Cervical Cancer Screening for women living with HIV in the Canadian HIV Women's Sexual and Reproductive Health Cohort Study (CHIWOS)

Running title: Cervical cancer screening in CHIWOS

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ABSTRACT

Background: Women with HIV experience an elevated risk of cervical cancer compared to HIV-negative women. In Canada, annual cervical cancer screening (CCS) by Pap test is recommended for women after HIV diagnosis. We explore adherence to current national CCS guidelines among women with HIV in three Canadian provinces and identify potential strategies for CCS improvement.

Methods: Data were obtained from the baseline survey of the Canadian HIV Women's Sexual and Reproductive Health Cohort Study (CHIWOS). Women were included if they were cisgender female, aged 21-70, and never had cervicectomy/hysterectomy. Multinomial logistic regression assessed independent correlates of self-reported suboptimal adherence to CCS guidelines.

Results: Of 1189 eligible participants, 68.5% received CCS <1 year ago (i.e. as recommended), 17.7% 1-3 years ago (i.e. moderate delay), and 13.7% ≥3 years ago or never (i.e. long delay). Overall, 26.0% never discussed the need for Pap test with a nurse/doctor. Factors associated with a long delay were living in Ontario [adjusted odds ratio (AOR) 2.51, 95% confidence interval (CI):1.29-4.88) or Quebec (AOR 3.70, 95%CI:1.79-7.67) (vs British Columbia); being sexually inactive in the past 6 months (AOR 2.02, 95%CI:1.25-3.25), unknown or <200 cells/mm^3 CD4 counts (AOR 1.78, 95%CI:1.11-2.85) and having a male HIV care provider (AOR 2.15, 95%CI:1.36-3.42).

Interpretation: Awareness of CCS recommendations should be improved for women with HIV in Canada. In addition to known predictors of delays in Pap testing (including sexual inactivity and poor engagement in HIV care) we found significant differences by province of residence and gender of her HIV care provider.

Introduction

An estimated one-quarter of all people living with HIV in Canada are women (1). Women with HIV experience a 5-24 times greater risk of invasive cervical cancer compared to HIV-negative women,(2-4) primarily driven by persistent high-risk human papillomavirus (HPV) infection.(5-7) Cervical cancer has been an AIDS-defining condition since 1993.(8-10) It is the 16th leading cause of death among women in Canada,(11) but the 3rd leading cause of death among women in low-income countries,(12) which are often regions with the greatest burden of HIV.(13)

Cervical cancer is largely preventable with routine cervical cancer screening (CCS) (Pap tests) and HPV vaccination.(14, 15) Since the introduction of Pap tests, cervical cancer incidence decreased dramatically in Canada and has stabilised since 2006 at 7-8 per 100,000 women.(11) Canadian guidelines recommend yearly cervical cytology for women with HIV and do not consider HPV co-testing in this population.(16-20) In United States, recommendations were recently modified to increase CCS intervals to every 3 years following three consecutive Pap tests with normal results, and included consideration of HPV co-testing, where available, for women with HIV above 30 years of age.(21, 22)

Previous studies using chart reviews have reported that women with HIV in high-income countries are insufficiently screened for cervical cancer, with estimates ranging from 29-58% of women being screened in the previous 1-3 years.(23-26) Higher HIV viral load and lower CD4 counts were associated with lower adherence to screening recommendations.(25)

Our primary objectives were to measure the prevalence of self-reported adherence to CCS amongst women with HIV in Canada, and to identify factors associated with CCS delays. A secondary objective was to identify participants' reasons for not receiving CCS according to length of delay in order to inform future care interventions.

METHODS

Study design

The Canadian HIV Women's Sexual and Reproductive Health Cohort Study (CHIWOS, www.chiwos.ca) is a prospective study of women with HIV (n=1422), grounded in community-based research principles.(27, 28) Eligible participants self-identified as women with HIV, 16 years or older, and residing in British Columbia, (BC) Ontario, or Quebec. The study was reviewed and approved by the Community Advisory Committee of the Canadian Institutes of Health Research - Canadian HIV Trials Network, and by the Research Ethics Boards of Simon Fraser University, University of BC Providence Health, Women's College Hospital, and McGill University Health Centre. Participants provided written and voluntary informed consent.

For the present analysis, we used data from the baseline questionnaire completed between August 2013 and May 2015. Trained peer research associates (women with lived experience with HIV who underwent research training) administered online questionnaires in English or French using FluidSurveys™ software. Interviews were conducted in-person at collaborating HIV clinics, AIDS service or community organizations, and in women's homes, or by phone or Skype for participants living in rural areas. Median survey completion time was 120 minutes [IQR: 90, 150]. We restricted the analysis to women eligible for CCS, i.e. who identified as cisgender females, aged 21-70 years. We excluded women who self-reported the removal of their cervix or hysterectomy, answered "don't know" or "prefer not to answer", or did not respond to the two questions on Pap testing.

The primary outcome was delay in CCS (either a moderate delay, i.e. reporting their last Pap test was 1-3 years ago, or a long delay, i.e. reporting their last Pap test was at least 3 years ago or never) compared to the recommended interval based on current Canadian guidelines. Two

questions were asked based on those from the Canadian Community Health Questionnaire.(29) Women were asked: "*Have you ever had a Pap test? a) yes; b) no; c) don't know; d) prefer not to answer.*" Women who answered yes were then asked "*When, approximately, was the last time you had a Pap test? a) less than 6 months ago; b) 6 months to less than 1 year ago; c) 1 year to less than 3 years ago; d) 3 years to less than 5 years ago; e) 5 years ago or more; f) don't know; g) prefer not to answer*."

Potential correlates for time since last Pap test included characteristics related to socio-demographic factors (age, education, ethnicity, household yearly income, city size and province of residence); sexual and reproductive health (sexual orientation, relationship status, sexual activity in previous 6 months, experience of sexual violence, having children, menopause status, use of hormonal birth control); self-reported markers of general health (smoking, drug use, body mass index, CD4 count, HIV viral load, antiretroviral therapy, general health); and, factors related to health care services (HIV medical care, gender and specialty of HIV care provider, location of clinic, travel time from residence to clinic, and whether Pap tests were offered at their HIV clinic). The use of a hormonal contraceptive method included the birth control pill, hormonal intrauterine device, patches, implants, rings, or injections.

Statistical analysis

Descriptive statistics (median and interquartile range (IQR) for continuous variables and n (%) for categorical variables) were used to characterize distributions of study variables, with 95% confidence intervals (95%CI) when pertinent. Multinomial regression analyses were conducted using a three-category outcome based on timing since last Pap test: less than one year ago (reference category, recent testing); between 1 and 3 years ago (moderate delay); and at least 3 years ago or never (long delay). For the analyses including variables on characteristic of health care, only women who had accessed HIV care in the last year were included. A multivariable

model was built retaining age by default, but other variables were included if unadjusted analyses revealed significant association for one of the outcome categories at p <0.20. Variables were then removed if they did not improve in significance or did not alter the significance of other variables. Knowledge of whether the clinic offered Pap tests was discarded from multivariable model because of concerns regarding reverse causality. Data were analysed with Stata version 11.2 (StataCorp LLC, College Station, Texas, USA).

RESULTS

A total of 1422 women completed the baseline interview. Of these, 233 were excluded from this analysis: 57 did not identify as cisgender female; 29 were aged <21 or >70; 98 had a cervicectomy; 36 had a hysterectomy; and 13 did not provide an answer to the CCS questions. This yielded a final analytical sample of 1189 women. The median age was 42 (IQR:35-50), 40% identified as White, 31% as African, Caribbean or Black, and 22% as Indigenous (**Table 1**). Most (95%) received HIV medical care in the previous year, 83% were taking combination antiretroviral therapy, and 77% reported their most recent HIV viral load was undetectable (<50 copies/mL).

Women reported their last Pap test was less than one year ago for 68.5% (95%CI:65.8-71.1), between 1 to 3 years ago for 17.7% (95%CI:15.6-20.0), between 3 to 5 years ago for 4.8% (95%CI:3.7-6.2), 5 years ago or more for 4.6% (95%CI:3.5-6.0) and 4.3% (95%CI:3.2-5.6) never had a Pap test.

Characteristics associated with delays in Pap testing

Several socio-demographic and HIV clinical care variables were associated with delays in Pap testing in unadjusted analyses (**Figure 1**). "Not knowing whether Pap tests were offered at

the HIV clinic" (OR 2.12, 95%CI:1.40-3.24 for 1-3 years ago, i.e. moderate delay; OR 3.54, 95%CI:2.31-5.44 for at least 3 years or never, i.e. long delay) and "Not having accessed HIV care in the last year" (OR 3.64, 95%CI:1.99-6.68 for moderate delay; OR 3.34, 95%CI:1.71-6.52 for long delay) showed the strongest associations.

In the adjusted model (**Table 2** and **Figure 2**), women had higher odds of a moderate delay in CCS if they were living in Ontario (adjusted odds ratio (AOR) 2.28, 95% CI:1.35-3.87) or if their HIV provider was a man (AOR 1.69, 95%CI:1.15-2.49). They had lower odds of a moderate delay if they identified as African, Caribbean or Black ethnicity (AOR 0.47, 95%CI:0.29-0.77) or if they were in a relationship (AOR 0.62, 95%CI:0.42-0.93). Women had higher odds of a long delay if they were living in Ontario (AOR 2.51, 95%CI:1.29-4.88) or Quebec (AOR 3.70, 95%CI:1.79-7.67), were sexually inactive (AOR 2.02, 95%CI:1.25-3.25), had unknown or less than 200 cells/mm^3 CD4 counts (AOR 1.78, 95%CI:1.11-2.85) and if their HIV provider was a man (AOR 2.15, 95%CI:1.36-3.42).

Reasons for Pap test delay

When participants were asked if a doctor or nurse ever discussed with them the need for regular Pap tests, 25.7% (306/1189, 95%CI:23.3-28.3) answered "no". This proportion rose to 57.1% (64/112, 95%CI:47.4-66.5) for women who previously had a Pap test but at least 3 years ago, and to 72.5% (37/51, 95%CI:58.3-84.1) for women who never had a Pap test. The most common self-reported reason for not having a Pap test in the past 12 months (women could select multiple answers) was "not getting around to it" (47%, 174/374), followed by "not thinking it was necessary" (38%, 142/374), "disliking having the procedure done" (20%, 74/374), "my health care provider has never mentioned it" (19%, 72/374) and "fear" (14%, 54/374, included fear of pain, embarrassment, HIV disclosure or finding something wrong). Reporting "not getting

around to it" was less common among women with long delays (36%, 58/163 versus 55%, 116/211 respectively), whereas the opposite was observed for "disliking having the procedure done" (25%, 41/163 versus 16%, 33/211 respectively) and "fear" (19%, 31/163 versus 11%, 23/211 respectively) (**Figure 3**).

Sub-analyses to examine interprovincial differences

Pap testing in the past year was reported by 81.1% (95%CI:76.1-85.4) of participants living in BC, 63.1% (95%CI:59.1-66.9) of participants living in Ontario and 67.3% (95%CI:61.7-72.7) of participants living in Quebec. To examine interprovincial differences, post-hoc analyses were conducted. In BC, 114 of the 288 included participants attended an HIV clinic for women with HIV and their families located in a provincial women's health hospital. There is no similar clinic in Quebec or Ontario. We stratified British Columbian women according to their HIV clinic and found that 93.0% (95%CI:86.6-96.9) of women followed at the clinic located in the women's health hospital reported a Pap test in the past year, compared to 74.1% (95%CI:67.0-80.5) for women of BC followed elsewhere, and 66.9% (95%CI:63.5-70.2) for women in Ontario and Quebec (combined).

Interprovincial differences were also identified when applying the adjusted model to women stratified by provinces. The gender of the HIV provider had no effect in Quebec, while having a male HIV provider strongly increased odds of long delay in BC (AOR 5.97, 95%CI:1.77-20.21) and of both moderate (AOR 1.79, 95%CI:1.02-3.14) and long delays in Ontario (AOR 2.18, 95%CI:1.12-4.67).

INTERPRETATIONS

In this large, cross-sectional analysis of Canadian women living with HIV, 68.5% of women self-reported having a Pap test within the preceding year, as recommended by current Canadian CCS guidelines.(16-20) Moderate delays were not uncommon with 17.7% reporting their last Pap test occurred 1-3 years ago. Among women who accessed HIV care in the previous year, women with moderate delays tended to live in Ontario; identify with an ethnicity other than African, Caribbean, or Black; be in a relationship; and have a male HIV provider. Long delays (i.e. ≥ 3 years or never), reported by 13.7%, were more common among women living in Ontario or Quebec, who were sexually inactive, who did not know or reported lower CD4 counts, and who reported their HIV provider was a man.

More than a quarter of participants reported that a nurse or doctor had never discussed with them the need for regular CCS (73% for women who had never had a Pap test). As previously reported in the general population, providers have a crucial role to play in the adherence to CCS recommendations(30) and our results underline the importance of better communicating the need for CCS to women with HIV. The specialty of the HIV provider as reported by participants did not change the odds of adherence to CCS. Others previously reported that women with HIV receiving care from a gynaecologist or family physician had increased receipt of Pap tests(24, 31-33), but when looking at the specialty of the HIV provider specifically, another study reported an absence of effect.(34) Our finding could also be due to misclassification of the specialty by participants. However, the gender of the HIV provider did affect delays in CCS, particularly in BC and Ontario. This finding may be due to a combination of male provider prioritizing different issues and women feeling uncomfortable having a gynaecological exam done by a man, especially if they have a history of sexual abuse or violence/trauma, as many women with HIV do.(35)

Being in a relationship and sexually inactive increased likelihood of CCS delays, as previously reported by others.(36, 37) Explanations on HPV-related cancers need to specify that the risk remains even if a woman is no longer sexually active, since decades can pass between an initial HPV infection and the development of cervical cancer. The effect direction of ethnicity differs widely in the literature, but the impact of lower CD4 counts on CCS adherence was previously reported by others.(38, 39). We hypothesize that multiple competing health or social priorities probably leads to postponing of preventive care. Although we could not explain interprovincial differences, results from women attending the women's HIV clinic within a women's hospital showed the benefit of their approach for CCS adherence.

There are many strengths to our analysis, including that the CHIWOS survey incorporated questions assessing multiple aspects and factors influencing receipt of CCS, incorporating both patient and health care system variables. The questionnaires were created and piloted by both women with HIV and medical experts.(40) CHIWOS is the largest Canadian cohort of women with HIV, and 81% of all women with HIV in Canada reside in the three participating provinces. Nevertheless, our study has limitations. Time since last CCS was measured using self-report, which may underestimate delays due to telescoping bias (i.e. women underestimating the time since the test occurred), which has been identified by others when compared to medical records.(41) Measurement via interview might also have underestimated delay via social desirability bias. Our questions on providers were specific to HIV providers. We did not ask whether participants received care from a primary care physician other than their HIV provider.

Our results confirm the need to improve delivery of CCS for women with HIV in Canada, and indicate multiple opportunities to do so. Women with HIV first need to access HIV care as lower immunity increases their risk for HPV persistence and development of cancers.(4-6) Once in care, discussions on CCS benefits need to occur regularly. More sensitive behaviour and

attention to patient's comfort by the Pap test performer can strongly impact the experience of patients, and ensuing adherence with screening recommendations. Being aware that women with HIV experience disproportionate rates of violence (35, 42) and providing trauma informed care(43), may also improve women's care experience. In circumstances where performing a Pap test is problematic for either the provider or the patient, potential solutions may include office/schedule organisation(23, 44); systematic reminders(45, 46); collaboration with a nurse, female colleague, family physician or gynaecologist to provide CCS; or offering self-sampling.(24, 31, 47) HIV care providers should facilitate awareness and access to CCS for all women with HIV.

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Figure 1: **Unadjusted correlates of self-reported time since the most recent Pap test among HIV-positive women, Canadian HIV Women's Sexual and Reproductive Health Cohort Study, 2013-2015**

Footnote: * Indicates analyses restriced to women who received HIV care in previous year (n=1129). BC British Columbia; ART antiretroviral therapy; IDU Injection Drug User; ID Infectious Disease Specialist; LGBTTQ Lesbian, Gay, Bisexual, Trans, Two Spirit, Queer; ACB African, Caribbean, Black.

Figure 2: **Adjusted correlates of self-reported time since the most recent Pap test among HIV-positive women who accessed HIV care in previous year (n=1129), Canadian HIV Women's Sexual and Reproductive Health Cohort Study, 2013-2015**

Footnote: BC British Columbia; ACB African, Caribbean, Black; IDU Injection Drug User; ART antiretroviral therapy.

Figure 3: **Reasons for not having Pap test in last 12 months according to different delays, Canadian HIV Women's Sexual and Reproductive Health Cohort Study, 2013-2015**

Table 1

Cervical cancer screening in CHIWOS

Table 1: Baseline characteristics of participants from the Canadian HIV Women's Sexual and Reproductive Health Cohort Study (CHIWOS) included in these analyses

Characteristic	Frequency N = 1189 N (%)
Age at interview date (years)	
21-34	271 (22.8%)
35-49	612 (51.5%)
50-70	306 (25.7%)
Province of residence	
British Columbia	291 (24.5%)
Ontario	604 (50.8%)
Québec	294 (24.7%)
Place of birth	
Canada	748 (62.9%)
Africa	307 (25.8%)
Caribbean	62 (5.2%)
Other	72 (6.1%)
Ethnicity	
Indigenous	256 (21.5%)
ACB	371 (31.2%)
White	478 (40.2%)
Other	84 (7.1%)
Size of city of residence	
Small (<30 000 population)	71 (6.0%)
Medium (30 000 - 99 999 population)	139 (11.7%)
Large (100 000 population or more)	979 (82.3%)

Table 1

Cervical cancer screening in CHIWOS

Education level	
Less than High school or Don't know / Prefer not to answer	181 (15.2%)
High school or higher	1008 (84.8%)
Household gross yearly income	
< 20 000 CAN$	738 (62.1%)
≥ 20 000 CAN$	418 (35.2%)
Smoking status	
Current/Occasional smoker	503 (42.3%)
Former smoker	140 (11.8%)
Never smoked	540 (45.4%)
Injection drug use	
Current user	99 (8.3%)
Former user	262 (22.0%)
Never used	808 (68.0%)
Time since HIV diagnosis (years)	
< 6	298 (25.1%)
6-14	466 (39.2%)
> 14	386 (32.5%)
Received HIV medical care in the last year	1129 (95.0%)
Currently taking combination antiretroviral therapy	981 (82.5%)
Most recent HIV viral load is undetectable	915 (77.0%)
Answers to the question: "Did a doctor or a nurse ever discussed the need for regular Pap tests?"	
Yes	880 (74.0%)
No or don't know	309 (26.0%)

Table 1

Cervical cancer screening in CHIWOS

Time since last Pap tests	
< 1 year	815 (68.5%)
1 to < 3 years	211 (17.7%)
3 to < 5 years	57 (4.8%)
5 years or more	55 (4.6%)
Never had a Pap test	51 (4.2%)

Note: totals do not always add up to 1189 because of missing values.

Table 2 – Correlates of self-reported time since the most recent Pap test among HIV-positive women who received HIV care in the last year, Canadian HIV Women's Sexual and Reproductive Health Cohort Study, 2013-2015 (multivariable model, n=1129)

Characteristic	n	Time since last Pap test				
		0 – 1 year (ref. cat.) (n = 791)	1 – 3 years (n = 190)		At least 3 years or never (n = 148)	
		Row %	Row %	OR (95%CI)	Row %	OR (95%CI)
Total	1129	70.1	16.8	Not applicable	13.1	Not applicable
Socio-demographics						
Province of residence	1129					
British Columbia	288	81.6	11.1	Reference	7.3	Reference
Ontario	556	64.9	21.6	**2.28 (1.35, 3.87)**	13.5	**2.51 (1.29, 4.88)**
Quebec	285	68.4	13.3	1.81 (0.99, 3.33)	18.3	**3.70 (1.79, 7.67)**
Age	1129					
21-49 years old	829	71.9	16.4	Reference	11.8	Reference
50-70 years old	300	65.3	18.0	1.35 (0.88, 2.06)	16.7	1.54 (0.96, 2.48)
Ethnicity	1129					
White	464	67.7	19.6	Reference	12.7	Reference
Indigenous	226	67.7	18.6	1.34 (0.82, 2.21)	13.7	1.43 (0.80, 2.57)
African, Caribbean or Black	357	76.2	10.6	**0.47 (0.29, 0.77)**	13.2	0.66 (0.37, 1.15)

Table 2 Cervical cancer screening in CHIWOS

Other	82	63.4	23.2	1.23 (0.65, 2.31)	13.4	1.27 (0.57, 2.82)
Education level [1]	1129					
High school or higher	954	70.0	18.0	Reference	12.0	Reference
< High school	175	70.3	10.3	0.56 (0.30, 1.05)	19.4	1.56 (0.90, 2.71)
Habits & Lifestyle						
Injection drug use [1]	1111					
Never	769	69.3	17.7	Reference	13.0	Reference
Former	253	74.3	15.4	0.73 (0.45, 1.19)	10.3	0.71 (0.39, 1.31)
Currently	89	67.4	13.5	0.87 (0.39, 1.93)	19.1	1.73 (0.80, 3.75)
Relationship status[1]	1121					
Single/ Separated / Divorced / Widowed	753	70.0	16.1	Reference	13.9	Reference
Legally married / Common-law / In a relationship	368	70.1	18.5	**0.62 (0.42, 0.93)**	11.4	0.70 (0.43, 1.12)
Had consensual sex in last 6 months[1]	1023					
Yes	517	75.6	15.7	Reference	8.7	Reference
No	506	64.4	18.8	1.26 (0.84, 1.87)	16.8	**2.02 (1.25, 3.25)**
Health & Medical History						
Have children	1129					
Yes	764	73.7	14.1	Reference	12.2	Reference
No	365	62.5	22.5	1.34 (0.92, 1.97)	15.1	1.18 (0.74, 1.86)
Most recent CD4 (self-report) (cells/mm3)	1127					
> 200	893	71.4	17.7	Reference	10.9	Reference
< 200 or Don't know / Prefer not to answer	234	65.4	13.3	0.79 (0.49, 1.29)	21.4	**1.78 (1.11, 2.85)**

Table 2 Cervical cancer screening in CHIWOS

Current Antiretroviral Therapy (ART) and HIV viral load[1]	1128					
Undetectable HIV viral load (below 50 copies/mL)	906	71.9	16.1	Reference	12.0	Reference
Taking ART but detectable HIV viral load (above 50 copies/mL)	119	61.3	19.3	1.53 (0.84, 2.76)	19.3	1.55 (0.82, 2.91)
Not currently on ART and detectable or unknown HIV viral load	103	65.1	19.4	0.73 (0.45, 1.19)	15.5	1.51 (0.77, 2.97)
Using a type of hormonal birth control method in past 6 months[1]	1127					
No	1001	68.4	17.5	Reference	14.1	Reference
Yes	126	83.3	11.1	0.53 (0.27, 1.03)	5.6	0.55 (0.24, 1.27)
Gender of primary HIV doctor in past year [1]	1119					
A woman	472	80.5	12.1	Reference	7.4	Reference
A man	647	62.6	20.6	**1.69 (1.15, 2.49)**	16.9	**2.15 (1.36, 3.42)**

[1] Participants who answered "Don't know" or "Prefer not to answer" were excluded from analyses.

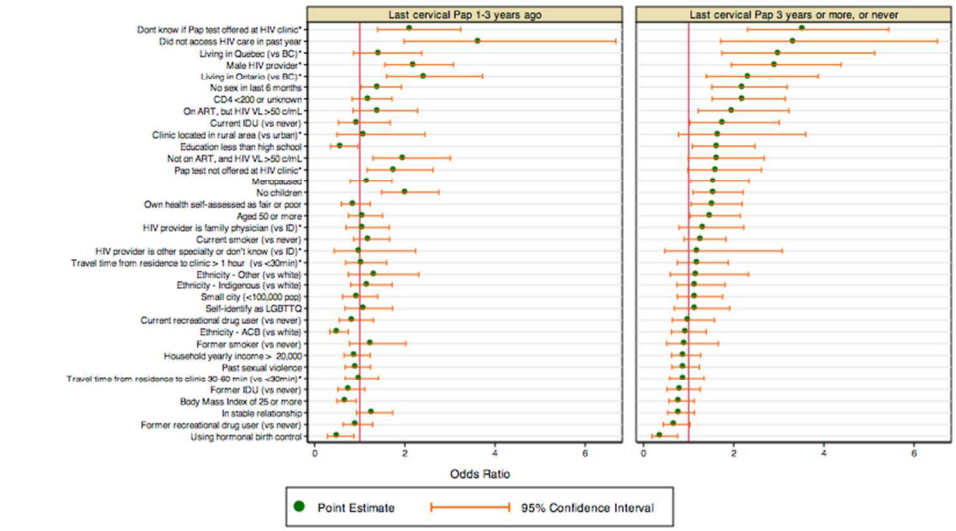

Figure 1: Unadjusted correlates of self-reported time since the most recent Pap test among HIV-positive women, Canadian HIV Women's Sexual and Reproductive Health Cohort Study, 2013-2015

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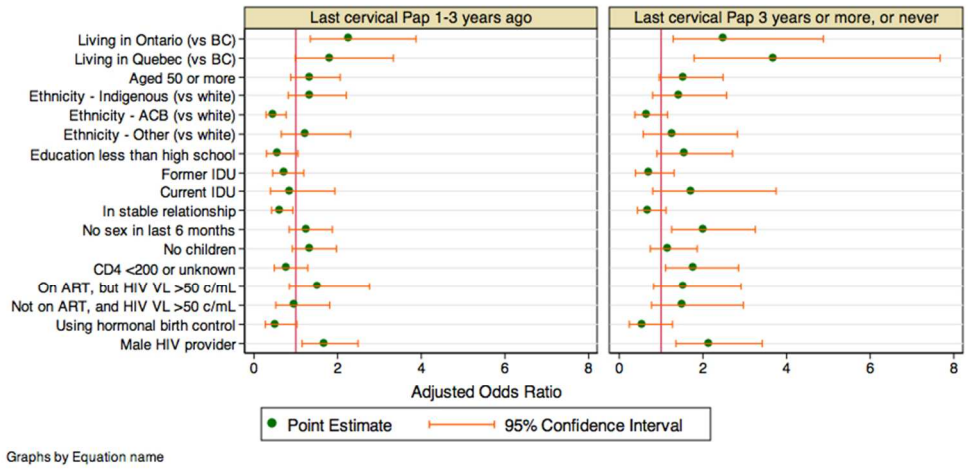

Figure 2: Adjusted correlates of self-reported time since the most recent Pap test among HIV-positive women who accessed HIV care in previous year (n=1129), Canadian HIV Women's Sexual and Reproductive Health Cohort Study, 2013-2015

Footnote: BC British Columbia; ACB African, Caribbean, Black; IDU Injection Drug User; ART antiretroviral therapy.

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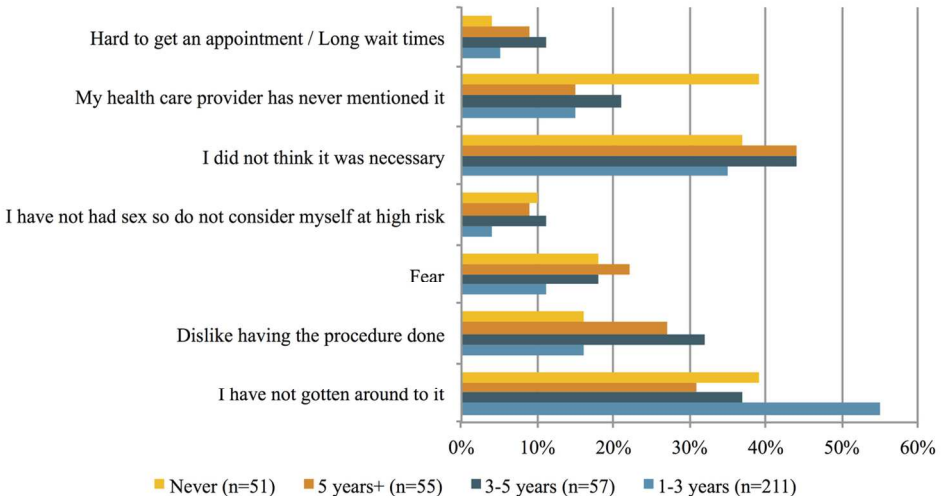

Figure 3: Reasons for not having Pap test in last 12 months according to different delays, Canadian HIV Women's Sexual and Reproductive Health Cohort Study, 2013-2015

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