

Impact of Loneliness on Brain Health and Quality of Life Among Adults Living With HIV in Canada

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Background: People aging with HIV are at risk for loneliness, with stigmatization and economic marginalization added to the health challenges arising from chronic infection. This study provides evidence for the extent, contributors, and consequences of loneliness in people living with HIV, focusing on brain health and quality of life.

Setting: Cross-sectional data from 856 middle-aged and older adults living with HIV recruited from 5 urban specialty clinics in Canada were drawn from the inaugural visit of the Positive Brain Health Now cohort study.

Methods: Participants completed an extensive assessment of biopsychosocial variables. The prevalence, severity, and quality of life impact of self-reported loneliness were described. Clinical and environmental factors hypothesized as contributing to loneliness, and

the consequences of loneliness on health and function were identified using logistic, ordinal, and linear regression.

Results: Eighteen percent reported being “quite often” and 46% “sometimes” lonely. Those with more loneliness were younger, less mobile, suffered more financial hardship, and were more likely to use opioids. HIV symptoms, pain, fatigue, low motivation, stigma, and unemployment were related to loneliness. Loneliness increased the odds of cognitive impairment, low mood, stress, and poor physical health. Those who were “quite often” lonely were over 4 times more likely to report poor or very poor quality of life than those who were “almost never” lonely.

Conclusion: Loneliness is common in middle-aged and older people living with HIV in Canada. Many of the associated factors are modifiable, offering novel targets for improving brain health, general health, and quality of life in HIV.

Key Words: cognition, mental health, quality of life, loneliness, aging, HIV

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INTRODUCTION

Loneliness, defined as “a distressing discrepancy between desired and actual levels of social contact,” is increasingly recognized as an important determinant of health, including mental health, cognitive function, and quality of life.^{1–3} In the general population, loneliness has also been associated with physical health outcomes including stroke and heart disease.⁴ A recent meta-analysis found that loneliness was independently associated with a 26% increased likelihood of death over the subsequent 7 years.⁵ Loneliness might act through a variety of mechanisms, including stress-related immune effects⁶ and through behaviors such as smoking, alcohol use, or reduced physical activity.⁷ Loneliness may take a particular toll on brain health: population-based studies of middle-aged and older adults identify it as a risk factor for dementia, with effect sizes similar to well-established risks such as diabetes.⁷

In the general population, there are higher rates of loneliness in those living with a chronic illness.^{8,9} People living with HIV may be at even greater risk, due to additional stigma and socioeconomic marginalization.^{10,11} As survivors of a devastating epidemic, the social networks of those who have lived the longest with HIV might be especially fragile.¹²

Those living with HIV may also be more vulnerable to the negative effects of loneliness on health, with high background rates of smoking, substance use, and mental health comorbidities.¹³

As the infection is reframed as a chronic health condition, research and clinical care increasingly focus on optimizing quality of life of those living with HIV.¹⁴ In this context, long-term brain health is an important concern, with cognitive and mood symptoms still prevalent despite effective viral suppression. The causes of these brain health symptoms remain uncertain and to date have largely been approached

within a biological framework focused on viral, inflammatory, or drug toxicity effects.¹⁵ We have argued for a broader approach that also considers social experiences such as stigma, based in part on emerging evidence that social isolation may be toxic to the brain.^{16–18}

Whether the focus is on brain health or on quality of life, loneliness is an obvious target for intervention, yet surprisingly, few studies have assessed the prevalence or impact of loneliness among older people with HIV.^{11,13,19,20} The existing literature has mainly reported on the influence of loneliness on poor mental health (depression, alcohol, and

TABLE 1. Structure of the Measurement Model and List of the Measures Used in the Positive Brain Health Now Cohort Study

Characteristics of the Individual: Age, Sex, Race, Education, Economic Status, Smoking, Alcohol, Drug use								
Biological and Physiological Factors		Symptoms		Functional Status			Health Perception	Quality of Life (QOL)
HIV-Related	Comorbidities	Physical	Emotional	Cognitive Function	Physical Function	Role Participation		
CD4 count, viral load, current antiretroviral treatment, duration of HIV infection, AIDS-defining illness	Comorbid conditions C-reactive protein	HIV-related signs and symptoms Pain Vitality	Anxiety/depression Stress Motivation Emotional well-being	B-CAM PDQ	RAND PFI Physical activity Mobility	Work status Leisure activities	Health utility Perceived health status	Personalized QOL Health-related QOL (hrQOL) HIV-specific hrQOL

Characteristics of the environment: social support, stigma, quality of the environment

Economic status: Item from WHOQOL_HIV_BREF: *Have you enough money to meet your needs?* [5-point scale: “not at all” to “an extreme amount.”] Insufficient funds considered to be present if response “not at all.”

Smoking, alcohol, drug use: Are you a current smoker? Yes vs. no. How many alcoholic beverages do you usually drink per week? *Never drink vs. other (Only drink on special occasions, 1–2 drinks, 3–6 drinks, 7–14 drinks, >14 drinks).* In the past 3 months, have you used any of the following drugs? *Yes (occasionally or monthly; weekly; daily or almost daily) vs. no.*

Comorbid conditions: Charlson Comorbidity Index.

HIV signs and symptoms: Selected items from the Revised Sign and Symptom Check-List for HIV (SSC-HIVrev) including presence (vs. absence) and intensity (mild, moderate, and severe) of weakness, loose stools, diarrhea, dizziness, headaches, weight gain in the stomach area, hump on the back of neck/shoulders, skinny arms and legs, prominent leg veins, and numbness/tingling of feet/toes/legs/hands/arms.

Pain: RAND SF-36 subscale.

Vitality (ie, energy and fatigue): RAND SF-36 subscale.

Anxiety/depression: RAND SF-36 Mental Health Inventory (MHI) subscale.

Stress: Trier Inventory for the Assessment of Chronic Stress (TICS), scored from 0 (less stress) to 100 (more stress).

Motivation: Items from the Starkstein Apathy Scale: “Do you have plans and goals for the future?” “Are you interested in learning new things?” (“not at all,” “some,” or “a lot”).

Emotional well-being: RAND SF-36 MHI; WHO5-Wellbeing, scored from 0 (worse) to 100 (better).

Brief cognitive ability measure (B-CAM), a computerized battery of cognitive tests including: Corsi block task (forward and backward), Eriksen flanker task-incongruent reaction time, mini Trail Making Test B, letter fluency and recall of 8 words; B-CAM is scored from 0 (worse) to 40 (better).²¹

Perceived Deficit Questionnaire (PDQ) (cognitive symptoms), scored from 0 (better) to 100 (worse).

Physical functioning: RAND SF-36 Physical Functioning Index (PFI) subscale.

Physical activity: What best describes your physical activity in the past 6 months? “Vigorously active for at least 30 min, 3 times per week”, “Moderately active at least 3 times per week”, “Seldom active, preferring sedentary activities.” Hours per week from CHAMPS Physical Activity Questionnaire: *Which of the following physical activities do you do regularly (at least 20 minutes per week)? (Light or heavy housework; light, moderate, or heavy vigorous activities) If yes, how many hours in a typical week (rounded up to the closest hour)?*

Mobility: Item from WHOQOL-HIV-BREF: “In the last 2 weeks, how well are you able to get around?” *Very poor, poor, neither poor nor good, good, very good.*

Work status includes working, volunteering, and/or studying.

Leisure activities: Item from CHAMPS Physical Activity Questionnaire: *Which of the following recreational activities do you do regularly (at least 20 minutes per week)? (Checking email, surfing the internet, work or games on the computer, crafts, and hobbies) If yes, how many hours in a typical week (rounded up to the closest hour)?*

Health utility: EuroQol-5D (EQ-5D), utility score from 0 (death) to 1 (perfect health).

Perceived health status: EQ-5D Visual analogue scale (VAS), from 0 (worst possible) to 100 (best possible); Short-Form Six-Dimension Health Index (SF-6D), scored from 0 (worse) to 1 (better).

Personalized Quality of Life (QOL): Patient Generated Index (PGI)²⁹ higher scores indicate better QOL.

Health-related QOL (HRQL): RAND SF-36.

HIV-specific HRQL: WHOQOL-BREF-HIV, including domains for physical health, psychological, level of independence, social relationships, environment, and spirituality/religion/personal beliefs.

Social support: Item from OARS Social Resource Scale,²² *How many people do you know well enough to visit in their homes?* “5 or more,” “3 to 4,” “1 to 2,” “none.”

Stigma: Item from WHOQOL-BREF-HIV: To what extent are you bothered by people blaming you for your HIV status? (5-point scale: “not at all” to “an extreme amount”) Stigma considered present if response “very much” or “an extreme amount.”

Quality of the environment: WHOQOL-BREF-HIV Environment Subscale: *How safe do you feel in your daily life? How healthy is your physical environment? Have you enough money to meet your needs? How available to you is the information that you need in your day-to-day life? To what extent do you have the opportunity for leisure activities? How satisfied are you with the conditions of your living place? How satisfied are you with your access to health services? How satisfied are you with your transport? (5-point scale: “not at all” to “an extreme amount”).*

substance use).^{11,13,19} Limited, conflicting data are available regarding potential effects on cognitive function among older adults living with HIV,^{13,20} and downstream effects on quality of life have been little studied. The purpose of this study is to estimate the extent to which loneliness has associations with characteristics of the individual and the environment, brain health and general health outcomes, and quality of life among middle-aged and older adults living with HIV in Canada. Understanding potential contributors to loneliness can identify targets for intervention; identifying the potential consequences of loneliness will motivate those interventions.

METHODS

Study Population and Design

The data for this study came from the inaugural visit of people enrolled in the Positive Brain Health Now cohort,¹⁶ a multisite Canadian study aimed at assessing brain health (including both cognition and mental health), understanding the factors contributing to brain health, and intervening to optimize brain health in adults living with HIV. Eligible participants were over 35 and had been diagnosed with HIV for at least a year. Those with clinically evident dementia (ie, incapable of informed consent), active central nervous system opportunistic infection, non-HIV-related neurological disorder likely to affect cognition, psychotic disorder, or substance use disorder within the previous 12 months were excluded. Participants were enrolled from 5 urban HIV outpatient clinics in Montreal, Toronto, Hamilton, and Vancouver, Canada. The study was approved by the Research Ethics Board of each participating institution, and all participants provided written informed consent. A well-established biopsychosocial model of health-related quality of life known as the Wilson–Cleary Model²¹ was used as the measurement framework for the Positive Brain Health Now cohort,¹⁶ assuring systematic consideration of potentially relevant variables in this study. The model provides a structured approach to studying quality of life in multifactorial health conditions, systematically considering variables starting with basic biological factors, then clinical symptoms, then function, health perception, and finally quality of life. The model also includes individual characteristics, such as demographic variables, and characteristics of the environment, such as socioeconomic factors.

Measures

Data were collected from personal interviews, direct measurements, self-report questionnaires, and chart review. The measures used in this study, organized according to the rubrics of the Wilson–Cleary model, are listed in Table 1, and have been described in detail elsewhere.²² Loneliness was assessed directly by one item from the widely-used Older Americans Resources and Services (OARS) Social Resource Scale²³ (item 5) “Do you find yourself feeling lonely: quite often, sometimes, or almost never?”

Statistical Analysis

Although this cross-sectional study cannot establish the direction of effects, a priori some factors were hypothesized to contribute to loneliness and others to be consequences of loneliness, to structure the analysis and interpretation. Broadly, we supposed that demographic (eg, age and gender), environmental (eg, socioeconomic factors), and biological (eg, HIV infection indicators) variables were likely to contribute to loneliness, while cognition, mental health, and quality of life were likely to be consequences of loneliness. Descriptive analyses on these variables are presented as mean values and SDs or proportions, as indicated. In accordance with current guidelines from the American Statistical Association, this article does not present *P*-values or refers to findings as “statistically significant.”²⁴

Variables hypothesized to contribute to loneliness were analyzed using proportional odds regression. The regression parameters from this model yield summary odds ratios (ORs) and 95% confidence intervals (CI) across the 3 ordinal responses to the loneliness item.

Variables representing the potential consequences of loneliness were measured on continuous scales, but not all were normally distributed. For normally distributed

TABLE 2. Prevalence of Loneliness According to Demographic and HIV-Related Variables

Potential Contributors	Do You Find Yourself Feeling Lonely?		
	Quite Often Mean (SD) or N (%)	Sometimes Mean (SD) or N (%)	Almost Never Mean (SD) or N (%)
No. of participants (row %)	146 (17.5%)	383 (45.9%)	305 (36.6%)
Age (y)*	51.3 (7.8)	52.5 (8.1)	54.4 (8.5)
Sex			
Women	24 (18.9%)	65 (51.2%)	38 (29.9%)
Men	122 (17.3%)	318 (45.0%)	267 (37.8%)
University education	47 (32.2%)	120 (31.6%)	110 (36.9%)
Insufficient funds*†	53 (36.8%)	71 (18.7%)	22 (7.3%)
Years with HIV	16.6 (7.8)	16.2 (8.1)	17.6 (7.6)
AIDS defining illness	84 (18.0%)	210 (45.7%)	164 (36.4%)
Nadir CD4 (cells/mm ³)	226.8 (204.3)	205.8 (151.1)	220.4 (170.9)
CD4 (cells/mm ³)	649.8 (316.4)	637.4 (283.9)	624.4 (259.1)
Viral load: >50 copies/mL	12 (8.6%)	32 (8.7%)	23 (7.8%)
C-reactive protein (mg/L)	5.6 (12.2)	4.2 (7.3)	4.2 (5.8)

*Variables that show meaningful differences (95% CI of OR excludes 1) across categories of loneliness.

†Item from WHOQOL_HIV_BREF: Do you have enough money to meet your needs? Response: Not at all.

outcomes, ordinary least squares regression was used, and the measure of association was the regression coefficient (β); a 95% CI that excludes the null value of 0 indicates an association beyond noise. When the normality assumptions did not hold, the outcome was categorized into quartiles (ordinal levels) or binary levels, and proportional odds regression or logistic regression models were used, yielding proportional ORs (PORs) or OR, respectively. The strength of the evidence is shown by the magnitude of the POR or OR and that the 95% CI excludes the null value of 1.0. All comparisons were made with models adjusted for age, sex, and education.

RESULTS

Between October 9, 2013, and June 8, 2016, 856 participants were enrolled. Of these, 834 answered the loneliness question during their baseline visit and were included in this analysis. The majority were men ($n = 707$, 85%) and white ($n = 560$, 73%). The mean age was 53 years

(SD: 8.3). There was a small proportion (1%–10%) of missing data on other variables.

Table 2 presents demographic and HIV-related characteristics according to the extent to which people endorsed the question “Do you find yourself feeling lonely?” Almost 18% of the sample said they “quite often” felt lonely, and an additional 46% said they were “sometimes” lonely. The proportions of women across categories of loneliness (19%, 51%, and 30%) did not differ from the proportions of men reporting comparable levels of loneliness (17%, 45%, and 38%). Of the variables in Table 2, only age and insufficient funds showed evidence of a difference (defined as a 95% CI of the OR, which excludes 1.0) across categories of loneliness. Unexpectedly, older age was associated with a lower likelihood of being “quite often” lonely (OR: 0.74 per 10 years of age; 95% CI: 0.63 to 0.87). Reporting “not at all” having enough money to meet needs (vs. “a little,” “moderately,” “mostly,” or “completely”) was associated with reporting loneliness “quite often” (OR: 3.75; 95% CI: 2.61 to 5.38).

TABLE 3. Distribution of Potential Contributors to Loneliness Across Levels of Loneliness

Potential Contributors (0–100; Higher Is Better unless Otherwise Stated)	Do You Find Yourself Feeling Lonely?			POR (95% CI)
	Quite Often Mean (SD) or N (%)	Sometimes Mean (SD) or N (%)	Almost Never Mean (SD) or N (%)	
No. (%) of participants	146 (17.5%)	383 (45.9%)	305 (36.6%)	
Lung disease	34 (23.3%)	89 (23.2%)	49 (16.1%)	1.45 (1.05 to 2.00)
HIV symptoms				
Average number/10	5.1 (2.4)	4.6 (2.5)	3.8 (2.5)	1.17 (1.11 to 1.23)
Severity (0–30)	8.6 (5.3)	7.0 (4.7)	5.8 (4.6)	1.09 (1.06 to 1.12)
Stigma*	30 (20.7%)	51 (13.4%)	18 (6.0%)	2.27 (1.51 to 3.42)
<5 close people†	104 (71.2%)	195 (51.1%)	91 (29.8%)	3.01 (2.28 to 3.97)
Lives alone	92 (63.0%)	196 (51.4%)	106 (35.1%)	2.26 (1.72 to 2.96)
Motivation‡:				
Plans and goals				
None vs a lot	33 (23.4%)	36 (9.8%)	21 (7.2%)	4.01 (2.51 to 6.42)
Some plans	75 (53.2%)	186 (50.7%)	133 (45.6%)	1.83 (1.37 to 2.45)
Interest in learning new things				
None vs. a lot	8 (5.7%)	9 (2.4%)	3 (1.0%)	3.73 (1.58 to 8.81)
Some vs. a lot	61 (43.6%)	155 (40.9%)	107 (35.2%)	1.37 (1.04 to 1.80)
RAND pain (≤ 61)§	58.3 (25.7)	63.2 (24.3)	71.5 (24.3)	1.59 (1.21 to 2.10)
RAND vitality (≤ 54)	37.4 (20.0)	51.5 (20.8)	63.5 (20.8)	4.34 (3.27 to 5.83)
RAND PFI (≤ 45)¶	74.6 (24.3)	81.1 (20.0)	85.6 (19.9)	2.13 (1.35 to 3.37)
Ability to get around#				
<Good vs very good	89 (87.9%)	187 (57.6%)	97 (54.5%)	4.77 (2.56 to 8.87)
Good vs. very good	55 (12.1%)	193 (42.4%)	207 (45.5%)	2.20 (1.65 to 2.92)
Not employed**	79 (54.9%)	187 (49.7%)	123 (41.0%)	1.73 (1.31 to 2.28)
Environment†† (/10)	57.0 (16.8)	68.9 (15.3)	78.5 (13.6)	1.77 (1.61 to 1.94)

All variables show meaningful differences (95% CI of OR excludes 1) across categories of loneliness. Proportions are calculated within levels of loneliness.

*Item from WHOQOL-HIV-BREF: To what extent are you bothered by people blaming you for your HIV status? (Answer: very much or an extreme amount). Modeled as 5 levels.

†Item from OARS Social Resource Scale: How many people do you know well enough to visit in their homes?

‡Items from Starkstein Apathy Scale.

§Pain modeled at median split.

||Vitality modeled at median split.

¶PFI (Physical function) modeled at cut point used to indicate frailty.

#Item from WHOQOL-HIV-BREF: In the last 2 weeks, how well are you able to get around? (Answer: very poor, poor, neither poor or good, good, very good).

**Not employed includes not working, volunteering, or studying.

††WHOQOL-HIV-BREF Environment Subscale; POR is per 10 units worse environment.

POR, proportional OR.

Table 3 presents the distribution of potential contributing factors to loneliness across the different categories of loneliness. In this table, the outcome is the ordinal variable loneliness. Each factor was modeled using the proportional odds model, and adjusted POR and the 95% CI are given. All variables in this table showed evidence of the hypothesized relationship with loneliness (ie, the 95% CI of the POR excludes 1.0). In terms of the directionality of observed associations, it is hypothesized that specific comorbidities and HIV-related symptoms, HIV-related stigma, restricted social network, lack of motivation, pain, fatigue, limited physical function, and not working, volunteering, or studying were all contributors to loneliness (Table 3). A poor-quality environment (as measured by the WHO-QOL-BREF Environment subscale), reflecting the physical health and safety of the home, financial resources and access to health services, information, leisure activities, and transport, was also identified and is likely a contributor to loneliness.

Table 4 presents lifestyle factors that were hypothesized to be consequences of loneliness. For each potential consequence, the mean value or prevalence across categories of loneliness is presented, along with the estimate of association (POR and OR), with “almost never” as the referent category. All measures of association are presented with estimates and 95% CI. Participants who reported “almost never” being lonely had more hours of physical activity than people who reported that they were “quite often” lonely. The association with fewer hours of physical activity and “quite often” feeling lonely (POR: 2.16; 95% CI: 1.50 to 3.11) held even after adjusting for mobility (not shown). This same magnitude of effect was observed for reporting being seldom active (OR: 2.27; 95% CI: 1.55 to 3.33). The only other lifestyle variable with evidence of being influenced by loneliness was opioid use (prescribed and nonprescribed opioids combined) (OR: 3.12; 95% CI: 1.52 to 6.41 for “quite often” lonely), and this effect held after being adjusted for pain.

Table 5 summarizes results of analyses on the potential health consequences of loneliness. Similar to Table 4, mean values or prevalence across categories of loneliness are presented, along with the estimate of association (β , POR, and OR) and associated 95% CI. In comparison with “almost never” feeling lonely, feeling lonely “sometimes” or “quite often” was consistently associated with poorer outcomes, including those reflecting cognitive ability {both measured with cognitive tests [Brief Cognitive Ability Measure (B-CAM)] and self-reported cognitive symptoms (PDQ)}, stress, depression, and anxiety, and those reflecting health-related quality of life and overall quality of life. For example, among people reporting “almost never” being lonely, the mean B-CAM score was 20.8 (SD 4.7), while those reporting more frequent loneliness had lower scores ($\beta_{\text{quite often}}$: -2.53; 95% CI: -3.45 to -1.61; $\beta_{\text{sometimes}}$: -1.58; 95% CI: -2.28 to -0.88). A difference of 2–3 points on the B-CAM is likely to be clinically relevant; for example, this is the difference in score between people in paid employment and those who are doing volunteer work (Brouillette et al, unpublished observations). Similarly, there were more self-reported cognitive symptoms among participants reporting more frequent lone-

TABLE 4. Potential Consequences of Loneliness for Lifestyle Choices

Potential Consequences	Do You Find Yourself Feeling Lonely?		
	Quite Often Mean (SD)/N (%) POR† or OR‡ (95% CI)	Sometimes Mean (SD)/N (%) POR† or OR‡ (95% CI)	Almost Never Mean (SD)/N (%) POR† or OR‡ (95% CI)
No. (%) of participants	146 (17.5%)	383 (45.9%)	305 (36.6%)
Hours/week physical activity*	6.8 (7.6)	8.1 (8.5)	9.8 (10.1)
POR (95% CI)†	2.16 (1.50 to 3.11)	1.30 (0.99 to 1.72)	Referent
Hours/week television	18.6 (17.0)	15.4 (17.7)	14.6 (11.2)
POR (95% CI)†	1.25 (0.87 to 1.81)	0.86 (0.65 to 1.13)	Referent
Hours/week computer	25.2 (37.3)	26.3 (30.6)	27.4 (30.7)
POR (95% CI)†	0.78 (0.54 to 1.13)	0.93 (0.70 to 1.22)	Referent
Seldom active*,‡	55 (37.9%)	84 (22.1%)	60 (19.9%)
OR (95% CI)‡	2.27 (1.55 to 3.33)	1.21 (0.91 to 1.61)	Referent
Current smoker	58 (40.0%)	118 (31.3%)	85 (28.2%)
OR (95% CI)‡	1.44 (0.94 to 2.22)	1.04 (0.73 to 1.46)	Referent
Risky alcohol consumption§	7 (4.8%)	21 (5.6%)	7 (5.8%)
OR (95% CI)†	1.00 (0.40 to 2.54)	1.11 (0.56 to 2.20)	Referent
Marijuana	53 (35.8%)	132 (35.0%)	107 (35.8%)
OR (95% CI)‡	0.97 (0.64 to 1.48)	0.96 (0.69 to 1.32)	Referent
Opioid use vs. none*	21 (14.8%)	39 (10.4%)	15 (5.1%)
OR (95% CI)‡	3.12 (1.52 to 6.41)	1.98 (1.06 to 3.73)	Referent

*Variables that show meaningful differences (95% CI of OR excludes 1; highlighted in bold) across categories of loneliness.

†POR (proportional OR) modeled on quartiles of the outcome: the proportional odds of a worse outcome compared with the referent group (“almost never” lonely).

‡OR from logistic regression: the odds of a worse outcome compared with the referent group (“almost never” lonely).

§Defined as 14 or more drinks per week.

ness. Many of the variables shown in Table 5 were strongly influenced by loneliness, with PORs greater than 10.0.

Finally, Figures 1 and 2 illustrate the widespread effects of loneliness on components of health-related quality of life (RAND-36, Fig. 2) and HIV-specific health-related quality of life (WHOQOL-BREF-HIV, Fig. 3). There were clear associations between loneliness and all aspects of health-related quality of life. Figure 3 provides a summary of key observed associations, organized by the hypothesized relationships as contributors to and consequences of loneliness.

TABLE 5. Potential Consequences of Loneliness for Brain Health, General Health, and Quality of Life Outcomes

Potential Consequences (Higher Is Better unless Otherwise Stated)	Do You Find Yourself Feeling Lonely?		
	Quite Often Mean (SD) or N (%) β †, POR‡ or OR§ (95% CI)	Sometimes Mean (SD) or N (%) β †, POR‡ or OR§ (95% CI)	Almost Never Mean (SD) or N (%) Referent
No. (%) of participants	146 (17.5%)	383 (45.9%)	305 (36.6%)
Cognitive ability			
B-CAM (0–40)*	18.5 (4.6)	19.3 (4.6)	20.8 (4.7)
β (95% CI)†	−2.53 (−3.45 to −1.61)	−1.58 (−2.28 to −0.88)	Referent
POR (95% CI)‡	2.38 (1.62 to 3.51)	1.80 (1.34 to 3.51)	Referent
PDQ (0–100 worst)*	43.9 (18.8)	35.5 (16.4)	27.6 (16.4)
POR (95% CI)‡	5.62 (3.82 to 8.27)	2.35 (1.77 to 3.11)	Referent
Stress TICS (0–100 worst)*	48.6 (19.7)	36.4 (18.3)	25.8 (16.0)
POR (95% CI)‡	7.66 (5.16 to 11.37)	2.87 (2.15 to 3.82)	Referent
Mental health			
RAND MHI (0–100)*	47.7 (18.7)	64.8 (17.7)	79.4 (15.2)
POR (95% CI)‡	20.14 (13.20 to 30.73)	4.32 (3.21 to 5.83)	Referent
Depression risk (<60)*	106 (73.6%)	126 (33.0%)	34 (11.2%)
OR (95% CI)§	20.26 (12.05 to 34.07)	3.68 (2.41 to 5.60)	Referent
General health			
WHO5-Wellbeing (0–100)*	37.5 (20.7)	56.4 (20.4)	69.5 (18.7)
POR (95% CI)‡	13.29 (8.85 to 19.96)	3.37 (2.52 to 4.52)	Referent
RAND-36*			
Excellent or very good	36 (24.7%)	172 (45.0%)	187 (61.3%)
Good	72 (49.3%)	155 (40.6%)	89 (29.2%)
Fair or poor	38 (26.0%)	55 (14.4%)	29 (9.5%)
POR (95% CI)‡	4.43 (3.0 to 6.51)	1.78 (1.34 to 2.37)	Referent
VAS (0–100)*	67.2 (16.9)	74.9 (15.8)	80.8 (14.0)
POR (95% CI)‡	4.93 (3.37 to 7.23)	2.03 (1.53 to 2.69)	Referent
Health-related QOL			
EQ-5D utility (0–1)*	0.70 (0.19)	0.81 (0.15)	0.88 (0.14)
POR (95% CI)‡	8.31 (5.57 to 12.40)	3.06 (2.28 to 4.09)	Referent
SF-6D (0–100)*	61.28 (10.77)	67.94 (10.92)	75.25 (12.41)
β (95% CI)†	−13.93 (−16.27 to −11.58)	−7.28 (−9.07 to −5.49)	Referent
Quality of life			
WHOQOL-BREF-HIV*			
Very good or good	55 (37.7%)	262 (68.6%)	273 (89.8%)
Neither poor or good	43 (29.5%)	93 (24.3%)	19 (6.3%)
Poor or very poor	48 (32.9%)	27 (7.1%)	12 (3.9%)
POR (95% CI)‡	4.43 (3.01 to 6.51)	1.78 (1.34 to 2.37)	Referent
PGI (0–10)*	4.44 (2.11)	5.26 (2.24)	6.00 (2.43)
POR (95% CI)‡	3.13 (2.15 to 4.56)	1.92 (1.44 to 2.55)	Referent

*Variables that show meaningful differences (95% CI of OR excludes 1) across categories of loneliness.

†Beta (β) and 95% CI from linear regression: the effect on outcome of a 1 category difference in loneliness.

‡POR (Proportional OR) modeled on quartiles of the outcome: the proportional odds of a worse outcome compared with the referent group.

§OR from logistic regression: the odds of a worse outcome compared with the referent group.

B-CAM, brief cognitive ability measure; MHI, Mental Health Index; PDQ, Perceived Deficits Questionnaire; PGI, Patient Generated Index (an individualized measure of quality of life); SF-6D, Short Form- 6 Dimensions; TICS, trier inventory for the assessment of chronic stress; WHO, world health organization; VAS, visual analogue scale.

DISCUSSION

As expected, loneliness was prevalent in this Canadian cohort of older HIV+ adults, with 64% experiencing loneliness “sometimes” or “quite often.” This agrees with a recent study of 356 people living with HIV in the United States with similar demographics (85% male, median age 56, urban) that found 58% of participants reporting at least mild loneliness.¹³ It is in stark contrast to the general Canadian population, where older adults report less loneliness than in other

countries.²⁵ A recent report from the community-based Canadian Longitudinal Study on Aging found that only 10.2% of Canadians aged 45–85 years reported persistent loneliness.⁹ This suggests that middle-aged and older people living with HIV in Canada are facing substantially greater social adversity than what might be expected due to aging alone.

The prevalence of loneliness was very similar in men and women in our sample. Participants with more loneliness

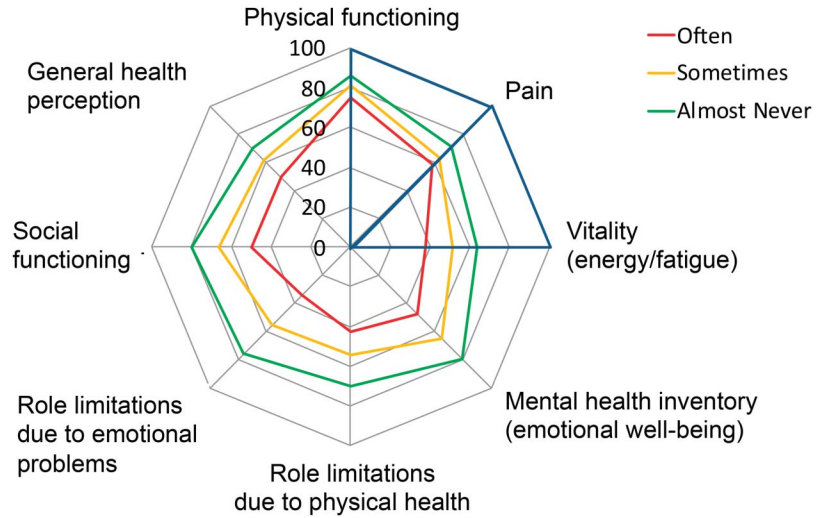


FIGURE 1. Radar plot showing the mean ratings of components of health-related QOL (assessed with the Rand 36) according to the degree of loneliness (often lonely, sometimes lonely, and almost never lonely). The shaded blue quadrant indicates factors hypothesized to contribute to loneliness; unshaded quadrants are hypothesized consequences.

did not differ from those with less loneliness with respect to HIV disease severity, indicated by current viral load or nadir CD4 count. Unexpectedly, those who endorsed being “almost never” lonely were older than those who reported more loneliness. This is in contrast to the general population, where loneliness in those middle-aged or older tends to increase with age.⁹ We cannot address the mechanism underlying this observation but speculate that this may reflect survivor bias: The oldest members of this cohort are most likely to have lived with HIV in the pre-highly active antiretroviral therapy era, when being part of resilient social networks (or perhaps being personally resilient to more restricted social networks) may have been vital to survival. In keeping with other work in HIV and in general, poverty was more frequent in those who reported more loneliness.^{9,13,25}

This study permitted a comprehensive examination of factors hypothesized as potential contributors to loneliness. Multiple factors, physical, cognitive, social, and environmental, were identified as increasing the odds of loneliness. These included symptoms of HIV infection and presence of comorbidities, particularly those that could limit mobility (lung disease and peripheral neuropathy), or that might visibly mark the person as being seropositive (lipodystrophy).

This is consistent with a previous longitudinal study among adults aged 50–68 years in the general population that showed that physical inactivity was independently associated with loneliness.²⁶ Greater self-reported fatigue, pain, and lower motivation also had important influences on loneliness in this study, emphasizing the protective effect of physical well-being on social functioning. Self-reported HIV stigma and a small social network were both associated with loneliness, as expected, as were practical constraints on the social environment, such as living alone or being unemployed, consistent with previous literature in older HIV+ adults¹³ and in the general population.⁸

Loneliness had wide-ranging consequences on lifestyle, cognition, mental health, and quality of life. Although smoking, alcohol, and marijuana use did not differ in those endorsing higher and lower loneliness, those with more loneliness were more likely to report opioid use, whether recreational or prescribed. Opioid use might contribute to loneliness through side effects such as apathy, lethargy, and fear of criticism.²⁷ The association held even after adjustment for physical pain, raising the possibility that opioids are being used to address psychological pain. However, this association should be treated as preliminary as there was relatively little

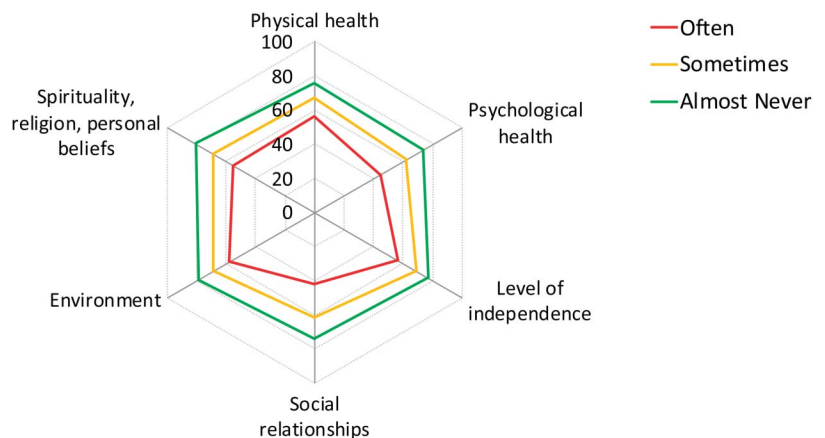


FIGURE 2. Radar plot showing the mean ratings of components of HIV-specific health-related quality (QOL) (assessed with WHOQOL-BREF-HIV) according to the degree of loneliness (often lonely, sometimes lonely, and almost never lonely).

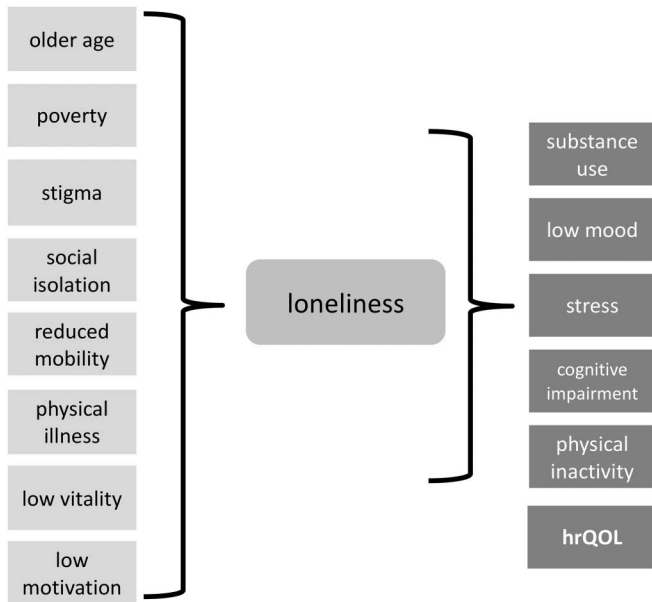


FIGURE 3. Summary of factors showing meaningful associations with level of loneliness, structured according to hypothesized contributors (left column: Demographic, environmental, and clinical variables) and consequences [right column: Brain health variables, function, and health-related quality of life (hrQOL)] to loneliness.

opioid use reported in the sample as a whole, reflecting the cohort exclusion criterion of active substance use disorder.

The cohort from which these data were drawn was designed to study brain health and therefore included comprehensive self-report and performance measures of cognition and extensive questionnaire assessment of mood symptoms. All these measures were affected by loneliness. Social experience changes the brain¹⁸; we therefore hypothesized mood symptoms and cognitive dysfunction as consequences of loneliness. The mental health consequences of loneliness included greater stress, anxiety, and depression, consistent with other studies of people living with HIV.^{1,11,19,28} Although loneliness had the largest effect on mental health outcomes, it also increased the odds of cognitive symptoms and of poorer performance on cognitive tests. The cognitive ability of those almost never lonely was about half a SD better than those quite often lonely, a difference likely to be clinically meaningful. Loneliness has been associated with age-related cognitive decline in the general population^{2,29} and among older Black adults living with HIV in the United States.²⁰

Our results also demonstrate that loneliness and its consequences had extensive downstream negative effects on self-rated health, health-related quality of life, and overall quality of life. These findings were consistent across the several validated quality of life instruments used in this study, including the Patient-Generated Index, measuring personalized quality of life.³⁰

This study has strengths, including the large, well-characterized sample and the use of an established biopsychosocial model to structure the analysis. The results provide

a rich description of the associations between loneliness and variables running the gamut from physical and cognitive symptoms to socioeconomic factors and show the impact of loneliness on key patient-centered outcomes including brain health, general health, and quality of life.

Loneliness was assessed with a single direct question in this study. This is a widely used and valid approach, but there are alternatives that may provide complementary information.³¹ Social conditions such as the quality of the environment and the experience of stigmatization were assessed only by self-report, and with only a few (albeit well-established and widely used) items. Thus, more work is needed to fully understand the experience of loneliness in people growing older with HIV and to define the environmental and social factors that contribute. Qualitative approaches or more detailed questionnaires will be helpful in this regard; some work in this vein has been undertaken already.^{11,13,19,32} The sample is primarily composed of relatively well-educated white men, reflecting the demography of the participating clinics. The results may not generalize to more diverse or less-educated samples. Both men and women showed similar levels of loneliness, but we lacked the power to test for interactions by gender in the associations we report. More focused work will be needed to further assess gender-specific considerations.

A priori, we conceptualized some variables as likely to contribute to loneliness, and others to be consequences of loneliness. However, these cross-sectional data do not allow directionality to be inferred. It is possible that some of the variables we propose as contributors are in fact consequences, and vice versa. Indeed, some might be classified as both, with vicious cycles emerging as, for example, mobility limitations reduce the opportunities for social interaction with the ensuing loneliness in turn worsening stress, cognition, and mental health, reducing the capacity to address mobility limitations. Longitudinal data are needed to determine the direction of the observed associations. Studies testing interventions that address loneliness will be particularly important, both for identifying underlying mechanisms and showing the most promising approaches to alleviating loneliness.

Such work could target loneliness directly, for example, by promoting social engagement or, indirectly, by addressing hypothesized contributors to loneliness, such as stigma. The multiple factors shown to be relevant in this study argue that interventions simultaneously addressing multiple targets may be needed. Existing work has shown, for example, that there are complex interactions between stigma, social isolation, and depression in people with HIV.^{10,11,33} Finally, interventions to promote social engagement in older adults living with HIV will need to overcome some of the environmental barriers identified here, such as impaired mobility and economic precarity.

In summary, we find that loneliness is common among older adults living with HIV in Canada and markedly higher than the prevalence among the general population of a similar age. We also show that loneliness has widespread negative impact on outcomes of high relevance to people living with HIV. Alleviating loneliness may provide a high-yield route to improving general health, mental health, and cognition, and in turn, quality of life. We identified a range

of loneliness-associated variables that are potentially modifiable. There is also some evidence from work in other populations that loneliness itself is a tractable intervention target. The influence of HIV-associated stigma on loneliness in this Canadian sample is a stark reminder of the persistent societal exclusion faced by those with this infection, despite the major advances in controlling the biological impact of the virus. Interventions to address loneliness must engage people living with HIV, as well as their family, friends, and colleagues. Indeed, society at large has an important responsibility in addressing this major challenge to health and quality of life.

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