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MAJOR ARTICLE

Seropositivity, Risks, and Morbidity From Varicella-Zoster Virus Infections in an Adult PWH Cohort From 2000–2020

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Background. Varicella-zoster virus (VZV) infection disproportionately affects people with HIV (PWH), primarily presenting as herpes zoster. However, VZV seroprevalence, its association with zoster, and clinical outcomes remain understudied in era of modern antiretroviral therapy (ART). We assessed VZV seroprevalence, rates of VZV illness, and associated health care costs in a large cohort of PWH over 20 years.

Methods. We performed retrospective chart reviews of patients followed at a regional HIV clinic from January 1, 2000, to December 31, 2020. Serological, immunization, clinical, and costing data were extracted from in-house databases. VZV-related inpatient admissions, emergency department (ED), and urgent care (UC) visits were identified using relevant International Classification of Disease (ICD-10) codes and validated where possible by 2 physicians. Health care utilization costs were adjusted to 2020 Canadian dollars.

Results. Of 3006 PWH, VZV serology was available for 2628; of these, 2503 (95.2%) were seropositive. Only 39% of known seronegative patients were subsequently immunized for varicella. During 29 768 years of patient follow-up, 38 hospitalizations and 138 ED/UC visits due to VZV infection were identified. Most occurred in VZV-seropositive PWH <50 years of age (82%) who were unimmunized (99.2%) and not on ART (64.8%). Nearly 25% of hospitalizations were due to laboratory-confirmed VZV meningitis/encephalitis. The average admission cost was CDN$33 001; the total measured cost of VZV illness was CDN$1 258 718.

Conclusions. Despite ART and vaccines for chickenpox and shingles, VZV still caused significant costs and morbidity for PWH, occurring at younger ages and often as encephalitis/meningitis. Supporting ART adherence may reduce VZV illness and hospitalization costs in PWH, and the cost-effectiveness of expanding shingles vaccine use warrants further study.

Keywords. HIV/AIDS; varicella-zoster virus; herpes zoster; hospitalizations; incremental cost of care.

Varicella-zoster virus (VZV) infection is well known for causing either chickenpox (varicella) or shingles (herpes zoster [HZ]) [1, 2]. While primary infection as varicella is nearly ubiquitous in humans, shingles is also common, with an estimated lifetime risk of ~30%, and predominantly affects individuals >50 years of age in the general population [3]. Despite the availability and effectiveness of both live attenuated and subunit zoster vaccines, the incidence of HZ and its complications, including hospitalization and treatment costs, continues to increase [4, 5]. Annual costs related to HZ-related illnesses have been estimated in the Canadian province of British Columbia to be >CDN$5 million, and they continue to increase [4]. HZ immunization has been shown to blunt the rise in incident HZ cases over time and reduce HZ-related hospitalization and emergency department (ED) visits [4, 6, 7]. Although the live attenuated vaccine has been licensed for use in Canada since 2011 and the adjuvant recombinant vaccine since 2017, free coverage under public health care is very limited, curtailing their widespread use [7–10]. In our setting, immunization against HZ, although promoted, is not covered by Alberta Health and requires private coverage or a personal expense to the patient.

VZV infection can cause substantial morbidity, particularly in immunocompromised individuals, including people with HIV (PWH) [11–13]. Even in the era of suppressive antiretroviral therapy (ART), when compared with the general population, PWH have a 4–10-fold greater incidence of HZ and may also develop HZ over a decade earlier on average [14–22]. PWH are also at increased risk of developing serious complications including disseminated zoster, post-herpetic neuralgia, and VZV meningoencephalitis [12]. While early potent ART regimens may have decreased the incidence of some HIV-associated neurologic complications, the rates of VZV encephalitis seem to be

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unchanged or increasing [23]. It has also been reported that the overall incidence of all HZ-related illnesses in PWH may have changed little in the early ART era and that ART use may not reduce rates of zoster complications [14, 22].

Few data are available on the current seroprevalence of VZV in PWH and its association with outcomes such as hospitalization and health care costs in this population. One 300-person case–control study in a US military cohort of PWH showed that quantitative VZV antibody levels were not predictive of zoster reactivation, but lack of ARV use/CD4 counts and exclusion of PWH with negative VZV serology or those who had previously received varicella or shingles vaccination limit its wider applicability [24]. Vaccine uptake and the preventable burden and costs of VZV illness in PWH are thus largely unknown.

Given the progressive burden of VZV illness in PWH, further exploration of the impact of modifiable risk factors such as vaccination rates is warranted. Through retrospective review of a large, well-established, geographically defined cohort of PWH over a 20-year study period, we aimed to characterize epidemiologic correlates of VZV immunity such as vaccination rates for varicella and HZ as well as VZV seropositivity rates. We also report the incidence and costs of VZV-related morbidity during the study period, presenting as inpatient admissions, ED visits, and urgent care (UC) visits.

METHODS

Since 1989, the Southern Alberta Clinic (SAC) has been the exclusive provider of all HIV care including laboratory testing and ART for all PWH ≥18 years of age living in Southern Alberta, Canada. HIV care is provided at no cost to the patient under the provincial universal health program. We included all adult PWH with an initial clinic visit to SAC from January 1, 2000, to December 31, 2020. Demographic and clinical characteristics including sex, age at first visit, self-reported ethnicity, level of education, country of birth, most likely HIV risk factor, date of HIV diagnosis, concurrent AIDS, and comorbidities were collected from SAC's database at the initial visit and updated at subsequent clinical visits. Since January 2000, initial bloodwork has included serologic testing for VZV, with free varicella immunization being offered to those who have negative VZV serology.

Clinical and Laboratory Data

Through the use of paper charts, electronic medical records, and database extracts, a retrospective review of clinical information including CD4 count, HIV viral load, antiretroviral use, immunization records, VZV serology, and VZV polymerase chain reaction (PCR) results was performed. The VZV immunoglobulin G (IgG) result closest to SAC intake or up to 5 years prior was defined as baseline VZV serology. If no VZV serology was found within the prior 5 years, any VZV serology result within 1 year after the intake visit was used. If a patient had a negative VZV-IgG result >1 year postintake, the baseline was classified as a negative at baseline. If no result was found, the baseline serology was reported as unknown. A patient's follow-up VZV serology was defined as the latest VZV-IgG result available after the baseline result up to December 31, 2020. We classified as positive any of the 23 patients (0.9%) with low-level VZV antibodies reported as indeterminate who later presented with clinical HZ.

VZV-Related Morbidity

Using the relevant International Classification of Diseases, Ninth and Tenth Revision (ICD-9 and ICD-10), codes in the Alberta Data Integration Measurement and Reporting (DIMR) system (listed in Supplementary Data), we identified relevant health care–attended VZV where primary (varicella) or secondary (zoster) VZV infection or VZV-related complications were listed as the most responsible diagnosis. The DIMR collects all ED visits, UC visits, and hospital admissions linked by diagnostic codes. If an ED/UC visit led to a hospitalization, it was counted as a hospitalization only within this study. The contemporary clinical data for each visit were extracted from the SAC database. Accuracy of every hospital discharge and of ICD coding was also confirmed by 2 clinicians (J.Z./M.J.G.). Encounters deemed by the 2 clinicians to be unrelated to VZV despite ICDN coding were omitted from the analysis. An additional data source from the Provincial Laboratory, which performs all VZV PCR testing on cerebrospinal fluid (CSF) and other samples for the province, was used to identify any additional hospitalizations associated with a positive VZV PCR result on CSF not identified by DIMR coding, as these are associated with severe VZV infection [24].

VZV-Related Costs

For VZV-related admissions between 2000 to 2010, the patient-specific hospitalization and cost data were captured only from hospitals within the Calgary zone (where 90% of SAC patients reside): From 2010, the data included all hospitals within Southern Alberta (AHS Calgary and South zones). Hospital costs included all drugs, supplies, equipment, salaries, nursing care, and laboratory and diagnostic testing) and indirect costs associated with hospital overheads (ie, costs of administration and support services). The total costs were adjusted for inflation and reported in 2020 Canadian dollars. For several very complex multisystem admissions, an arbitrary distribution of costs attributable to VZV infection was made based on review by 2 physicians (J.Z./M.J.G.). Cost data were reported on a "per 100 patient-years of follow-up" basis.

Costs for ED and UC visits were determined using the Canadian Institute for Health Information (CIHI) estimate of average ED visit costs in Alberta, which was CDN$430

(excluding physician compensation) in the fourth quarter of 2020, corresponding to our study end date. We added CDN $130 to this to account for physician billing. Based on the timing of each ED/UC visit, we then back-adjusted each ED/UC visit occurring before the fourth quarter of 2020 for inflation.

Statistical Analysis

Study outcomes were described using descriptive statistics: Categorical data (eg, proportion of patients with health care–attended VZV with positive vs negative VZV serology) were compared using chi-square tests or Fisher exact test where appropriate, while continuous data (eg, health care costs of patients with positive vs negative VZV serology) were compared using the Student *t* test. Observations with missing data (13%) were excluded from regression analysis. Logistic regression estimated the crude and adjusted odds ratios and 95% confidence intervals for having a negative baseline VZV-IgG compared with a positive baseline VZV-IgG. Models were adjusted for age per 10-year increase, sex, ethnicity, level of education, and CD4 count. For the bivariate analysis of predictors for VZV morbidity (VZV seropositivity, ART use, viral load suppression, CD4 count), patients missing data were excluded from the analysis and the patient's "last known" value was defined as the latest value available in our database on or before the date of the event. Microsoft Excel, OpenEpi (https://www.openepi.com), and STATA, version 16.0 (StataCorp, College Station, TX, USA), were used to perform all analyses.

This study was approved by the University of Calgary Conjoint Health Research Ethics Board as a quality improvement initiative (Ethics ID REB21-1494).

RESULTS

Baseline VZV Serology and Vaccine Uptake

The demographics of 3006 PWH followed at SAC between January 1, 2000, and December 31, 2020, are shown (Table 1). Of 378 patients (12.6%) with missing baseline serology, 116 were subsequently found on follow-up testing to be positive. Of the 2628 PWH with baseline serology results, 2503 (95.2%) were positive (Figure 1). Those with negative serology were more likely to be younger, to have been born outside of Canada, to have completed postsecondary education, and to have been diagnosed with HIV later (Table 1). Non-Caucasians were more likely to be seronegative (Table 1). There was no association between the sex of the patient or mean CD4 count at intake and baseline VZV seropositivity (Table 1). Of the 102 patients with negative baseline VZV serology, 40 (39.2%) subsequently received at least 1 dose of chickenpox vaccine. Of these 40, 5 seroconverted, 9 did not seroconvert, and 26 did not have any follow-up serology. Of the remaining 62 seronegative patients

Table 1. Crude and Adjusted Odds Ratios of Risk Factors Associated With Seronegative VZV-IgG at Baseline Compared With Baseline VZV-IgG Positive Among PWH Followed at the Southern Alberta Clinic Between 1/1/2000 and 12/31/2020

Characteristic	Patients With Baseline Test[a]	Baseline VZV-IgG-Negative	Baseline VZV-IgG-Positive	*P* Value[b]	Crude Odds[c] Ratio (95% CI)	Adjusted Odds[d] Ratio (95% CI)
No. (%)	2584	101 (3.9)	2483 (96.1)		…	…
Demographics						
Age per 10-y increase in age, mean (SD)	38.7 (10.4)	36.1 (9.7)	38.8 (10.5)	.02	0.78 (0.64–0.97)	0.79 (0.64–0.98)
Sex, No. (%)	…	…	…		…	…
Male	1875 (72.6)	67 (66.3)	1808 (72.8)	.15	Ref	Ref
Female	709 (27.4)	34 (33.7)	675 (27.2)		1.36 (0.89–2.07)	1.31 (0.83–2.06)
Canadian born, No. (%)	1380 (53.4)	29 (28.4)	1351 (54.4)	<.01	Ref	Ref
Non-Canadian born	1204 (46.6)	72 (71.3)	1132 (45.6)		2.96 (1.91–4.59)	2.62 (1.46–4.73)
Ethnicity, No. (%)	…	…	…		…	…
Caucasian	1182 (45.7)	30 (29.7)	1152 (46.4)	<.01	Ref	Ref
Non-Caucasian	1402 (54.3)	71 (70.3)	1331 (53.6)		2.05 (1.33–3.16)	0.94 (0.51–1.72)
Education, No. (%)	…	…	…		…	…
Completed ≤12 y education	1019 (39.4)	25 (24.8)	994 (40.0)	<.01	Ref	Ref
Completed >12 y education	1163 (45.0)	60 (59.4)	1103 (44.4)		2.16 (1.35–3.48)	2.20 (1.35–3.59)
Other/unknown	402 (15.6)	16 (15.8)	386 (15.6)		1.64 (0.87–3.12)	1.58 (0.82–3.01)
CD4 count at clinic intake, mean (SD), cells/mm^3	384 (248)	381 (251)	384 (247)	.81	…	…
>200 cells/mm^3, No. (%)	1973 (76.4)	76 (75.3)	1897 (76.4)	.79	Ref	Ref
≤200 cells/mm^3, No. (%)	611 (23.7)	25 (24.8)	586 (23.6)		1.06 (0.67–1.69)	1.19 (0.74–1.92)
Duration of HIV per 10-y increase, mean (SD)	13.0 (7.2)	11.0 (6.7)	13.1 (7.2)	<.01	0.63 (0.47–0.87)	0.70 (0.51–0.96)

Abbreviations: IgG, immunoglobulin G; PWH, people with HIV; VZV, varicella-zoster virus.

[a]Twenty-three patients had an indeterminate serology at baseline and were not included; 378 patients did not have a serology result at baseline, 16 patients were excluded as they had missing CD4 count measures at clinic intake or initial HIV diagnosis dates were missing, 5 individuals were intersex and excluded, all had positive baseline VZV-IgG.

[b]*P* value comparing baseline VZV-IgG-negative patients with baseline VZV-IgG-positive patients.

[c]Logistic regressions to estimate odds of having a negative baseline VZV-IgG.

[d]Adjusted model includes sex, race/ethnicity, place of birth, education level, CD4 count at clinic intake, age at clinic entry, and duration of HIV infection at study end date.

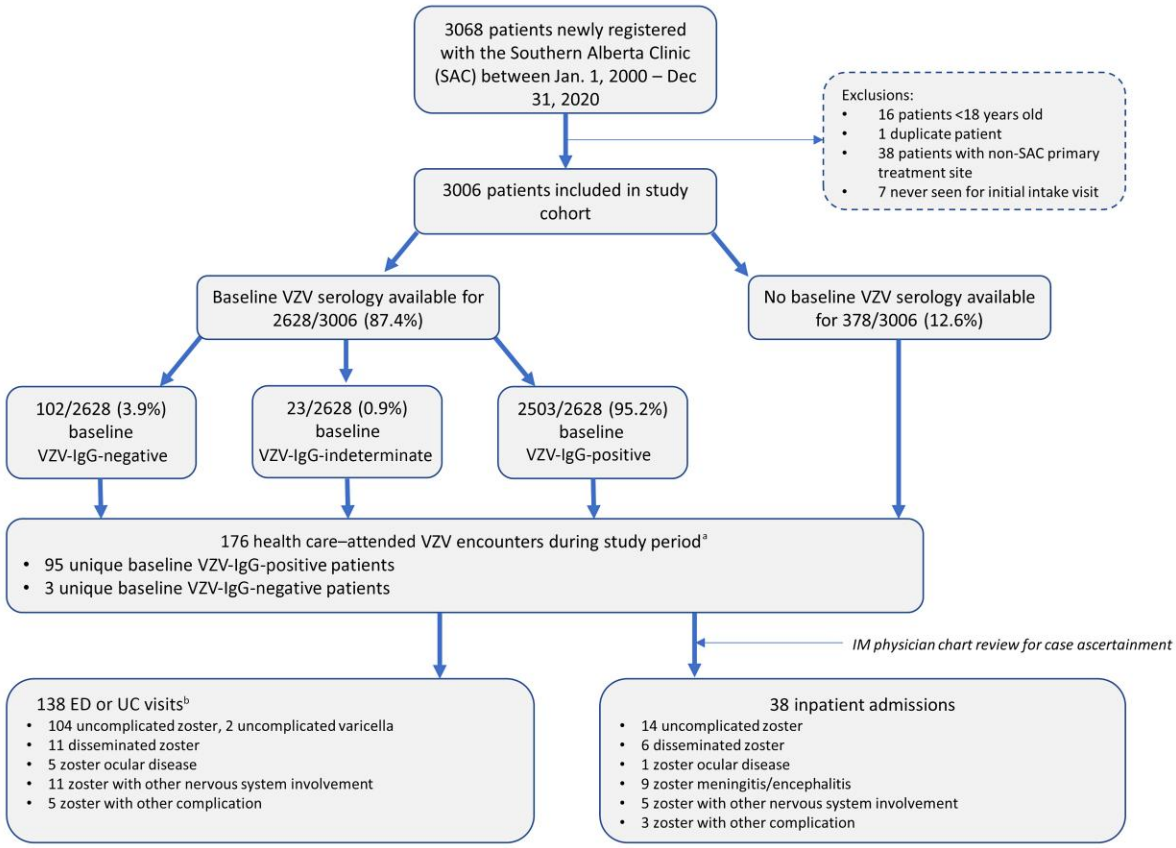

Figure 1. Study population, VZV serology, and health care–attended VZV encounters of patients followed at the Southern Alberta Clinic between January 1, 2000, and December 31, 2020. [a]Patients with >1 inpatient or ED/UC encounter within the study period were included. [b]ED and UC visits leading to inpatient admissions already included in the study were not counted. Abbreviations: ED, emergency department; IgG, immunoglobulin G; UC, urgent care; VZV, varicella-zoster virus.

(not documented by us to be vaccinated), 5 seroconverted on repeat serology, 1 remained seronegative, and 56 had no subsequent serology. In only 15/2503 (0.6%) individuals with positive baseline VZV serology could we document receipt of any HZ vaccination. Of those 15 vaccinated for HZ, 80% received the subunit conjugate vaccine and 20% the live attenuated vaccine.

Incidence of VZV Infection

We identified, during 29 768 total years of patient follow-up, 176 VZV-related episodes in 123 unique patients leading to a health care visit to a hospital ED or UC facility. Most were seropositive for VZV (129/137, 94.2%), but only 1 PWH was immunized against zoster (1/123, 0.8%). Of the 176 VZV visits, 38 required inpatient admissions (incurred by 29 individual patients), and 138 were only ED and UC visits, corresponding to 0.59 VZV health care visits per 100 patient-years, or 0.46 ED/UC visits and 0.13 inpatient admissions per 100 patient-years (Table 2).

Seven of the 9 ED/UC visits, coded as chickenpox (9/138, 6.5%), occurred in PWH with a preexisting positive VZV serology and were recoded to the more likely diagnosis of HZ, as positive VZV-IgG serology is incompatible with primary VZV infection. None required admission. Most visits were coded as related to HZ (167/176, 94.9%), with two-thirds having uncomplicated zoster (118/176, 67%). One-quarter of hospitalizations were due to laboratory-confirmed zoster meningitis/encephalitis (9/38, 23.7%) (Figure 1).

Five of the 43 inpatient admissions identified by ICD-9 or ICD-10 codes as being VZV associated were excluded as a double clinician review deemed the code incorrect/misclassified. Four hospital admissions coded similarly to the above as primary varicella were reassessed as HZ upon chart review. Thirteen hospital admissions could not be reviewed due to missing documentation, and for these the VZV-related ICD code was assumed correct as the most responsible diagnosis.

Risk Factors for ED Visits and Hospitalization for VZV Infection

Patients missing data on risk factors for VZV illness were excluded from the analysis (Table 2). Patients requiring hospital admission for VZV were more likely to be off ART (69% vs 36.2%; $P < .01$), to have a detectable HIV viral load (75.9% vs 23.1%; $P < .01$), and to have a lower mean CD4 count (210 vs 522/mm^3; $P < .01$) (Table 2). PWH requiring only an ED/

Table 2. Characteristics of Health Care–Attended VZV Visits by All Unique Patients Followed at the Southern Alberta Clinic Between 1/1/2000 and 12/31/2020

	No Health Care–Attended VZV Visits[a]	Any VZV Inpatient Admission[a]	Any VZV ED/UC Visit[a]	*P* Value (Any VZV Inpatient Admission vs No Health Care–Attended VZV)	*P* Value (Any VZV ED/UC Visit vs No Health Care–Attended VZV)[b]
No. of unique patients[c]	2883	29	104		
Positive VZV serology before event, No. with data (% of those with data)	2513/2628 (95.6)	21/23 (91.3)	81/85 (95.3)	.54	>.99
On ARV at visit or admission, No. with data (% of those with data)	1839/2883 (63.8)	9/29 (31.0)	42/104 (40.4)	<.01	<.01
Suppressed viral load <50 before event, No. with data (% of those with data)	2156/2805 (76.9)	7/29 (24.1)	47/104 (45.2)	<.01	<.01
CD4 count before event, median (IQR)[d]	503 (285–522)	175 (158–210)	290 (202–321)	<.01	<.01

Abbreviations: ARV, antiviral; ED, emergency department; IgG, immunoglobulin G; IQR, interquartile range; UC, urgent care; VZV, varicella-zoster virus.

[a]For those with no health care–attended VZV, values represent the latest on record during the study period. For those with inpatient admissions or ED/UC visits, values represent the latest on record before the first admission or ED/UC visit, respectively.

[b]*P* value indicated is for chi-square testing for proportions (VZV seropositivity, ARV use, viral load suppression) and *t* test for mean CD4 count.

[c]Total number of unique patients is >3006 (ie, 3016) as some patients had >1 ED/UC visit or hospital admission.

[d]Forty-one patients with no health care–attended VZV (1.4%) were missing CD4 data and were excluded from analysis. No patients with inpatient admissions or ED/UC visits were missing CD4 data.

UC visit for VZV had higher rates of current ART use, undetectable viral loads, and higher CD4 counts than those requiring admission (Table 2). Those with the most severe form of VZV-related illness in the form of meningitis or encephalitis had similar rates of ART adherence (44.4%) and viral load suppression (33.3%) but significantly lower mean CD4 counts than patients requiring ED/UC visits (129/mm^3 vs 321/mm^3; $P < .01$). Patients with inpatient or ED/UC visits for VZV were no more likely to be seronegative than those without VZV illness during the study period ($P > .99$). Most patients were <50 years old when requiring ED/UC or in patient care for VZV infection (101/123), with a mean and median age of 41 years.

The median length of admission for hospitalized patients was 7.5 days. Of the 38 admissions, 19 had a length of stay ≤1 week: 7 visits were between 8 and 14 days, and 12 lasted >2 weeks. Seven of 29 patients with inpatient admissions had >1 VZV-related admission compared with 21 of 104 patients with ED/UC visits having >1 ED/UC visit for VZV. No deaths were attributed to VZV in the study period.

Costs of VZV Illness Requiring Hospitalization

Patient-specific costs were available in 36/38 hospital admissions. The 2 remaining admissions accompanying the HIV diagnosis were 1-day admissions and were costed as per an ED/UC visit. The total costs, not adjusted for inflation, incurred by these 38 admissions, were CDN$1 046 939. This represents an average of CDN$27 551 per admission and CDN$3517 per 100 patient-years in our study. Adjusted for inflation, this represents CDN$1 189 092 in total costs or an average of CDN$31 292 per admission. The 138 ED/UC visits resulted in CDN$69 626 in estimated costs during the study period after adjustment for inflation or CDN$234 per 100 patient-years in our study.

DISCUSSION

We documented a VZV seropositivity rate of 95% among PWH in Southern Alberta. This is similar to the 97%–98% seropositivity seen in earlier studies of PWH populations and higher than some reports of 78%–94% VZV seropositivity in the general population [25–30]. As seen in a report in the Dutch adult general population, we also found that immigrant status was predictive of VZV seronegativity [29]. Given that primary VZV infection in adults carries a 25-fold higher mortality than in children, our findings show that ∼3.9% of our adult PWH remain at risk for chickenpox, supporting the ongoing need for VZV screening and primary immunization of PWH at intake, as recommended by the latest guidelines from the HIV Medicine Association of the Infectious Diseases Society of America [31, 32].

The uptake of both live and conjugate vaccines for HZ has been studied in PWH, with 1 study having examined live zoster vaccine uptake and subsequent HZ incidence and among PWH in the US Military. They reported low vaccine uptake, with only 11% of patients being immunized, and further vaccine uptake of 3.4% following HZ [15]. Low vaccine uptake has been suggested to be related to limited provider awareness regarding the higher rates of VZV incidence in PWH, unclear practice guidelines surrounding vaccination in PWH, and provider confidence in PWH care [33]. Another possible contributor may be the sparsity of public funding for shingles vaccination in Canada, which imposes an additional economic burden on an already socially vulnerable population [10]. This is a very likely contributor in our study.

We noted that not taking ART, having a detectable HIV viral load, and having a lower CD4 count are major risk factors for both VZV-related hospitalizations and ED/UC visits. A gradient for these factors was noted, as worse markers were related to

increased risk of hospitalizations over an ED/UC visit. This is generally consistent with the published literature [15, 19]. Even among patients who did not experience VZV-related illness during the study period, there was a significant proportion of patients (37%) who were not actively on ART, illustrative of potential challenges with follow-up in our cohort of PWH that may pose an additional barrier to increasing HZ vaccine uptake. A recent large US retrospective cohort study using administrative health claims data in the general population suggested that recent COVID-19 infection may increase the risk of subsequent herpes zoster [34]. Although we did not assess for COVID-19 as a risk factor in this study, as none of our inpatient admissions or ED/UC visits occurred after March 2020, we do not anticipate that VZV incidence in our study was influenced by COVID-19.

All inpatient VZV-related admissions were due to HZ (ie, VZV reactivation), and none (after a 2-physician review) were due to primary varicella. We report an overall rate of 590 health care–attended VZV cases per 100 000 patient-years over 20 years of follow-up. A recent Canadian review of all incident HZ cases in the general population accessing any form of health care described a rate of 300–400 cases per 100 000 patient-years [35]. A similar rate in the general US population of 320 HZ cases per 100 000 patient-years was reported in a review of health claims data [18]. Our results clearly document the higher risk in PWH for severe HZ-*related* illness. We did not capture milder disease that might still be present in our population, which would expand the risk further [18, 20, 35]. Our results further emphasize the importance of optimal HIV care in controlling viral replication and normalizing CD4 counts.

Due to small numbers who received HZ vaccines, we cannot document their ability to reduce incidence or complications of VZV infection in PWH, and, while presumed, it requires further study. We note that, as reported by others, the age at presentation or our PWH was younger (median age, 41 years, with 82% presenting <50 years) compared with a median age of 59 typically seen in general population [14, 15, 19, 22]. This suggests that earlier timing of HZ immunization in PWH is appropriate [8, 9, 14]. Whether HZ will become more problematic with aging PWH remains unclear. Some have suggested age as a protective factor for HZ in PWH, although the reasons remain unclear [1, 2, 15]. Funding of HZ vaccination appears challenging, but documenting the potentially avoidable costs (>CDN$1 200 000 in hospital costs) may be an initial step in justifying the economic argument for funded zoster vaccines in PWH. Introduction of a publicly funded live zoster vaccination program in Ontario reduced the monthly rate of medically attended HZ by 19.1% and more severe disease (ED visits/hospitalization) by 38.2%, while a publicly funded VZV vaccine program in British Columbia caused a trend of rising HZ incidence to plateau [4, 7].

The limitations of our study include the geographically restricted nature of the study population; findings from our program may not reflect other populations of PWH with differing VZV immunization practices and seroprevalence or rates of ART adherence. We only were able to report serious VZV-related disease in the form of admissions or ED/UC visits and did not capture outpatient general practitioner visits for mild HZ, which may have underestimated incident HZ rates in our study compared with other epidemiologic studies. We were unable to measure the impact of longer-term morbidity and indirect costs of VZV infection such as post-herpetic neuralgia or long-term neurologic disability from VZV infection. We noted in 8/137 either VZV-seronegative or indeterminate serology but clinical illness compatible with zoster, and we assume that these cases most likely represent a previous infection but with antibody titers below the limit of detection. We were unable to assess the effect of timing of ART initiation and subsequent immune reconstitution on the incidence of VZV illness. We also could not identify if lack of HZ vaccination was due to patient refusal or not being offered free immunization, although historically vaccine hesitancy around free immunizations has seldom been a challenge. Lastly, we were unable to perform a formal cost-effectiveness analysis of zoster vaccination as our study was underpowered for this due to low numbers of PWH having received zoster vaccination.

Our study has several strengths. To our knowledge, this is the first large-scale study to describe over 2 decades VZV seroprevalence, immunization status, the incidence of serious VZV disease in PWH and associated costs. We also confirm the validity of most ICD codes using a 2-physician review. Due to the centralized nature of HIV care, data from a large number of highly characterized patients with >29 000 years of follow-up could be analyzed.

Despite widescale use of modern ART, our findings in a large cohort of PWH indicate that HZ still occurs more frequently and at an earlier age in PWH than the general population, causing both morbidity and significant costs to health care. The majority of PWH appear to be VZV seropositive and eligible for shingles vaccination. Despite availability of licensed vaccines for this population, they appear to be underutilized, thereby presenting a missed opportunity for improving care and minimizing health care costs. Further cost-effectiveness studies of shingles vaccination are warranted to address the continued burden of VZV and its complications in PWH.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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Patient consent. Study patients were never contacted directly, and individual patient consent was not required. Use of administrative data collected in this study is covered under University of Calgary Health Research Ethnics Board REB21-1494.

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