Risk of Multiple Sclerosis in People Living with HIV: An International Cohort Study

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Objective: There has been interest in a possible negative association between HIV and multiple sclerosis (MS). We aimed to compare the risk of MS in a cohort of individuals living with HIV to that in the general population.

Methods: Population-based health data were accessed for 2 cohorts of HIV-positive persons from Sweden and British Columbia, Canada. Incident MS was identified using MS registries or a validated algorithm applied to administrative data. Individuals with HIV were followed from 1 year after the first clinical evidence of HIV or the first date of complete administrative health data (Canada = April 1, 1992 and Sweden = January 1, 2001) until the earliest of incident MS, emigration, death, or study end (Canada = March 31, 2020 and Sweden = December 31, 2018). The observed MS incidence rate in the HIV-positive cohort was compared to the expected age-, sex-, calendar year-, income-specific, and region of birth-specific rates in a randomly selected sample of >20% of each general population. The standardized incidence ratio (SIR) for MS following the first antiretroviral therapy exposure ("ART-exposed") was also calculated.

Results: The combined Sweden-Canada cohort included 29,163 (75% men) HIV-positive persons. During 242,248 person-years of follow-up, 14 incident MS cases were observed in the HIV-positive cohort, whereas 26.19 cases were expected. The SIR for MS in the HIV-positive population was 0.53 (95% confidence interval [CI] = 0.32–0.90). The SIR for MS following the first ART exposure was 0.55 (95% CI = 0.31–0.96).

Interpretation: This international population-based study demonstrated a lower risk of MS among HIV-positive individuals, and HIV-positive ART-exposed individuals. These findings provide support for further exploration into the relationship among HIV, ART, and MS.

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Over the past 2 decades, considerable evidence has accumulated to suggest that viruses, such as the Epstein–Barr virus and human herpesvirus-6, play an important role in the pathogenesis of multiple sclerosis (MS).[1] More recently, the potential role of the human immunodeficiency virus (HIV), has been considered in

modifying MS risk in 3 observational studies.[2–4] A study from England reported a significantly lower MS incidence among individuals with HIV than expected,[3] whereas 2 studies, from Denmark and Taiwan, were unable to demonstrate evidence for an association.[2,4] However, these studies were either limited in power,[2,4] or unable to capture exposure to antiretroviral therapy (ART),[2,3] so the question of whether HIV or its treatment with ART has a mitigating effect on MS risk remains unresolved. A sufficiently powered study is required, in different populations of individuals living with HIV, while also considering HIV treatment exposure, to confirm or refute the findings from the population in England and to advance knowledge of the possible role of ART in MS risk.[5] An understanding of this relationship offers the opportunity to generate novel ideas about MS etiology, pathogenesis, and treatment.

The aim of this study was to estimate the risk of MS in an international cohort of persons living with HIV from Sweden and Canada and compare this to the risk of MS in the equivalent general population without HIV. In addition, as ART exposure could modify the risk of MS, we aimed to explore the potential influence of ART exposure on this risk.

Materials and Methods

Data Sources and Study Population

The HIV study population comprised 2 population-based cohorts of individuals with a confirmed diagnosis of HIV (the HIV-positive "COAST" cohort from the "Comparative Outcomes And Service Utilization Trends Study" in the province of British Columbia (BC),[6] Canada, and the Swedish InfCareHIV cohort[7]). The Canadian HIV cohort included all individuals who accessed the HIV Drug Treatment Program, through which ART is provided at no cost to all medically eligible persons at risk of or living with HIV in BC. Data from the InfCareHIV cohort is captured through the Swedish HIV clinics which serve virtually all (>99%) people living with HIV in Sweden. HIV-specific clinical data captured in both cohorts include date of first evidence of HIV and ART exposure dates. Additional individuals living with HIV, included in both cohorts of patients with HIV, were identified in the health administrative data by a validated case-finding algorithm that required people to have at least 3 International Classification of Disease (ICD) codes for HIV on separate dates from physician visits or one ICD code from a hospital admission (Table S1).

A large sample of individuals from each general population included people who were randomly and evenly selected from among individuals living in Sweden or Canada (BC) during each calendar year of the study period, for a total of 4.1 million individuals in BC, Canada, and 2.1 million individuals in Sweden. Residents born outside of Sweden were oversampled to ensure stable expected MS incidence rates once the population was stratified by region of birth. Individuals represented in the HIV cohorts or with at least one ICD code for HIV were excluded from the general population samples.

Individually linked health administrative data were accessed for the HIV patient cohort and the general population sample. These data included sex, birth and death dates, the dates and diagnostic ICD-9 or 10 codes for all physician encounters and hospitalizations, and registration dates in the universal healthcare program in BC, Canada, and migration dates in Sweden, which were used to confirm residency. An estimate of income (as a proxy for socioeconomic status [SES]), expressed as quintiles, was generated from postal codes and neighborhood income data in BC and from individualized disposable family income data in Sweden. Individuals with missing income data were assigned to the middle-income quintile for the primary analyses. Region of birth (available in Sweden only) was categorized as: (1) Nordic countries, the European Union, United Kingdom, Canada, and United States; (2) Sub-Saharan Africa; and (3) all other countries. Individuals with missing country of birth in Sweden, and all individuals in Canada, were assigned to region 1.

MS clinical data were captured by the BC MS Registry and the Swedish MS Registry. The BC MS Registry contains information on patients with MS who visited an MS clinic in BC, Canada, capturing approximately 60% of people with MS in the province.[8] The Swedish MS Registry, a national quality register, captures 80% to 85% of MS cases in Sweden.[9] Both data sources provided neurologist-confirmed MS diagnosis and date of symptom onset. All data sources and the years that they covered are summarized in the Appendix, Table S2. Approval for the study was obtained from the Clinical Research Ethics Board at the University of British Columbia and the Swedish Ethical Review Authority, and from the bodies regulating access to the HIV and MS clinical data and health administrative data.

Outcomes

The outcome was incident MS after HIV infection. MS was identified using both the MS clinical data-sources (a neurologist-confirmed diagnosis of MS), and a previously validated algorithm using ICD codes (≥ 3 MS-specific physician or hospital encounters [see Table S1] on different dates) in the health administrative data.

The earliest of the MS symptom onset date (captured in the MS clinical data sources) or the first demyelinating disease-related claim (see Table S1) in the health administrative data was considered the MS incident date. If no MS symptom onset date was available, a minimum 3-year period (while registered in the health system) was required before the first demyelinating disease-related claim to confirm incident MS. A minimum of 1 year between the first clinically confirmed evidence of HIV infection and the MS incident date was required to provide confidence that MS followed the HIV infection.

Analyses

The beginning of the primary follow-up period coincided with the date of full administrative data availability in each region (April 1, 1992, in Canada and January 1, 2001, in Sweden). Persons living with HIV were followed from the most recent of 1 year after first evidence of HIV infection, immigration, or first data availability, until the earliest evidence of incident MS, emigration from Sweden or Canada (BC), death, or the study end date (March 31, 2020, in Canada and December 31, 2018, in Sweden). The

Table 1. Characteristics of the populations of persons living with HIV in Sweden and Canada

	HIV-positive population Sweden[a] (N = 10,390)	HIV-positive population BC, Canada[b] (N = 18,773)
Sex		
F	3,543 (34.1%)	3,762 (20.0)
M	6,847 (65.9%)	15,004 (79.9)
Age at first evidence of HIV[c]		
Mean (SD) yr	35.5 (12.4)	39.4 (11.9)
Region of birth, n (%)		
Nordic countries, EU-28, Canada, and USA	5,662 (54.4%)	NA
Sub-Saharan Africa	3,062 (29.5%)	NA
All other countries	1,629 (15.7%)	NA
Missing	37 (0.4%)	NA
Total available follow up time		
Mean (SD) yr	19.0 (11.7)	20.1 (11.0)
Person-yr	118,042	152,923
Primary follow-up period		
Mean (SD) yr	10.1 (6.1)	8.9 (6.5)
Person-yr	90,424	151,824
SES quintile,[d] n (%)		
1 (least affluent)	3,409 (37.6)	5,989 (31.9)
2	1,263 (14.0)	3,367 (18.0)
3	1,255 (13.8)	2,704 (14.4)
4	1,314 (14.5)	2,015 (10.7)
5 (most affluent)	1,217 (13.4)	1,711 (9.1)
Missing	622 (6.8)	2,970 (15.8)
ART exposure[e] (≥ 1 dose)		
n (%)	8,515 (93.8)	13,099 (87.8)
Duration of ART exposure,[e] mo		
Mean (SD)	112.5 (69.5)	113.1 (91.5)

Abbreviations: ART = antiretroviral therapy; BC = British Columbia; COAST = Comparative Outcomes And Service Utilization Trends Study; EU-28 = the 28 member states of the European Union between 2013 and 2018; ICD = International Classification of Disease; NA = not applicable; SD = standard deviation.

[a]Sweden: Individuals living with HIV identified in InfCareHIV (N = 10,246) and via the HIV algorithm (N = 144).

[b]British Columbia: Individuals living with HIV identified in the COAST cohort (N = 14,913) and via the HIV algorithm (N = 3,860).

[c]First evidence of HIV = earliest evidence of HIV diagnosis in the HIV-related clinical data, or the first ICD code for HIV in the administrative health data.

[d]At start of primary follow-up (the more recent of "First evidence of HIV," immigration, or start date of available data (January 1, 1996 in BC and January 1, 2001 in Sweden).

[e]Information on ART use is for those in the clinical cohorts who contributed person-years to the primary follow-up period (n = 9,073 in Sweden; n = 14,910 in BC).

secondary follow-up period (for complementary analyses) commenced on the earliest date of partial administrative data availability (April 1, 1986, in Canada and January 1, 1987, in Sweden).

Expected rates of MS, stratified by sex, 5 year age group, calendar year, SES quintile, and region of country of birth, were generated from the general population samples. Observed MS incidence rates in the HIV population, stratified by the same factors, were compared with the expected rates to generate the standard incidence ratio (SIR) and 95% confidence intervals (CIs) using the lognormal distribution.

In order to explore the potential effect of ART use on MS risk, we calculated SIRs for MS in the clinical HIV-positive population (excluding those identified via the HIV case-finding algorithm) separately for the person-years following initiation of ART ("ART exposed"; assuming once exposed, always exposed) and before they were exposed to ART ("ART unexposed").

Aggregated data were generated in Canada (BC) and Sweden separately using a common approach, and subsequently combined. The follow-up time was combined using random effects meta-analyses.

Complementary and Sensitivity Analyses

Sensitivity analyses to assess the robustness of our findings included: limiting the HIV-positive population to only those included in the HIV registries; limiting the MS outcome to only the MS registry or to only those identified by ICD codes in the health administrative data; following for incident MS from as early as 1986 when partial data were first available (secondary follow-up); and assigning individuals with missing income data to the lowest or highest income quintile.

These analyses were conducted using SAS software version 9.4 of the SAS system for Windows Copyright 2002–2021 and R: A language and environment for statistical computing (R Foundation for Statistical Computing, Vienna, Austria) version 4.0.2.

Results

The combined Canadian and Swedish population living with HIV included 29,163 individuals. The median age at first clinical evidence of HIV was similar between the cohorts (Sweden = 34 years and Canada = 37 years;

Table 1). As expected, there was a preponderance of men in both HIV-positive cohorts (79.9% in Canada and 65.9% in Sweden). These cohorts were not evenly distributed across the SES quintiles; 37.6% in BC, Canada, and 31.9% in Sweden fell in the lowest (least affluent) quintile. Approximately half (54.4%) of the Swedish HIV-positive cohort were born in the European Union, United Kingdom, Nordic countries, Canada, or the United States, whereas 29.5% were born in Sub-Saharan Africa.

There were 242,248 person-years at risk during the primary follow-up period, and 86.1% of that time (208,481 person-years) was "ART-exposed" (see Table 1).

The age-, sex-, calendar year-, SES-, and region of birth-standardized incidence ratio of MS in the HIV-positive population was 0.53 (95% CI = 0.32–0.90), based on 14 observed and 26.19 expected MS cases. Whereas stratifying by quintile of SES did not change the estimated SIR, adding region of birth strata attenuated the estimates, although the SIR remained significantly reduced. There were fewer observed cases of MS among HIV-positive women than expected (SIR = 0.28, 95% CI = 0.09–0.88). Similarly, there were fewer men developing MS in the HIV population than expected, but this did not reach statistical significance (SIR = 0.70, 95% CI = 0.39–1.27). Results are shown in Table 2.

Following from the first ART exposure, the standardized incidence ratio for MS was 0.55 (95% CI = 0.31–0.96; Table 3). There was minimal ART unexposed follow-up time, resulting in an imprecise estimate (SIR = 0.46, 95% CI = 0.12–1.85). In sex-specific analyses, the SIR for MS incidence following the first ART exposure was significantly reduced for women with HIV (SIR = 0.25, 95% CI = 0.06–0.98), but not for men with HIV (SIR = 0.72, 95% CI = 0.39–1.35). In the unexposed (pre-ART) period, there was limited follow-up time and the CIs were wide and included one for both women (SIR = 0.41, 95% CI = 0.06–2.93) and men (SIR = 0.53, 95% CI = 0.07–3.74; see Table 3).

Table 2. Overall and sex-specific standardized incidence ratios and 95% confidence intervals of multiple sclerosis in the HIV-positive population, Sweden and Canada combined

	Standardized for age, sex, yr	Standardized for age, sex, yr, SES	Standardized for age, sex, yr, SES, region of birth
Overall	**0.44 (0.26–0.75)**	**0.45 (0.26–0.75)**	**0.53 (0.32–0.90)**
Men	0.67 (0.37–1.21)	0.67 (0.37–1.21)	0.70 (0.39–1.27)
Women	**0.20 (0.06–0.62)**	**0.20 (0.06–0.62)**	**0.28 (0.09–0.88)**

Note: The bold values represent statistically significant findings at the *p* < 0.05 level.
Abbreviation: SES = socioeconomic status.

Table 3. Overall and sex-specific standardized incidence ratios and 95% confidence intervals of multiple sclerosis in an HIV-positive population during the "ART exposed" period (once exposed, always exposed) and during the "ART unexposed" period, Sweden and Canada combined

	ART exposed period			ART unexposed period		
	Standardized for age, sex, yr	Standardized for age, sex, yr, SES	Standardized for age, sex, yr, SES, region of birth	Standardized for age, sex, yr	Standardized for age, sex, yr, SES	Standardized for age, sex, yr, SES, region of birth
All	**0.45 (0.25–0.79)**	**0.45 (0.25–0.79)**	**0.55 (0.31–0.96)**	0.43 (0.11–1.70)	0.42 (0.11–1.70)	0.46 (0.12–1.85)
Men	0.69 (0.37–1.28)	0.69 (0.37–1.28)	0.72 (0.39–1.35)	0.51 (0.07–3.59)	0.50 (0.07–3.56)	0.53 (0.07–3.74)
Women	**0.16 (0.04–0.65)**	**0.16 (0.04–0.65)**	**0.25 (0.06–0.98)**	0.37 (0.05–2.62)	0.37 (0.05–2.63)	0.41 (0.06–2.93)

Note: The bold values represent statistically significant findings at the $p < 0.05$ level.
Abbreviations: ART = antiretroviral therapy; SES = socioeconomic status.

Complementary and Sensitivity Analyses

The analyses including only persons living with HIV identified in the clinical registries or outcomes identified only in the MS registries or the health administrative data, and those exploring a longer follow-up period and different assumptions for missing data, yielded similar results to the primary analyses (results not shown).

Discussion

Using an international multicenter approach, we report a lower occurrence of MS in individuals living with HIV than expected. The rate of MS was also significantly lower than expected after first exposure to ART. There were too few pre-ART exposure person-years to obtain a precise estimate of MS risk among HIV-exposed only. These results suggest that infection with HIV or treatment with ART may confer a protective effect against the development of MS.

The human immunodeficiency virus leads to a progressive loss of CD4+ T cells, an increase in pro-inflammatory cytokines, and, in the absence of intervention, acquired immunodeficiency syndrome (AIDS).[10] MS is a chronic condition which stems from aberrant immune functioning and results in myelin degradation and axonal loss within the central nervous system (CNS). Myelin-reactive CD4+ T cells are implicated in the early phase of MS, by initiating the cascade of events that leads to CNS inflammation.[11] Indeed, certain MS therapies may act by effectively reducing the CD4+ T cell count,[12] although a small randomized controlled trial of a monoclonal anti-CD4 antibody in people with MS reported no effect in reducing the number of new lesions on magnetic resonance imaging (MRI).[13] Nevertheless, these counteracting processes led to the hypothesis that HIV, by reducing

peripheral CD4+ T cell counts, modifies the pathogenesis of MS.[5] In contrast to this line of reasoning, it is noteworthy that HIV positivity has been linked to a heightened incidence of other autoimmune diseases,[14,15] perhaps related to the chronic activation of CD8+ cells.[16]

The suggestion that ART might alter MS risk appears to have partly stemmed from a series of case reports of persons with comorbid HIV and MS.[5] These reports included observations of limited MS disease activity and disability progression, which led to speculation that ART exposure might translate to a lowered MS risk.[5] Possible mechanisms for the effectiveness of ART in reducing MS disability, or even MS risk, include the inhibition of human endogenous retroviruses or Epstein–Barr virus.[5,17,18] With regard to EBV, it is known that individuals with HIV have a higher risk of EBV-related Hodgkin's lymphoma than individuals without HIV. Since the advent of ART though, whereas the risk of Hodgkin's lymphoma has remained higher, the prognosis has markedly improved in persons living with HIV.[19,20]

Our findings significantly extend those of the 3 previous studies which explored the incidence of MS in populations living with HIV.[2–4] A Danish study reported a single case of MS among 5,018 HIV-positive individuals.[2] Although the MS incidence was lower among those with HIV than among a comparison cohort from the general population, the CI included one.[2] This study was unable to consider the possible confounding influence of region of origin on the difference in MS risk, although approximately 80% of people with HIV in Denmark are of European origin and 13% are from Africa,[21] representing a larger proportion of non-Europeans than in the general Danish population (where it is less than 10%).[22] A subsequent study from England included a

population of 21,207 HIV-positive patients identified exclusively from hospital discharge reports and reported a significant reduction in their risk of MS as compared to the general population.[3] The incidence of MS remained lower than expected when only persons identified as "White British" were included, however, data on race or ethnicity were missing for over 50% of the English cohort and the CI for this risk estimate included one. Last, a Taiwanese study found no significant difference in MS incidence between 20,444 persons living with HIV and expected rates estimated from the general population.[4] However, the power of this analysis was limited by the low MS incidence in the Taiwanese population, with less than 2 expected cases over the study period.

Our study is unique and provides novel information in that it accessed a large cohort of persons living with HIV, with clinical HIV data including ART exposure in 2 regions of high MS incidence,[23,24] used validated definitions of both MS and HIV, provided sex-specific risk estimates, and considered the potential confounding influences of region of birth and SES.

A difference in risk for HIV and MS by region of origin is a conceivable explanation for the low risk of MS in persons with HIV. Because HIV is more prevalent in certain regions, including Sub-Saharan Africa,[25] whereas MS occurs with greater frequency in countries further from the equator.[26] There is a high proportion of people born in Sub-Saharan Africa in the Swedish HIV cohort, and we were able to take this into account by stratifying the analyses by region of birth.

We observed a moderate attenuation of the SIR estimate following adjustment for region of birth, although it remained far below one, suggesting that the lower risk of MS in the HIV population was not explained by the differences in the distribution of region of birth between the Swedish HIV cohort and the general population. We did not have access to region of birth information for the Canadian cohort; however, of what is known of the demographic profile of the HIV population in BC, Canada, it is predominantly of European origin and there is a higher proportion of people of Indigenous ethnicity than in the provincial general population.[27] For the primary merged analyses, we assumed no difference in region of birth between the Canadian HIV cohort and general population. Although this led to certain misclassification, we assume that by underestimating the region of birth diversity in the general population (and therefore assuming a higher proportion were from "high MS risk" world regions) our estimates would tend toward the null.

The SIR for MS risk in HIV-positive individuals regardless of ART exposure, and that for MS risk in HIV-positive individuals after ART exposure were similar, reflecting the minimal ART unexposed time. The SIRs for MS risk in HIV-positive individuals before ART exposure were also low, but due to the small number of person-years, the estimates were imprecise. There was, sadly, a low survival rate among persons living with HIV in the pre-ART era so the limited follow-up time is not surprising. Only one prior study was able to separate ART-exposed and unexposed time.[4] In that study, one individual was diagnosed with MS after ART initiation, during the ART-exposed period, whereas 2 people who had never been treated with ART were diagnosed with MS.[4] Although the small numbers limit interpretation of the findings (neither SIR was significant), the estimated SIR for the ART-exposed period was the lower. The significantly lower risk of MS following initiation of ART treatment implies there is a lower risk of MS even when the HIV virus is suppressed by ART.

Both men and women living with HIV had lower rates of MS than expected, but the sex-specific analyses revealed that the SIRs were statistically significant only for women. There are several sex differences in the pathogenesis of HIV, including differences in viral loads, pharmacological properties of treatments, and immune responses and pathways[28] some of which may explain these differences. However, research would be required to determine if this is a true difference and to understand the underlying mechanisms driving it.

Whereas there is biological rationale to support a true negative association between HIV and MS, we cannot exclude the possibility that our findings were influenced by residual confounding or misclassification. Human herpes virus-6 (HHV-6) has been associated with an increased risk of MS,[29] for example, and HHV-6 is believed to work in concert with HIV to heighten immunosuppression and progression toward AIDS.[30] We did not have information on HHV-6 status, therefore, we could not account for this potential confounding effect. It is also possible that cases of MS were missed (undiagnosed), particularly in the pre-ART era when the survival time post-HIV infection was limited.[31] In individuals with complex medical needs related to their HIV infection, MS could have been missed due to competing demands or mistakenly attributed to the infection itself.[32] On the other hand, there is accumulating evidence that individuals living with HIV have a greater risk of being diagnosed with other conditions, including inflammatory diseases, such as inflammatory bowel disease[15,33] and diabetes,[34] which argues against a lack of medical recognition of comorbidities in this population.

Conclusions

This large population-based international study revealed a significantly lower risk of MS among individuals living with HIV, and among HIV-positive ART-exposed individuals, than expected based on the risk in the general population.

Further work on the relationship between ART use and MS risk is warranted. However, our findings might also motivate a more concerted effort to ascertain whether ART use, or specific ART combinations, could beneficially alter subsequent MS disease progression. In the face of limited research resources, this line of inquiry may yield a more immediate clinical benefit, addressing the major unmet need to develop better treatment strategies aimed at preventing or ameliorating the unrelenting progression in MS.[35]

Author Contributions

E.K., H.T., J.M.W., A.M., F.Z., R.S.H., and A.M.E. contributed to the conception and design of the study. E.K., H.T., A.M., F.Z., J.M.A.W., M.G., J.H., R.S.H., P.S., J.T., M.Y., J.L., and K.K. contributed to the acquisition and analysis of data. K.A.M., J.M.A.W., A.M., F.Z., H.T., and E.K. contributed to drafting the text or preparing the figures.

Potential Conflicts of Interest

Nothing to report.

Data Availability

Data cannot be shared publicly. Access to data provided by the Data Steward(s) is subject to approval, but can be requested for research projects through the Data Steward(s) or their designated service providers.

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