Final version published as:
Puskas CM, Kaida A, Miller CL, Zhang W, Yip B, Pick N, Montaner JS, Hogg RS. The adherence gap: a longitudinal examination of men's and women's antiretroviral therapy adherence in British Columbia, 2000-2014. *AIDS*. 2017 Mar 27;31(6):827-833. doi: 10.1097/QAD.0000000000001408.

The adherence gap: a longitudinal examination of men's and women's antiretroviral therapy adherence in British Columbia, 2000–2014

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Objective: The aim of this study was to observe the effect of sex on attaining optimal adherence to combination antiretroviral therapy (cART) longitudinally while controlling for known adherence confounders – IDU and ethnicity.

Design: Using the population-based HAART Observational Medical Evaluation and Research cohort, data were collected from HIV-positive adults, aged at least 19 years, receiving cART in British Columbia, Canada, with data collected between 2000 and 2014. cART adherence was assessed using pharmacy refill data. The proportion of participants reaching optimal ($\geq$95%) adherence by sex was compared per 6-month period from initiation of therapy onward. Generalized linear mixed models with logistic regression examined the effect of sex on cART adherence.

Results: Among 4534 individuals followed for a median of 65.9 months (interquartile range: 37.0–103.2), 904 (19.9%) were women, 589 (13.0%) were Indigenous, and 1603 (35.4%) had a history of IDU. A significantly lower proportion of women relative to men were optimally adherent overall (57.0 vs. 77.1%; $P < 0.001$) and in covariate analyses. In adjusted analyses, female sex remained independently associated with suboptimal adherence overall (adjusted odds ratio: 0.55; 95% confidence interval: 0.48–0.63).

Conclusion: Women living with HIV had significantly lower cART adherence rates then men across a 14-year period overall, and by subgroup. Targeted research is required to identify barriers to adherence among women living with HIV to tailor women-centered HIV care and treatment support services.

Introduction

Adherence to combination antiretroviral therapy (cART) is essential to the maintenance of health for people living with HIV (PLWH) [1] and to reduce individual and community viral load, keeping with the goals of treatment as prevention [2]. Although the specific level of adherence required to decrease mortality, viral rebound, and drug resistance varies by medication and treatment regimen, higher levels of adherence have overwhelmingly been linked with better health outcomes, including the prevention of HIV transmission among serodiscordant sex partners [1,3].

The past decade has seen a global increase in the prevalence of HIV among women [4]. In North America

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DOI:10.1097/QAD.0000000000001408

and in other resource-rich settings, the same sex and structural inequities that result in vulnerability to HIV infection among women may result in increased vulnerabilities to poor HIV-related health outcomes among women living with HIV [5]. Even with favorable clinical results initially, women have shown worse health outcomes over time than men living with HIV [6] and disproportionately exhibit suboptimal cART adherence, regardless of the type of cART [7]. In comparison with men living with HIV, studies have shown that women have lower use of primary care services and higher use of the emergency department [8], lower quality of initial HIV care [9], and an increased risk of death, even when controlling for cART use [10]. These disparities may be exacerbated among certain subpopulations, including people who inject drugs (PWID) and ethnic minorities, including Indigenous people in Canada [11,12]. Canada's history of colonization, including the forced separation of families via the residential school system, the '60s scoop', and the resultant multigenerational trauma, has had direct and indirect impacts on the myriad of health outcomes experienced by Indigenous people [13]. Even after controlling for such potential confounding characteristics, poorer clinical outcomes among women living with HIV have been observed [6].

The current study was undertaken within a population-based cohort in British Columbia, Canada, where cART is universally available and offered free of charge to PLWH. Our objectives were to determine the effect of sex on cART adherence over time while adjusting for two known predictors of suboptimal adherence, IDU, and Indigenous ancestry [12,14]. The study is unique in that it examines sex differences in cART adherence longitudinally in a large population-based cohort without the limitation of financial barriers to treatment while accounting for IDU status, ethnicity, and elapsed time from initiation of therapy.

Methods

The current study is based upon HIV-positive individuals in British Columbia, Canada, enrolled in the HAART Observation Medical Evaluation and Research (HOMER) cohort. Established in 1996, HOMER is a population-based cohort of antiretroviral-naïve HIV-positive adults who have initiated a HAART regimen of at least three medications [15]. On initiation of antiretroviral therapy (ART) in British Columbia, individuals are automatically enrolled in the provincial Drug Treatment Program. At initial prescription refill, informed consent for the use of medical and sociodemographic data is requested; with refusal in no way limiting access to ART or medical care [16]. Prescription refill compliance was based on medication dispensation dates. Sociodemographic information, based on self-report, was collected at entry into HOMER. Clinical data are collected on an ongoing basis and is based on physician or laboratory record. In British Columbia, HAART is provided free of charge within a universal healthcare system and distributed to eligible individuals according to established guidelines that were updated regularly over the study period (2000–2004, 2005–2008, and 2009 onwards) [17]. Ethical approval for the HOMER cohort and this study has been provided through University of British Columbia and Simon Fraser University Offices of Research Ethics.

Analyses were limited to individuals in HOMER who were at least 19 years of age and had accessed HAART for a minimum of 6 months between 1 January 2000 and 31 December 2014. Individuals were excluded from this study if they self-identified as transgender or had a prescribed treatment interruption. Transgender individuals were excluded due to small sample sizes ($n = 39$) and as they would experience unique barriers to optimal ART adherence. Individuals who had initiated HAART prior to 2000 were excluded because of changes in antiretroviral medications and guidelines, specifically the use of fixed-dose combination HAART after 2000 [18].

Optimal adherence to cART, defined as at least 95%, was the main outcome variable. Adherence was assessed for 6-month periods, with an individual considered optimally adherent for the period if the number of days for which they have been dispensed medications divided by the number of days between prescription refills was equal to or greater than 95%. For example, in a 6-month period or 183 days, an individual may be 7 days late to fill their prescription. In this case, adherence would be calculated by dividing 176 (the period for which the individual has medications) by 183, resulting in optimal adherence with medication coverage for 96.2% for the period. This study included adherence measurements from initiation of cART from January 2000 until the end of December 2014 or the date of last contact with the patient, which could include loss from care, movement from the province, or death. Prescription refill compliance has previously been validated as a reliable measure of cART adherence, using an adherence cutoff of at least 85% [19]. Despite the ability to predict virologic failure with lower adherence cutoffs, the adherence cutoff of at least 95% was used in this study for the sake of comparability, as it is the most frequently used adherence cutoff [20].

The main explanatory variable of interest was sex (female vs. male). Additional explanatory variables included self-reported Indigenous ancestry (Indigenous vs. non-Indigenous), history of injection drug use (yes vs. no), and year of cART initiation grouped according to innovations in cART and treatment guideline revisions (2000–2004, 2005–2008, and 2009–2014) [18]. Additional explanatory sociodemographic and psychosocial variables were not included in our analysis,

as only limited sociodemographic information was collected with HOMER.

Chi-squared tests were used to assess differences in the proportion of women and men who met the criteria for optimal adherence for each 6-month period and to compare the mean proportion of individuals attaining optimal adherence over 90 months of follow-up. These analyses were conducted on the study sample as a whole and also among covariates, injection drug use status, and Indigenous ancestry, as women were more likely to belong to these subgroups; within the Canadian context, Indigenous women are overrepresented in the HIV epidemic, and a high proportion of women report IDU as a transmission category [21].

A generalized linear mixed model using a logistic link function was used to examine sex as an independent predictor of suboptimal adherence, adjusting for injection drug use, Indigenous ancestry, MSM, age, and the period in which cART was initiated. The logistic model included data up to 90 months of follow-up, within the 2000–2014 period. Statistical analyses were completed using SAS version 9.3 (SAS; Cary, North Carolina, USA) with a level of significance set at 0.05.

Results

The sample comprised 4534 individuals, of whom 904 (19.9%) were women. A total of 273 (4.4%; 16.1% women) individuals were excluded from the study due to accessing cART for a period of less than 6 months. Of the 4534 individuals, 2502 (55.2%) had an unknown history of injection drug use and 2381 (52.5%) had unknown Indigenous ancestry.

A larger proportion of women than men identified as being of Indigenous ancestry (28.7 vs. 9.1%; $P < 0.001$) and having a history of injection drug use (55.3 vs. 30.4%; $P < 0.001$) (Table 1). The study population had a median time on therapy of 65.9 months (interquartile range: 37.0–103.2 months), with similar proportions of men and women who started therapy early enough to allow 90 months of observation for this study (75.4 vs. 72.3%; $P = 0.205$). Of note, a significantly larger proportion of women experienced mortality during the study period (15.9 vs. 11.6%; $P < 0.001$); however, in multivariate analysis (not shown), sex was not found to be independently associated with mortality [adjusted odds ratio (AOR): 0.99; 95% confidence interval (CI): 0.89–1.09]. Cause of death did not differ substantially between men and women (not shown).

Table 2 shows the mean proportion of men and women who attained optimal adherence over the full 90-month study period. Women were significantly less likely to be optimally adherent than men overall (57.0 vs. 77.1%; $P < 0.001$) and within stratified analyses. The largest difference between men and women was observed among non-Indigenous individuals who do not have a history of injection drug use (69.9 vs. 83.8%; $P < 0.001$). Of note, the proportion of women with lower vulnerability (no history of injection drug use or non-Indigenous ancestry) was found to be similar in adherence to the proportion of men with higher vulnerability (history of injection drug use or Indigenous ancestry) (Figs. 1 and 2).

Table 1. Characteristics and mortality within the study population (HAART Observational Medical Evaluation and Research), 2000–2014 ($n = 4534$; women = 904, men = 3630).

Sociodemographic characteristics	Women: *n* (%) or median (IQR)	Men: *n* (%) or median (IQR)	*P* value
History of injection drug use (PWID)	500 (55.3%)	1103 (30.4%)	<0.001
Mortality	109 (21.8%)	215 (19.5%)	0.318
Indigenous ancestry	259 (28.7%)	330 (9.1%)	<0.001
Mortality	58 (22.4%)	72 (21.8%)	0.946
PWID, Indigenous ancestry	193 (21.4%)	230 (6.3%)	<0.001
Mortality	45 (23.3%)	50 (21.7%)	0.787
PWID, non-Indigenous ancestry	126 (13.9%)	461 (12.7%)	0.349
Mortality	21 (16.7%)	78 (16.9%)	0.990
No ID history, Indigenous ancestry	39 (4.3%)	79 (2.2%)	<0.001
Mortality	5 (12.8%)	15 (19.0%)	0.563
No ID history non-Indigenous ancestry	104 (11.5%)	842 (23.2%)	<0.001
Mortality	7 (6.7%)	66 (7.8%)	0.838
HAART Initiation			
2000–2004	236 (26.1%)	910 (25.1%)	0.549
2005–2008	282 (31.2%)	1120 (30.9%)	0.874
2009 onward	386 (42.7%)	1600 (44.1%)	0.478
Age at HAART initiation	38 (31–46)	42 (36–49)	<0.001
Living in an urban setting	609 (67.4%)	2811 (77.4%)	0.098
Health service delivery area: Vancouver	357 (39.5%)	2010 (55.4%)	<0.001
HIV risk through heterosexual intercourse	322 (35.6%)	667 (18.4%)	<0.001
HIV risk through blood products	12 (1.9%)	36 (1.6%)	0.584
Overall mortality during study period	144 (15.9%)	421 (11.6%)	<0.001

ID, injection drug; IQR, interquartile range; PWID, person who injects drugs.

Table 2. Mean proportion of men and women in the HAART Observational Medical Evaluation and Research cohort attaining optimal adherence (≥95%) per 6-month observation period (2000–2014).

	Mean proportion (SD)		
	Women	Men	*P* value
Total sample	57.0 (2.3)	77.1 (1.6)	<0.001
PWID, Indigenous ancestry	47.8 (4.6)	57.7 (4.9)	<0.001
PWID, non-Indigenous ancestry	58.7 (4.2)	66.9 (3.1)	<0.001
No ID history Indigenous ancestry	59.5 (7.1)	71.3 (5.4)	<0.001
No ID history non-Indigenous ancestry	69.9 (4.2)	83.8 (2.3)	<0.001

ID, injection drug; PWID, person who injects drugs.

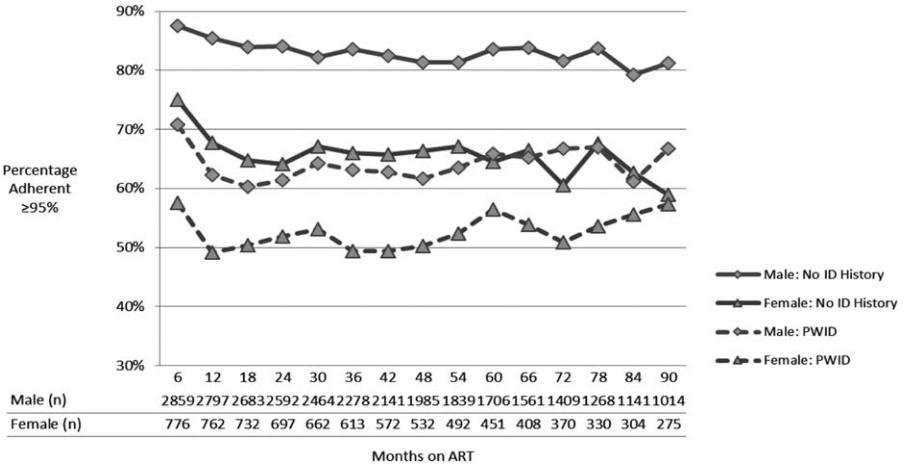

Fig. 1. Proportion of men and women attaining optimal antiretroviral therapy adherence (≥95%) in HAART Observational Medical Evaluation and Research, from initiation to 90 months on therapy, by injection drug use status, between 2000 and 2014.

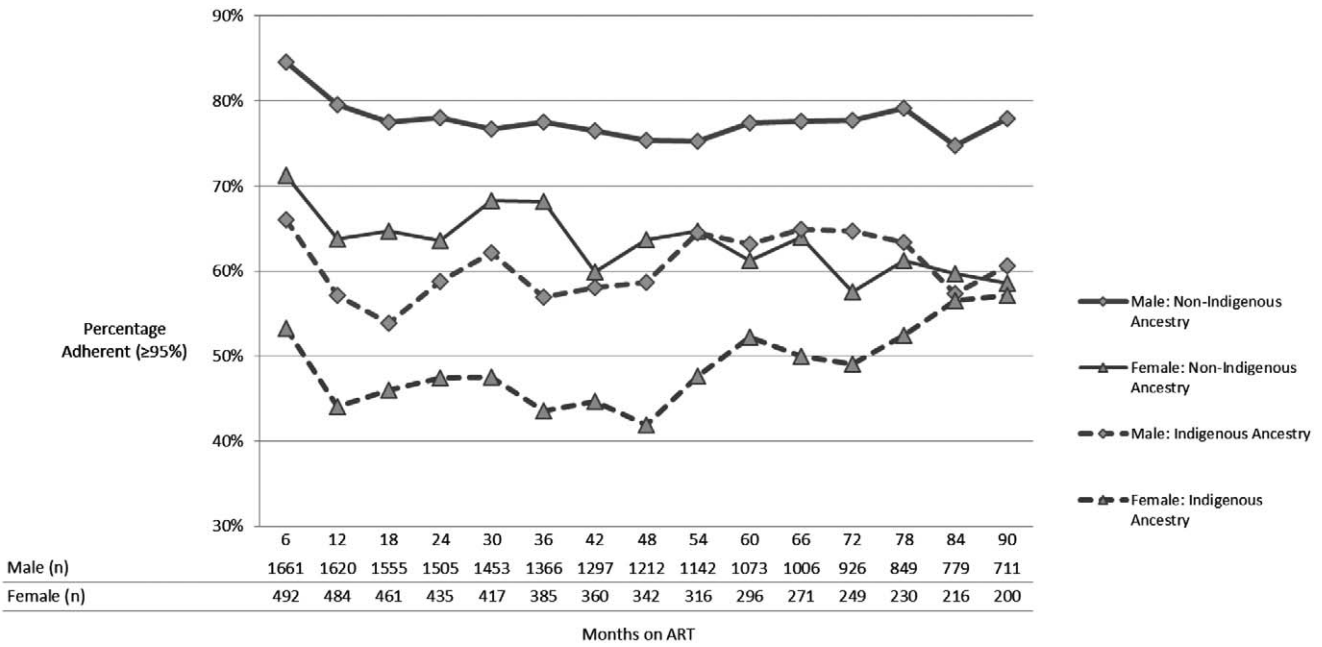

Fig. 2. Proportion of men and women attaining optimal antiretroviral therapy adherence (≥95%) in HAART Observational Medical Evaluation and Research, from initiation to 90 months on therapy, by Indigenous ancestry, between 2000 and 2014.

Table 3. Logistic regression confounder model for the odds of being adherent to HAART (≥95%) by sex in HAART Observational Medical Evaluation and Research, 2000–2014 ($n = 4534$).

	Unadjusted odds ratio (95% confidence interval)	*P* value	Adjusted odds ratio (95% confidence interval)	*P* value
Sex: female vs. male	0.31 (0.27–0.36)	<0.001	0.55 (0.48–0.63)	<0.001
Age at ART initiation (per 10-year increase)	1.49 (1.41–1.58)	<0.001	1.36 (1.28–1.44)	<0.001
History of injection drug use				
No vs. yes	3.90 (3.44–4.41)	<0.001	2.64 (2.23–3.12)	<0.001
Unknown vs. yes	3.48 (2.96–4.10)	<0.001	2.83 (2.19–3.66)	<0.001
MSM				
Yes vs. no	3.31 (2.87–3.83)	<0.001	1.34 (1.12–1.60)	<0.001
Unknown vs. no	2.82 (2.46–3.83)	<0.001	0.98 (0.79–1.23)	0.896
Indigenous ancestry				
No vs. yes	3.60 (3.01–4.32)	<0.001	1.90 (1.59–2.28)	<0.001
Unknown vs. yes	3.61 (3.04–4.29)	<0.001	1.68 (1.41–2.00)	<0.001
Year of ART initiation				
2000–2004 vs. 2008+	0.55 (0.47–0.63)	<0.001	0.60 (0.52–0.69)	<0.001
2005–2008 vs. 2008+	0.93 (0.81–1.07)	0.292	0.96 (0.84–1.09)	0.533

ART, antiretroviral therapy.

Table 3 shows the multivariate confounder analysis of factors affecting adherence. Female sex was independently and significantly associated with suboptimal adherence when controlling for age, history of injection drug use, Indigenous ancestry, MSM, and year of therapy initiation (AOR: 0.55; 95% CI: 0.48–0.63).

Discussion

Our findings indicate that women are significantly less likely to achieve optimal adherence to cART than men. These findings are consistent with other studies focusing on women in high and very high human development index countries [7]. Although both Indigenous ancestry and history of injection drug use have previously been found to impact adherence [11,12,14], our study shows that sex maintains a significant and independent effect on adherence. The finding of significantly lower adherence among women relative to men continued across different cART guidelines and public health campaigns to improve access to care, early diagnosis, retention in care, and adherence (e.g. the Maximally Assisted Therapy and STOP programs) [22,23].

Vulnerabilities that women face may be amplified by multiple intersecting identities, including ethnic minority status, histories of trauma, and injection drug use [24,25]. Within this study, we observed marked disparity between Indigenous and non-Indigenous individuals, compounded by sex. Among Indigenous people in Canada, there is a disproportionately high prevalence of HIV [26], lower quality of HIV-related care [9], as well as poorer health outcomes among Indigenous PLWH despite more favorable clinical characteristics at baseline [12]. Poorer health outcomes among Indigenous people, such as HIV-related morbidity and mortality, cannot be discussed without connecting these conditions with Canada's history of colonization, marginalization, and criminalization of culture [27]. The negative impact of Canada's colonial legacy can certainly still be observed in the disproportional rates of injection drug use, alcoholism, and suicide, in addition to the high HIV incidence [12,13,28]. In the context of colonialism, there is a need for culturally competent HIV-related care to support cART adherence and to build trust between Indigenous people and non-Indigenous HIV-care providers [29].

Although injection drug use does increase the likelihood of suboptimal adherence among PLWH, this study shows that sex maintains a central role in predicting adherence. This is consistent with existing literature, though the effect of sex may be modified by drug use characteristics (e.g. frequent heroin injection or frequent crack use may further lower cART adherence) [30]. Injection drug use can yield additional barriers to cART adherence, including unstable housing, food insecurity, social instability, competing priorities, and low perception of adherence self-efficacy [11,31]. Women who inject drugs may be more likely to be involved in street-based survival sex work and experience greater marginalization than men [30], undermining self-efficacy and their relationship with healthcare services.

Reasons for differing levels of adherence were not directly explored in this study. Clinically, women have been observed to experience greater risk for adverse drug-related events relative to men, including gastrointestinal, hematological, metabolic, and toxicity-related symptoms [32], which could affect adherence and retention to therapy. Psychosocial and structural factors may also result in the sex differences observed in this study. Psychosocial differences, including self-efficacy and social support, between men and women may be related to differences in coping with HIV and sustaining cART adherence [33,34]. Anticipated or experienced HIV-related stigma may isolate the woman from previously

supportive relationships and cause additional emotional stress [35]. Many women also need to contend with competing life demands, particularly the care of children and her partner [36], in addition to the basic needs of housing and food security [22,37]. These demands can be further exacerbated by experiences of abuse and an absence of local women-centered care [38,39].

Among high-risk groups targeted for HIV care interventions, such as PWID and ethnic minorities, it is simply not enough to develop group-specific interventions without considering sex. Acknowledging women's care needs, specific barriers to entry and retention into care and adherence to therapy require more attention, both within research and in program implementation. However, as observed within our study and elsewhere [24], women living with HIV cannot be considered a homogenous group. Though women are less likely than men to attain adherence goals, a unique hierarchy emerged indicating increasing vulnerability to suboptimal cART adherence among PWID, followed by Indigenous peoples. More research is necessary to identify women-centered, culturally well tolerated interventions if we are to reduce outcome disparities between women and men, as well as between the various intersections of women's identities [39].

Although this study highlights the overall vulnerability of women to suboptimal cART adherence, it cannot speak to other aspects of vulnerability, such as sexual orientation, transgender identity, experiences of pregnancy, HIV-related stigma, mental health, or health service usage. In addition, this study did not address discontinuation of cART, which has previously been found to be associated with female sex [40]. Another limitation of this study is that pharmacy refill compliance does not indicate whether PLWH are taking medications as prescribed, or picking them up at the time of dispensation, as may be the case with automated refills. Underreporting of injection drug use due to social desirability bias may also be present, appearing as either unknown history or no history of injection drug use. This may have the effect of artificially reducing the proportion of optimally adherent individuals within the subpopulations that did not identify as PWID. Lastly, the results of this study may not be generalizable outside of Canada, due to the accessibility of the Canadian healthcare system and the specific impacts of colonialism on the Indigenous peoples of Canada.

In our study, we have demonstrated sex disparities in adherence to cART, compounded by Indigenous ancestry and injection drug use history. To reach the goals of 90-90-90 and Treatment as Prevention, there is a need to identify where women are being lost along the Cascade of Care, under what circumstances, and how they can best be supported in their care at the varying levels of the Cascade. Existing interventions to support cART adherence may not identify and care for the specific needs of women and, thus, may not be sufficient for the women who access them. The care needs of women and barriers to women's care along the Cascade are particularly important to address if we are to meet the goals of UNAIDS' 90-90-90 campaign to end AIDS by 2030.

Acknowledgements

The study was conceived and designed by C.M.P., C.L.M., R.S.G., and A.K.; B.Y. assisted in the development of the longitudinal cART adherence data design; W.Z. developed the statistical design and conducted the analysis. C.M.P. wrote the manuscript, and all authors edited and shaped the final manuscript.

Conflicts of interest

There are no conflicts of interest.

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