Adherence to oral antiretroviral therapy in Canada, 2010–2020

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Objective: To assess antiretroviral therapy (ART) adherence among people with HIV (PWH) in Canada and identify baseline characteristics associated with suboptimal adherence (<95%).

Design: Retrospective observational study using data from the National Prescription Drug Utilization Information System and Régie de l'assurance maladie Quebec (RAMQ) Public Prescription Drug Insurance Plan.

Methods: This analysis included PWH aged 18 years or older who initiated an ART regimen and were followed for at least 12 months (2010–2020). Patient characteristics were summarized using medical/pharmacy claims data from seven provinces (Alberta, Manitoba, New Brunswick, Newfoundland and Labrador, Ontario, Saskatchewan, and Quebec). ART regimen at index date (first dispensing of a regimen including a core agent) was defined as a single-tablet or multitablet regimen (MTR). Adherence was calculated using a Proportion of Days Covered approach, based on ART dispensing, recorded between April 2010 and the last available date. Multivariate linear regression analysis was used to determine correlations between suboptimal adherence and baseline characteristics.

Results: We identified 19 322 eligible PWH, 44.7% of whom had suboptimal adherence (<95%). Among 12 594 PWH with evaluable baseline data, 10 673 (84.8%) were ART-naive, 74.2% were men, mean age was 42.9 years, and 54.1% received a MTR as their ART. Based on multivariate regression analysis, suboptimal adherence was significantly associated with multitablet ART ($P < 0.001$) and younger age ($P < 0.001$) but not sex.

Conclusion: Almost half of adult PWH in Canada had suboptimal adherence to ART. Better understanding of factors influencing adherence may help address gaps in current care practices that may impact adherence.

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Keywords: adherence, antiretroviral therapy, demography, knowledge/attitude/practice studies, oral medicine, primary discipline – clinical

Introduction

According to national estimates from the Public Health Agency of Canada, approximately 62 050 individuals were living with HIV in Canada at the end of 2018 [1]. The annual rates of new infections have remained steady over the last decade with 2122 new HIV diagnoses recorded in 2019 [1].

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The significant reduction in morbidity and mortality among people with HIV (PWH) globally [2–7] can be attributed to modern combination antiretroviral therapy (ART). Treatment with ART leads to viral load suppression, improved clinical outcomes, and prevention of disease transmission [8–10]. Although benefit is still derived from delayed treatment initiation, ART should be started as early as possible following diagnosis [8,9]. At the end of 2018, 85% of diagnosed PWH in Canada were receiving ART, 94% of whom had suppressed viral loads [11]. However, achieving complete and sustained viral suppression requires stringent adherence to ART [12–15]. This is influenced by patient-related and psychosocial factors, including age, sex, socioeconomic status, substance use, and psychiatric conditions such as depression or anxiety [16–21], as well as by factors related to the ART regimen itself (e.g. pill burden, dosing frequency, food requirements) [22–24]. Suboptimal ART adherence can lead to treatment failure, development of viral resistance, fewer subsequent ART treatment options, increased morbidity and mortality [12,25], and substantial healthcare burden [26]. Despite the development of approaches to reduce pill burden [e.g. single-tablet vs. multitablet regimens (MTRs)] and/or frequency of administration (e.g. once-daily vs. twice-daily dosing) [14,15,26], some PWH do not consistently maintain the ART adherence levels required to achieve and sustain viral suppression [16,27–29].

Data from individual Canadian provinces have shown that sex, social and behavioral factors, as well as drug coverage (insurance that covers the cost of drug or treatment and drug-dispensing models), can impact adherence and viral suppression [17,19,30,31], but quantitative data reporting real-world adherence patterns in the wider Canadian population are currently unavailable. The aim of this study was to describe real-world ART adherence patterns among PWH across a broad Canadian population; to our knowledge, this is the first study of its kind to do so. To identify factors associated with suboptimal adherence that may help facilitate strategies to improve current care practices and disease outcome, the study also explored associations between baseline characteristics of PWH and ART adherence.

Materials and methods

Study design and data source

We performed an observational retrospective study (ViiV study HO-19-20018) using pharmacy claims data from the National Prescription Drug Utilization Information System (NPDUIS) to identify adult PWH who initiated ART between 1 April 2010 and 29 February 2020 (study end). The NPDUIS contains prescription claims-level data, focusing primarily on publicly funded therapies, including ART, as well as formulary and medicinal product information. An estimated 40% of the Canadian adult PWH population is covered in the NPDUIS, from six provinces (Alberta, Manitoba, New Brunswick, Newfoundland and Labrador, Ontario, and Saskatchewan). Claims data for Quebec were obtained from the Régie de l'assurance maladie Quebec (RAMQ) Public Prescription Drug Insurance Plan. For the remaining three Canadian provinces (British Columbia, Nova Scotia, Prince Edward Island) and three territories (Yukon, Nunavut, Northwest Territories), claims or prescription data either were not available for this analysis or had already been used for adherence estimation (British Columbia) [19]. Secondary data, not part of the NPDUIS, were also included in this analysis to obtain individual-level data; this included data from the Pharmaceutical Information Network (PIN) of Alberta, hosted by Alberta Health. All datasets captured treatment covered by public insurance in Ontario, New Brunswick, Quebec, and Newfoundland and Labrador, whereas private and public insurance coverage were captured in Manitoba, Saskatchewan, and Alberta.

Each record in the database represented an ART-dispensing event, which was used as a proxy for treatment use and adherence. The Anatomical Therapeutic Chemical (ATC) classification system categories for commonly used drugs in Canada are shown in Supplemental Table 1, http://links.lww.com/QAD/C921. The index date was defined as the date of first dispensing of an ART regimen, including a core agent ART (i.e. an integrase strand transfer inhibitor, protease inhibitor, or nonnucleoside reverse transcriptase inhibitor) (Fig. 1). The baseline period, used to identify potential associations between patient demographics/co-medication use and calculated adherence rates, was defined as the 6-month period from the start of data capture to the index date. For cases with a baseline period shorter than 6 months, the time from the start of data capture to index date was used as the baseline period. Duration of follow-up was at least 12 months, starting from the index date to the first of the following: end of the study period (29 February 2020), date of the last dispensed ART, end of health insurance coverage, or end of data capture by the registry.

Study population

Eligible individuals were 18 years of age or older at index date and had one or more claims for dispensing of a core ART or single-tablet regimen (STR), based on the ATC classification code between 1 April 2010 and the end of study. Individuals with no claims for a core ART or STR (Supplemental Table 1, http://links.lww.com/QAD/C921) over the study period were excluded from the analysis, to ensure HIV-negative individuals taking two antiretroviral agents without a core agent for HIV preexposure prophylaxis were not included. PWH taking ART with less than 12 months of follow-up were excluded. PWH were classified as treatment-naive if

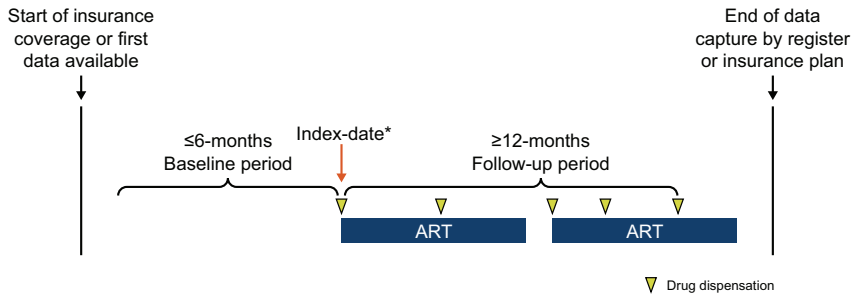


Fig. 1. Overview of study design. *The date of the first dispensing of a core agent antiretroviral therapy (defined as an integrase strand transfer inhibitor, protease inhibitor, or nonnucleoside reverse transcriptase inhibitor). ART, antiretroviral therapy.

they had no dispensing of a core agent or STR before 1 April 2010 and at least 6 months between the start of data capture and the index date. Otherwise, they were classified as treatment experienced.

Study outcome variables

Variables incorporated into the interim dataset to facilitate Proportion of Days Covered (PDC) calculation are listed in the Supplemental Methods, http://links.lww.com/QAD/C921. The sum of comorbidity categories (per coded concomitant medications) and Chronic Disease Score were calculated by recording dispensing of any treatment that fell into any comorbidity category as defined by the ATC category code transformation (Supplemental Table 2, http://links.lww.com/QAD/C921). Pill burden, a proxy for the daily number of pills taken during the preindex period, was calculated by dividing the total number of concomitant pills dispensed during the baseline period by the total duration of the baseline period (in days).

Adherence assessment

Adherence rates were estimated by calculating the PDC by ART between 1 April 2010 and available date at the time of end of study. PDC by ART was calculated by dividing the sum of all days covered with a complete ART regimen by the duration of follow-up. STR at index was defined as dispensing of at least one pharmaceutical classified as an STR, prescribed exclusively. MTR at index was defined as dispensing of at least one pharmaceutical classified as core agent and another ART medication/agent (core agent or nucleoside/nucleotide reverse transcriptase inhibitor). Days of nonadherence were defined as all days when patients were not adherent to MTR or STR during the follow-up period, identified by a gap in days' supply of ART.

The service date, defined as the date on which the prescription was filled, and days' supply within each therapeutic class at the patient level were used to determine the treatment period and estimate adherence rate for each ART regimen. The end date of treatment was defined as the service date plus days' supply minus 1 day. For cases in which a new ART (same or different treatment regimen) was dispensed before the end of the previous supply, the overlapping days were carried forward to the end of the later supply period, and the refill date was shifted forward to the day after the end of supply of the previous fill [32]. Key variables extracted to determine adherence rates included patient identification number, ATC classification code or Drug Identification Number, service date, days' supply, age, sex, province and coverage start and end dates (Supplemental Table 3, http://links.lww.com/QAD/C921). Adherence status (yes/no) and ART regimen (STR/MTR) were noted longitudinally on each day during the follow-up period to determine the adherence status of individual patients at a given time point. Any adherence gaps that arose because of a switch in ART regimen were assigned to the initial regimen, not the new ART regimen.

Because databases may not cover the full duration of follow-up for each patient, missing data may result in treatment gaps that cannot be attributed to nonadherence. To ensure that loss to follow-up was not counted as patient nonadherence (resulting in underestimation of adherence), patients were followed until they had an interruption in the dispensing of ART equivalent to 1.5 times the number of days' supply of the last ART treatment dispensed (e.g. 45 days for monthly dispensing) and end of follow-up was set to the last date of adherence before the treatment gap.

Statistical analyses

Baseline characteristics were summarized using descriptive statistics. PDC was calculated for each patient and then summarized at a population level using descriptive statistics. To describe and compare adherence rates for different baseline characteristics and estimate predictors of adherence, mean [standard deviation (SD)] and median (interquartile range [IQR]) adherence were calculated for each subgroup for the full follow-up period. *T*-tests were used to estimate the differences between subgroups. Paired tests were used to evaluate the differences between STR and MTR. The numbers and proportions (%) of PWH stratified by age, sex, and ART treatment type and experience were determined to evaluate baseline demographics of the wider Canadian population and for a

subpopulation from Western Canada (Manitoba, Saskatchewan, and Alberta). Chronic Disease Scores based on concomitant medications, HIV-specific concomitant medications, and pill burden were determined for the Western Canadian subpopulation only, as these data were not available for all provinces. Covariates were categorical or continuous, and the impact of each demographic and clinical characteristic was assessed using multivariate linear regression analysis: PDC was modeled as a continuous variable. Statistical significance was evaluated at $\alpha = 0.05$ level. The Quebec dataset was analyzed separately because of restrictions on data transfer across provinces, and results were pooled by conducting a meta-analysis. All statistical comparison and regression tests were conducted on the Canada dataset, excluding the Quebec data.

Sensitivity and subgroup analysis

To assess the robustness of the data to changes in model parameters, sensitivity analyses included a model in which a treatment interruption up to 1.5 times the number of days' supply did not result in censoring of data from the analysis. The long treatment interruption model was also combined with revised MTR adherence criteria whereby MTR adherence was defined as PWH receiving at least one medication classified as a core agent (prescribed either exclusively or simultaneously with other ART medications). The impact of private claims data not being available in all provinces was assessed by comparing the overall dataset (seven provinces) with data for Western Canada (Manitoba, Saskatchewan, and Alberta) for which the available datasets have the most comprehensive coverage of ART prescriptions and concomitant medications, covered by both public and private insurance.

Results

Baseline demographics and clinical characteristics

Overall, 19 322 PWH from seven Canadian provinces were included in the ART adherence analysis; 12 594 PWH met study eligibility criteria and had more than 6 months of baseline data to describe patient characteristics at the index date. A large majority of PWH [10 673/12 594 (84.7%)] were confirmed to be ART-naive when included in the study (Table 1). Most PWH were aged 35–64 years (68.6%) and 24.6% were younger than 35 years, 74.2% were male, and most resided either in Ontario (38.7%) or Alberta (29.6%) (Table 1). ART regimen at index date was balanced between STR (45.9%) and MTR (54.1%).

Baseline characteristics of the Western Canada subpopulation, constituting 38.4% of the total cohort (4842/12 594), were comparable with those of the wider Canadian population (Table 1). The mean (SD) daily pill burden of all non-ART medications was 0.8 (1.5) with a median (IQR) of 0.05 (0.94). The most common concomitant medications were prescribed for depression (17%), insomnia (10.6%), hypertension (10.2%), and dyslipidemia (7.8%) (Supplemental Table 4, http://links.lww.com/QAD/C921).

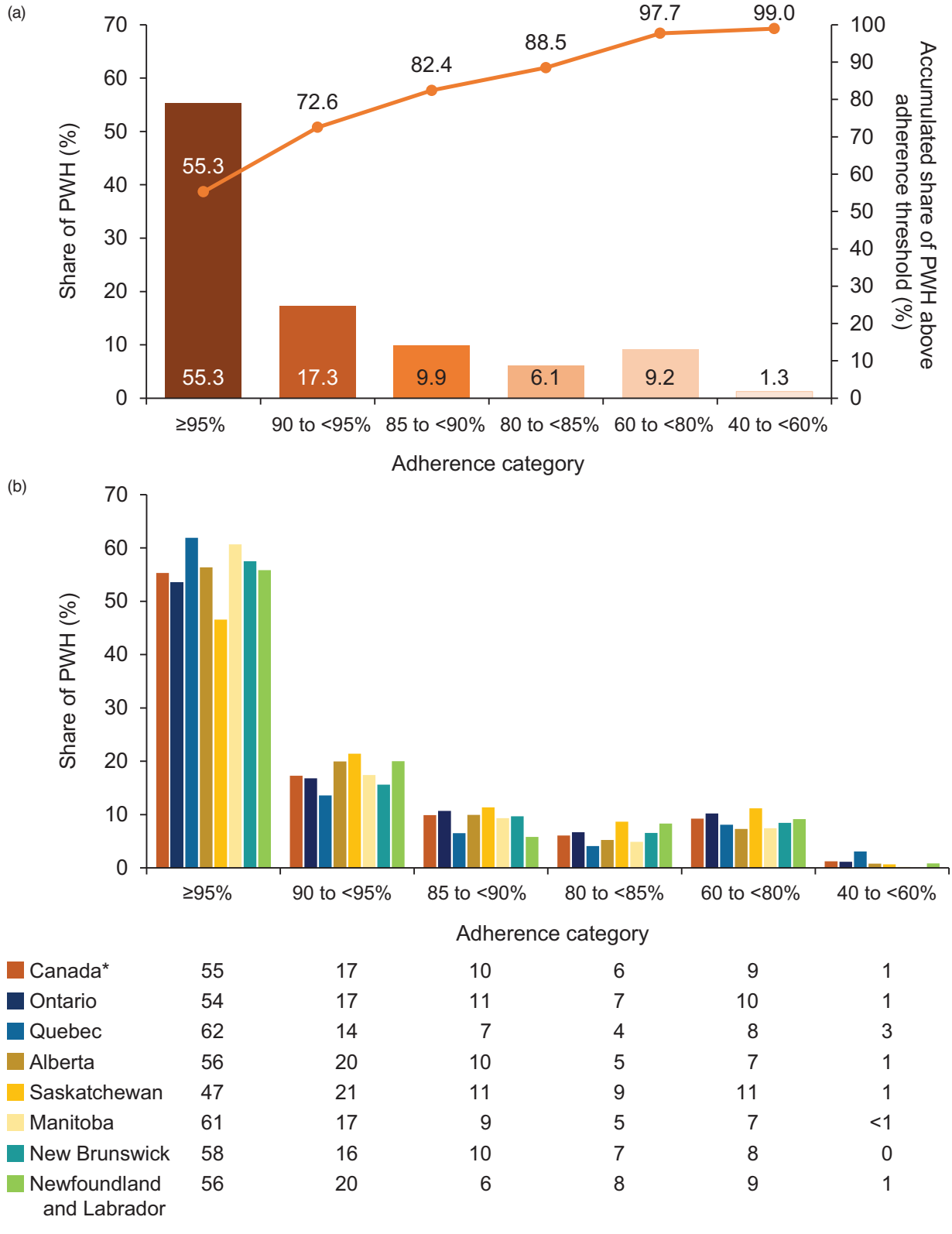
Table 1. Baseline demographics of people with HIV in Canada.

Characteristic	*N* (%)	
	Canada[a] (*N* = 12 594)	Western Canada[b] (*n* = 4842)
Age in years		
Mean (SD)	42.9 (12.0)	42.9 (11.2)
≥18 to <35	3101 (24.6)	1253 (25.9)
≥35 to <65	8642 (68.6)	3449 (71.2)
≥65	851 (6.8)	140 (2.9)
Sex		
Male	9345 (74.2)	3347 (69.1)
Female	3033 (24.1)	1495 (30.9)
Unknown	216 (1.7)	0
Province		
Ontario	4869 (38.7)	–
Alberta	3732 (29.6)	3732 (77.1)
Quebec	2693 (21.4)	–
Saskatchewan	911 (7.2)	911 (18.8)
Manitoba	199 (1.6)	199 (4.1)
New Brunswick	131 (1)	–
Newfoundland and Labrador	59 (0.5)	–
ART treatment regimen		
Single-tablet regimen	5781 (45.9)	2141 (44.2)
Multitablet regimen	6813 (54.1)	2701 (55.8)
Treatment experience		
ART-naive	10 673 (84.7)	4312 (89.1)
ART-experienced	1921 (15.3)	530 (11.0)

ART, antiretroviral therapy; SD, standard deviation.
[a]Excluding British Columbia, Nova Scotia, Prince Edward Island, Yukon, Nunavut, and the Northwest Territories.
[b]Manitoba, Saskatchewan, Alberta.

Antiretroviral therapy adherence in Canada

Among the 19 322 PWH included in the ART adherence analysis, mean (SD) adherence rate was 91.6% (12.0), and 55.3% achieved the at least 95% adherence threshold. Of 43.7% of PWH who had suboptimal adherence (<95%), 17.3% had 90 to less than 95% adherence, 9.9% had 85 to less than 90% adherence, 6.1% had 80 to less than 85% adherence, 9.2% had 60 to less than 80% adherence, and 1.3% had 40 to less than 60% adherence (Fig. 2a). A similar trend across ART adherence thresholds was observed among the 5985 PWH in the Western Canadian subpopulation, 55.2% of whom achieved the at least 95% adherence threshold, whereas 19.8, 10.1, 5.9, 8.1, and 0.7% had adherence rates of 90 to less than 95%, 85 to less than 90%, 80 to less than 85%, 60 to less than 80%, and 40 to less than 60%, respectively. The mean (SD) adherence rate in Western Canada was 92.7% (9.3). ART adherence rates across provinces were similar, with only Saskatchewan deviating with a smaller proportion of PWH achieving adherence thresholds at least 95% and at least 90% (Fig. 2b).



Canada*	55	17	10	6	9	1
Ontario	54	17	11	7	10	1
Quebec	62	14	7	4	8	3
Alberta	56	20	10	5	7	1
Saskatchewan	47	21	11	9	11	1
Manitoba	61	17	9	5	7	<1
New Brunswick	58	16	10	7	8	0
Newfoundland and Labrador	56	20	6	8	9	1

Fig. 2. Antiretroviral therapy adherence in Canada by share of people with HIV (a) overall and (b) by regional comparison. Number of patients for each region: Canada overall $N = 19\,332$; Ontario $N = 10\,214$; Quebec $N = 2693$; Alberta $N = 3732$; Saskatchewan $N = 1190$; Manitoba $N = 1063$; New Brunswick $N = 320$; Newfoundland and Labrador $N = 120$. *Excluding British Columbia, Nova Scotia, Prince Edward Island, Yukon, Nunavut, and the Northwest Territories. PWH, people with HIV.

Table 2. Impact of baseline characteristics on antiretroviral therapy adherence in people with HIV in Canada[a].

Group	*n*	Mean (SD)	Adherence category[b], % ≥95%	90 to <95%	85 to <90%	80 to <85%	60 to <80%	40 to <60%	*P* value[c]	*P* value[d]
Age (years)										
≥18 to <35	3015	91.4 (11.1)	52.9	17.58	11.18	7.2	8.92	1.19	–	–
≥35 to <65	8514	92 (10.33)	58.6	16.78	8.89	5.25	7.75	1.2	0.06	–
≥65	849	92.3 (13.5)	72.08	11.43	3.65	2.47	5.54	1.53	0.4	–
Sex										
Male	7142	91.9 (12.6)	56.3	17.8	9.7	5.6	8.3	1.0	0.03	–
Female	2543	91.3 (11.0)	50.9	18.5	11.6	7.4	9.95	1.0	0.03	–
Province										
Ontario	4653	90.9 (14.2)	55.0	15.8	10.3	6.3	9.5	1.3	–	–
New Brunswick	131	89.3 (19.4)	57.3	15.3	9.2	6.1	6.9	0.0	0.4	–
Newfoundland and Labrador	59	91.7 (9.5)	52.5	18.6	8.5	8.5	10.2	1.7	0.5	–
Manitoba	199	93.8 (7.5)	61.3	17.6	8.0	4.5	8.5	0.0	<0.001	–
Saskatchewan	911	91.5 (9.4)	46.8	21.6	11.5	8.5	10.7	0.8	0.1	–
Alberta	3732	92.8 (9.5)	56.4	20.0	9.9	5.3	7.3	0.8	<0.001	–
Quebec	2693	90.7 (15.9)	69.0	12.0	5.0	4.0	5.0	2.0	–	–
ART regimen										
Single-tablet regimen	7414	93.5 (10.0)	62.8	15.9	8.34	4.98	6.53	0.81	<0.001	<0.001
Multitablet regimen	7374	90.2 (16.5)	56.2	15.2	9.02	5.79	9.02	1.99	<0.001	<0.001
Western Canada[e]										
Chronic disease score[f]										
Low	2237	92.9 (9.0)	56.1	20.0	10.2	5.3	7.6	0.6	–	–
Medium	1901	92.4 (9.5)	53.9	20.2	10.1	6.2	8.4	1.0	0.1	–
High	704	92.3 (10.6)	53.0	20.9	10.1	6.7	8.2	0.6	0.1	–
Pill burden[g]										–
Low	2111	93.0 (9.0)	56.3	19.9	10.3	5.3	7.4	0.6	–	–
Medium	2092	92.1 (9.8)	52.1	20.1	10.7	6.5	9.4	1.0	0.002	–
High	639	93.3 (9.9)	58.7	21.4	8.1	5.3	5.5	0.5	0.4	–
Opioid dependence[h]										
Yes	345	90.7 (9.9)	43.2	23.9	11.5	8.1	11.5	1.4	<0.001	–
No	4422	92.8 (9.4)	55.7	19.9	10.1	5.7	7.7	0.7	<0.001	–
Dislipidemia[h]										–
Yes	372	94.4 (10.8)	67.5	19.6	5.8	2.4	3.2	0.5	0.001	–
No	4395	92.5 (9.3)	53.7	20.2	10.5	6.1	8.4	0.8	0.001	–
Depression[h]										–
Yes	809	92.1 (10.2)	50.4	22.0	10.7	6.6	9.5	0.4	0.07	–
No	3958	92.7 (9.3)	55.7	19.8	10.1	5.7	7.7	0.8	0.07	–
Diabetes[h]										
Yes	212	93.8 (8.5)	59.1	25.1	5.6	2.8	6.5	0.5	0.03	
No	4555	92.6 (9.5)	54.6	20.0	10.4	6.0	8.1	0.8	0.03	

ART, antiretroviral therapy; SD, standard deviation.
[a]Excluding British Columbia, Nova Scotia, Prince Edward Island, Yukon, Nunavut, and the Northwest Territories.
[b]The percentage adherence was determined by calculating (gap/total time) × 100, where the total time was the sum of the gap time and prescription time.
[c]Nonpaired test performed on results from dataset excluding patients from Quebec.
[d]Paired test performed on results from dataset excluding patients from Quebec.
[e]Manitoba, Saskatchewan, Alberta.
[f]Chronic disease Score (CDS) = sum of 24 comorbidity categories; divided into tertiles – tertile with the highest CDS = high; tertile with second highest CDS = medium; tertile with lowest CDS = low.
[g]Divided into tertiles – tertile with greatest pill burden = high; tertile with second greatest pill burden = medium; tertile with the least pill burden = low.
[h]Ascertained by concomitant medication use.

Impact of baseline characteristics on antiretroviral therapy adherence

In the wider Canadian population, mean adherence was significantly lower for PWH receiving MTR than for those receiving STR (90.2 vs. 93.5%; $P < 0.001$) and for women versus men (91.3 vs. 91.9%; $P = 0.03$) (Table 2). The proportion of PWH with adherence at least 95% was 56.2% for those receiving MTR and 62.8% for those receiving STR, and 50.9% for women and 56.3% for men. In the Western Canadian subpopulation, several concomitant medications were associated with a negative effect on adherence, including those prescribed for opioid dependence ($P < 0.001$), dyslipidemia ($P = 0.001$), and diabetes ($P = 0.03$) (Table 2).

Regression analyses: multivariate modelling

In multivariate regression analysis, patient characteristics associated with suboptimal ART adherence (<95%) among PWH in Canada were younger age ($P < 0.001$) and MTR at index date ($P < 0.001$) (Table 3). In the

Table 3. Impact of covariates on antiretroviral therapy adherence: multivariate modelling.

	Model coefficient (95% CI; *P* value)	
	Univariate model	Multivariate model
Canada[a]		
Age	0.0045 (0.0019 to 0.0070; <0.001)	0.0056 (0.0031 to 0.0082; <0.001)
Sex, male vs. female	0.11 (0.044 to 0.18; 0.001)	0.053 (−0.014 to 0.12; 0.1)
ART regimen (index date), MTR vs. STR	−0.39 (−0.45 to −0.33; <0.001)	−0.39 (−0.46 to −0.33; <0.001)
Western Canada[b]		
Age	0.011 (0.0072 to 0.014; <0.001)	0.0091 (0.0055 to 0.013; <0.001)
Sex, male vs. female	0.23 (0.15 to 0.31; <0.001)	0.16 (0.075 to 0.24; <0.001)
ART regimen (index date), MTR vs. STR	−0.33 (−0.41 to −0.26; <0.001)	−0.34 (−0.42 to −0.26; <0.001)
Chronic disease score	0.014 (−0.0067 to 0.035; 0.2)	−0.041 (−0.075 to −0.0071; 0.02)
Pill burden, high vs. low	0.048 (0.021 to 0.075; <0.001)	0.081 (0.038 to 0.13; <0.001)

ART, antiretroviral therapy; CI, confidence interval; MTR; multitablet regimen; STR, single-tablet regimen.
[a]Excluding British Columbia, Nova Scotia, Quebec, Prince Edward Island, Yukon, Nunavut, and the Northwest Territories.
[b]Manitoba, Saskatchewan, Alberta.

Western Canada subpopulation, younger age ($P < 0.001$), female sex ($P < 0.001$), lower daily non-ART pill burden ($P < 0.001$), greater comorbidity ($P = 0.02$), and MTR at index date ($P < 0.001$]) were associated with suboptimal adherence.

Sensitivity analysis outcomes

Inclusion of long treatment interruption periods had the greatest impact on adherence rates, resulting in a reduction in mean adherence from 91.6 to 81% and approximately 23% more PWH in low (<80%) adherence categories (Supplemental Table 5, http://links.lww.com/QAD/C921). Adjusting the definition of MTR adherence to include exclusive use of a core agent had a smaller impact on adherence, with an increase in mean adherence from 91.6 to 93.5% and approximately 6% more PWH meeting the optimal adherence threshold (≥95%).

Discussion

To our knowledge, this study provides the first data on real-world ART adherence patterns in a broad Canadian HIV population, based on data pooled from seven provinces. As expected, approximately 55% of PWH achieved the optimal adherence threshold of at least 95%, similar to rates reported across other countries [29]. This meant that 45% had suboptimal adherence to ART, with approximately 18% having less than 85% adherence, a level potentially associated with drug resistance, disease progression, increased transmission, and poorer quality of life [12,25]. Similar ART adherence was estimated for the Western Canadian subpopulation, for which the most comprehensive coverage of ART prescriptions and concomitant medications were recorded, further validating our findings. Although viral suppression data could provide additional information on both the level of adherence and the impact suboptimal adherence may have on patient outcomes, these data were not available from the claims databases included in this analysis. The Canadian HIV Observational Cohort Collaboration study identified a lower prevalence of viral suppression and a shorter time to viral rebound in younger adults (≤29 years) compared with older adults; of those who experienced viral rebound, a higher proportion of younger adults were female (45%) than older adults (21%). These findings are discussed in the context that reduced adherence may be an important contributor to reduced viral suppression and increased viral rebound [33].

In contrast to our findings, only 17.4% of a US Medicaid population with HIV achieved optimal adherence (≥95%) in a claims database study that also evaluated adherence using the PDC approach, but which employed a stricter definition of MTR adherence, requiring patients to receive two or more pills per day [26]. Our data indicate suboptimal adherence to MTR and fewer patients adhering to 95 and 90% thresholds in the 'core agent plus another ART agent' model than with the 'core agent only' model, supporting this finding of poorer adherence to more complex regimens.

Consistent with national estimates from the Public Health Agency of Canada [34], most PWH in this analysis (74%) were male individuals, and 25% were younger than 35 years. A study of a population-based cohort in British Columbia (a province not included in the current analysis) from 2000 to 2014 reported significantly fewer women attaining the 95% adherence threshold (57%) than men (77%) [19]. Although mean adherence was lower among women than men in our study, multivariate analysis showed that sex was not associated with adherence, whereas multitablet ART and younger age were significantly associated with suboptimal adherence.

Although administrative claims data provide valuable real-world information, associated challenges and limitations should be considered when interpreting the results. Race/ethnicity information was not available in this dataset, limiting analyses of demographic characteristics. In addition, lack of information on socioeconomic aspects, education, and marginalized behaviors such as

illicit drug use or alcohol use limit in-depth evaluation of adherence predictors. As a retrospective registry study of pharmacy claims data, the quality of available data could not be verified [35–37]. The use of dispensing dates and prescription refills from claims data as a proxy of adherence does not confirm adherence to prescribed treatment regimen. Wastage of dispensed medication is also not captured, which may lead to an overestimation of adherence rates. The 6-month baseline period we used here may not have been sufficient to accurately determine whether PWH were ART-naive. Despite these recognized limitations, the methodology employed in the current study is recognized as an appropriate adherence-measuring method and a commonly reported approach [26,38].

For provinces providing data outside of Western Canada, analyses were limited to publicly funded pharmacy claims data. Among these datasets, patients who switched between public and private insurance plans may have had gaps in therapy that could potentially impact the results. To minimize error rates that may result from these supply gaps being recorded as nonadherence, a sensitivity analysis was conducted on public pharmacy claims data in Western Canadian provinces for which the dataset included both public and private providers. Similar adherence rates between the Western Canada subpopulation and the wider Canadian population confirm the robustness of the overall data with respect to correct identification of treatment supply gaps. The PDC approach used in this study counts individual, nonconsecutive days equally to consecutive days, but consecutive days of nonadherence may be more clinically relevant for ART.

Estimation of comorbidity based on concomitant medication use and not on medical diagnosis codes may lead to underestimates of relevant comorbid conditions such as addiction or mental health conditions [36]. For instance, the classification 'depression' encompasses medications prescribed for other mood disorders as well as pain; capturing these exclusively as 'depression' in our analysis may have introduced some inaccuracies.

Although our study provides data pooled from several provinces in Canada, covering approximately 45% of the total population of Canadian adult PWH, large and populous provinces such as British Columbia, and the smaller provinces and territories of Prince Edward Island, Nova Scotia, Yukon, Nunavut, and the Northwest Territories are not reported to NPDUIS. British Columbia was not included as adherence estimates already exist. Despite sourcing data from each separate public health authority, data for Quebec were delayed by the COVID-19 pandemic and were analyzed separately, and Prince Edward Island, Nova Scotia, Yukon, Nunavut, and the Northwest Territories do not have processes for accessing data for research. Therefore, caution is advised when generalizing the findings of this study to all PWH across Canada. Additionally, the large sample size of Ontario, relative to the other six provinces included in the analyses, may lead to bias owing to greater representation. To account for such errors, we conducted feasibility assessment and statistical power calculations to highlight the coverage of the database in relation to population size. A margin of error within each province was within acceptable limits, indicating that our data are representative of the Canadian HIV population in the provinces included. Finally, the requirement for at least 12 months of continuous data led to exclusion of patients with data of inadequate quality, and the analysis could not capture nonadherence after the last dispensing record (at which point follow-up had been terminated). However, these measures were necessary to ensure exclusion of patients who were lost to follow-up.

In conclusion, data from the current observational retrospective study indicate that a subgroup of PWH in Canada have low adherence to ART, even with simplified one-pill, once-daily regimens. Comparable data in the Western Canada subpopulation suggest that trends in ART adherence rates and baseline characteristics are unaffected by the absence of private claims data in all provinces. Though the results cannot be generalized to all PWH across Canada, the findings illustrate the importance of understanding factors that may influence treatment adherence among PWH to help address gaps in current care practices. As the key barriers to ART adherence are likely to be similar across multiple settings and countries [39], the findings of this study may be representative of ART adherence patterns among PWH in other developed nations.

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Data availability: the datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval: as an analysis of patient claims data, using anonymized data, Ethics Committee/Institutional Review Board evaluation and approval were not required for this observational, retrospective study.

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Conflicts of interest

Conflicts of interest and source of funding: J.B.A. has served on advisory boards and undertaken contract work including clinical research for Viiv Healthcare and Gilead. J.F. received funding from ViiV Healthcare to conduct this study. E.A. and J.K.B. are employees of GSK. J.L. has received research funding from AbbVie Canada, Gilead Canada, GSK Canada, and ViiV Healthcare. V.C. is an employee of ViiV Healthcare Ltd. M.H. has received honoraria, paid to the institution, for consultancy fees and advisory board participation from ViiV Healthcare, Gilead Sciences Canada Inc., and Merck Canada Inc and is an employee of BC Centre for Excellence in HIV/AIDS, Vancouver, BC, Canada.

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