1.10)	1.27 (1.11 to 1.45)
2006–2010	11.5 (10.6 to 12.6)	9.2 (9.1 to 9.2)	1.26 (1.15 to 1.38)	1.56 (1.41 to 1.73)
2011–2015	9.6 (8.8 to 10.5)	9.1 (9.0 to 9.1)	1.06 (0.97 to 1.16)	1.20 (1.08 to 1.33)

Note: CI = confidence interval.
*Adjusted for socioeconomic status, urban versus rural residence, comorbidity, age, sex (nonstratified models) and year (overall models only).
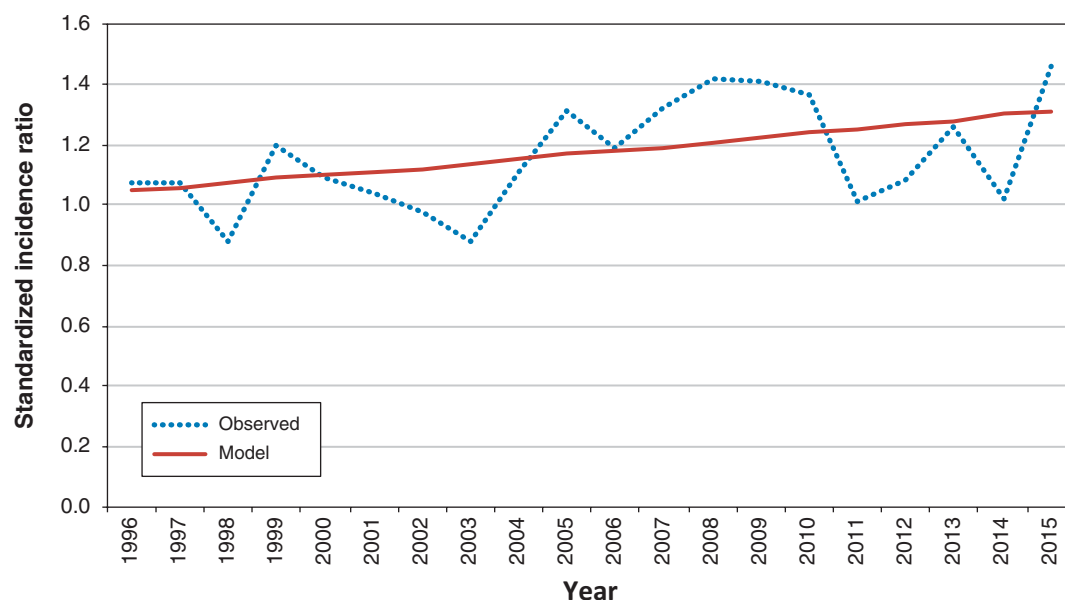

Figure 1: Trend in standardized incidence ratio of chronic obstructive pulmonary disease according to joinpoint regression model between people in Ontario with and without HIV, 1996–2015.

Veterans Affairs study,[21] other studies have found no differences in the rate of lung function decline according to HIV treatment status.[42] Because most people with HIV who are in care in Ontario are receiving antiretroviral therapy, it is unlikely that low treatment uptake accounts for the increased risk of COPD in our cohort, particularly in later periods.[43]

We identified COPD using health administrative data rather than spirometry. Although it is possible that our validated case-finding algorithm identifies mostly people with clinically significant COPD and misses milder forms of the disease, thereby underestimating incidence, clinically significant disease would be more likely among people with HIV, in whom the prevalence of abnormal spirometry appears higher than in the general population.[44,45] Finally, we could not identify people with undiagnosed HIV infection. Consequently, our estimates are most appropriately interpreted as representing the burden of COPD in people with diagnosed HIV infection who are in care.

Conclusion

We found higher than expected rates of COPD in people with HIV relative to HIV-negative people. Our findings of a younger age at COPD diagnosis and higher rate among women with HIV relative to HIV-negative women are especially notable. Future areas of research include comparisons of the risk of spirometry-confirmed COPD in people with and without HIV and confirmation of our findings in large data sets that include missing confounders and HIV-related clinical information. In addition, research exploring the role of screening spirometry, the causal contribution of smoking and the longitudinal trajectory of COPD in people with HIV are required to better inform the clinical management of COPD in these patients.

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