AIDS. Author manuscript; available in PMC 2015 September 25.

Published in final edited form as:

AIDS. 2015 May 15; 29(8): 965–973. doi:10.1097/QAD.0000000000000642.

The causal effect of opioid substitution treatment on HAART medication refill adherence

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Abstract

Background—People who inject drugs (PWID) account for roughly 13% of the prevalent HIV/AIDS population outside of sub-Saharan Africa, and access to opioid substitution treatment (OST) is limited in many settings globally. OST likely facilitates access to HAART, yet sparse evidence is available to support this hypothesis. Our objective was to determine the causal impact of OST exposure on HAART adherence among HIV-positive PWID in a Canadian setting.

Methods—We executed a retrospective cohort study using linked population-level data for British Columbia, Canada (January 1996–March 2010). We considered HIV-positive PWID after meeting HAART initiation criteria. A marginal structural model was estimated on a monthly timescale using inverse probability of treatment weights. The primary outcome was 95% HAART adherence, according to pharmacy refill compliance. Exposure to OST was defined as 95% of OST receipt, and we controlled for a range of fixed and time-varying covariates.

Results—Our study included 1852 (63.3%) HIV-positive PWID with a median follow-up of 5.5 years; 34% were female and 39% had previously accessed OST. The baseline covariate-adjusted odds of HAART adherence following OST exposure was 1.96 (95% confidence interval: 1.72–2.24), although the adjusted odds estimated within the marginal structural model was 1.68 (1.48–1.92). Findings were robust to sensitivity analyses on model specification.

Conclusion—In a setting characterized by universal healthcare and widespread access to both office-based OST and HAART, OST substantially increased the odds of HAART adherence. This underlines the need to address barriers to OST globally to reduce the disease burden of both opioid dependence and HIV/AIDS.

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Conflicts of interest

There are no conflicts of interest.

Keywords

health administrative data; HAART; HIV/AIDS; marginal structural modelling; opioid dependence; opioid substitution treatment

Introduction

Globally, it is estimated that there may be as many as 15.9 million (range 11.0–21.2 million) people who inject drugs (PWID), with as many as 3 million (range 0.8–6.6) being HIV-positive [1]; this accounts for roughly 13% of all people with HIV/AIDS outside of sub-Saharan Africa [2,3]. The largest numbers of injectors were found in China, the USA and Russia, where estimates of HIV-prevalence among PWID were 12, 16 and 37%, respectively [3]. Past studies have shown that HAART can reduce plasma HIV RNA thereby reducing morbidity and mortality and reducing HIV transmission [4–6], with a specific demonstration of the effect of diminishing plasma viral load on HIV incidence within a community of urban PWID in a Canadian setting [7]. Unfortunately, PWID are known to have poor access and adherence to HAART. A recently published global survey suggests that only four out of every 100 HIV-positive PWID (range: 2–18) are accessing HAART, with many of those concentrated in Europe, and sparse reporting in many regions [3].

Opioid substitution treatment (OST) with methadone or buprenorphine is currently indicated for the treatment of opioid dependence in most developed-world countries [3]. In British Columbia (BC) Canada, methadone is covered for reimbursement under standard provincial drug benefit formularies, although buprenorphine is available as a second-line option at the physician's discretion. There is clearly a potential for positive synergies between OST and HAART for HIV-positive, opioid-dependent individuals, yet OST remains highly restricted in many settings [3]. Several studies have reported that methadone treatment was independently associated with decreased time to HAART initiation [8,9]. Engagement in OST has also been associated with decreases in HIV risk behaviour and adherence to HAART and resulting health gains [10–14]. Once HAART adherent, PWID have been noted to have a similar risk of mortality to noninjectors [15]. Although OST has no direct effect on HIV disease progression or HIV-related mortality, it has the potential to improve HAART uptake and adherence, which impact these more distal outcomes.

Measuring the causal impact, or the true extent to which OST may influence HAART adherence is, however, complicated by competing hypotheses on the effect of OST on HAART, and HAART on OST. Specifically, OST is hypothesized to influence HAART adherence via the stability provided to its clients through reduced need to constantly address opioid withdrawal and craving [16]. Linkage to the healthcare system afforded by stable access to OST may further influence HAART adherence; however, the same hypothesis can be made for the effect of HAART on OST [17]. Marginal structural models are designed specifically to handle time-varying confounding effects such as that of HAART on OST in our context, allowing for causal interpretations of results.

Thus, our objective is to determine the causal effect of OST exposure, as well as a range of other individual-level factors, on HAART medication refill adherence among HIV-positive

PWID using data from a linked population-level database with comprehensive OST and HAART dispensation records.

Materials and methods

Patient population

This study was based on a provincial-level linkage of seven health administrative databases and disease registries, including the province-wide antiretroviral dispensation, virology and HIV-testing registries [antiretroviral dispensations, plasma viral load (pVL), CD4⁺ cell count tests, nominal HIV diagnoses], the Medical Services Plan database (physician billing records), the discharge abstract database (hospitalizations), the BC PharmaNet database (nonantiretroviral drug dispensations) and the BC Vital statistics database (deaths). Further details regarding the construction of the HIV-positive cohort and available databases were described elsewhere [18].

We selected all individuals identified as HIV-positive and either identified as having a history of injection drug use at diagnosis or having accessed OST before HAART eligibility, as indicated by methadone or buprenorphine dispensation records in the BC PharmaNet database, from 1 April 1996 to 31 March 2010. OST dispensations were identified by unique drug identification numbers (DINs). These codes encompass current and past DINs used for the medications in question and are specific to indications for opioid dependence (as opposed to pain). Previous studies have defined methods to clean and process PharmaNet data for accurate estimation of OST episodes [19]. OST dispensation record capture was complete for the province of BC.

For each individual, we consider follow-up data from the point of initial HAART eligibility, as determined by IAS-USA criteria from 1996 to 2010, based on CD4⁺ cell count and pVL tests and AIDS-defining illness after the HIV diagnosis date, or by HAART initiation. Individuals were followed up until death, administrative loss to follow-up or censorship (ongoing care as of 30 March 2010). Administrative loss was defined as no records in any of the linked databases for a period of at least 18 months. The database is thus arranged longitudinally, with one row per month of observation following the date of HAART eligibility, until the last observed contact date within the database or the end of the study follow-up period.

The study cohort was followed in a unique environment wherein medical care (HIV and non-HIV related), antiretroviral treatment and laboratory monitoring is fully subsidized by the BC provincial government for people with HIV/AIDS. Antiretroviral drugs are centrally distributed according to provincial treatment guidelines that have remained consistent with those put forward by the International AIDS Society-USA ('IAS-USA') since the summer of 1996 [20] and until the most recent guidelines released in 2012 [21]. Antiretroviral medication and viral load data capture in the BC-CfE registries are complete for the population of individuals with HIV/AIDS in the province, and CD4⁺ cell count data capture have previously been estimated at 80% [22]. This study received approval from the University of British Columbia/Providence Healthcare Research Ethics Board.

Measures

The dependent variable in the study was HAART adherence, defined as at least 95% pharmacy refill adherence in a given calendar month. Exposure to OST, defined by at least 95% days of OST dispensed in a calendar month, was the key independent variable considered. We considered HAART medication refill adherence as our primary outcome as opposed to more distal outcomes such as viral suppression or HIV-related mortality because it is the most proximal outcome in the causal pathway between OST and HIV-related outcomes, and because OST is not known to have a direct effect on HIV disease progression or HIV-related mortality.

We also considered a selection of other baseline and time-varying covariates hypothesized to be associated with the dependent and primary independent variable. Baseline covariates included age (30–39, 40–49, 50+), sex, aboriginal ethnicity, BC health authority of residence, CD4⁺ cell count (<200, 200–499, ≥500 cells/μl), calendar year (1996–1999, 2000–2003, 2004–2010) and AIDS status, all made available through the BC-CfE HIV registry. The Charlson comorbidity index (CCI) score [23] (1 vs. 0) and OST history (number of prior OST episodes) at the time of HAART eligibility were also incorporated, as well as time-varying measures of CD4⁺ cell count, health authority of residence, time since HAART eligibility, AIDS status and CCI.

Statistical analysis

Marginal structural models are designed to handle cases in which time-dependent variables are simultaneously confounders of the effect of interest and are predicted by previous treatment. Past HAART medication refill adherence can be considered a time-dependent confounder for the effect of OST on future HAART adherence, as it may be hypothesized to not only predict future HAART adherence but also subsequent initiation of OST, and as past OST history is an independent predictor of subsequent HAART adherence. The hypothesized relationship is characterized in the directed acyclic graph illustrated in Fig. 1. We hypothesized that exposure to OST at time t affects HAART medication refill adherence at time $t+1$, which in turn influences OST exposure at time $t+2$. Time-invariant and time-varying confounding at time t affects OST exposure, HAART medication refill adherence and confounders at time $t+1$, and those confounders at $t+1$ are also predicted by OST exposure at t . This relationship is analogous to the longitudinal relationship between zidovudine therapy and CD4⁺ cell count, which has served as an example of a repeated-measures application of marginal structural modelling [24].

To control for time-varying confounding in the exposure-outcome relationship, inverse probability of treatment weights (IPTWs) were estimated for each time point of the study. Under the four assumptions of consistency, exchangeability, positivity and no misspecification of the model used to estimate the weights, weighting intuitively creates a pseudo-population in which the exposure is independent of the measured confounders [25]. The pseudo-population is the result of assigning each participant a weight that is inversely proportional to the participant's probability of receiving her own exposure history. In such a pseudo-population, one can regress the outcome on the exposure using a conventional regression model that does not include the measured confounders as covariates. Fitting a

model in the pseudo-population is equivalent to fitting a weighted model in the study population. The parameters of such weighted regression models, which equal the parameters of marginal structural models [26], can be used to estimate the average causal effect of exposure in the original study population.

Weighted estimation of the parameters of marginal structural models requires fitting several models: the structural (i.e. weighted) model; the exposure model; and the censoring model. The exposure and censoring models were used to estimate the IPTW by a pooled logistic regression. The IPTWs were constructed according to their standard formulation [25], and the model specification was presented in a supplementary appendix, <http://links.lww.com/QAD/A670>. The final structural model was performed using PROC GENMOD [generalized estimating equation (GEE) regression model using independent working covariate matrix] for HAART medication refill adherence (≥ 95%), with independent variables of OST (≥ 95%), and baseline covariates included [27]. All analyses were executed using SAS version 9.3 (SAS Institute Inc., Cary, North Carolina, USA).

Sensitivity analysis

We considered a range of sensitivity analyses to protect against model misspecification. Correct model specification applies to exposure, censoring and structural (weighted) models. In the context of the structural model, we considered subgroup analyses on those having no OST experience prior to HAART eligibility and those having OST experience. We also considered beginning follow-up at HAART initiation, as well as alternate definitions of OST receipt, including OST adherence at the minimum effect dose (60 mg/day) [28,29], OST adherence during periods of maintenance treatment (excluding periods of dose titration and tapering) [30] and alternate adherence thresholds for both HAART and OST adherence.

In the context of the exposure/censoring models used to construct the IPTW, first, we compared stabilized and unstabilized IPTW. We also considered truncated (stabilized) weights, assessing the stability of the IPTW (i.e. evaluating mean, standard deviation of IPTW) for appropriateness. We included variables statistically associated with HAART medication refill adherence for exposure/censoring models. For the assumption of positivity or correct model specification to hold, the mean of IPTWs should be approximately equal to one.

Results

Characteristics of study cohort

Study sample selection is outlined in Fig. 2. Among 12 349 HIV-positive individuals in the STOP HIV/AIDS cohort, a total of 2928 (23.7%) HIV-positive individuals were identified as ever having received OST or having a history of injection drug use at HIV diagnosis. After excluding 584 individuals whose HAART eligibility status could not be verified and another 492 due to insufficient follow-up and unknown injection drug use status at HAART eligibility (i.e. identified as PWID through OST receipt after HAART eligibility only), the selected study cohort consisted of 1852 HIV-positive PWID.

The study sample was 34% female, median-aged 35 years and 27% of known Aboriginal ethnicity (Table 1). At the time of HAART eligibility or HAART initiation, 20% were on OST, and 39% had ever accessed OST in the past; individuals had a median of 0 (interquartile range: 0–1) prior OST episodes. The majority (46%) of the cohort became HAARTeligible pre-2000. By the end of follow-up, 50% of the cohort accessed OST.

Longitudinal exposure to opioid substitution treatment and HAART

The cohort was followed up for a median duration of 5.5 years (2.2–10.1), and 25% of the cohort died during follow-up (Table 2). Individuals spent a median 44% of follow-up on HAART, 0% of follow-up on OST and 0% on both forms of treatment, jointly. Most importantly, individuals spent a median of 56% of the time they were in OSTreceiving HAART; when out of OST, individuals were receiving HAART only 38% of the time.

Inverse probability of treatment weight estimation

Variables that were associated with the outcome were selected for models for weight estimation. Excluded variables were baseline measures of aboriginal ethnicity, health authority of residence, CCI, as well as time-varying CCI. Stabilized weights were substantially more stable, with means at 1.00 and smaller standard deviations (IPTW model results and weights are presented in a supplementary appendix, <http://links.lww.com/QAD/A670>). Truncating weights at the first and 99th or fifth and 95th percentile resulted in smaller standard deviations with means close to 1. Stabilized, truncated weights (at the first and 99th percentiles) were thus used in baseline models.

Causal effect of opioid substitution treatment on HAART

Results of the structural model are presented in Table 3. The unadjusted odds of HAART medication refill adherence given OSTwas 1.54 [95% confidence interval (95% CI) 1.36–1.75]. Adjusting for baseline covariates in a GEE model (with logit link and binomial distribution) yielded an adjusted odds ratio (AOR) of 1.96 (1.72–2.24), with similar results after including time-varying covariates (AOR 1.91, 95% CI 1.68–2.19). Finally, adjusting for the potential effect of prior HAART medication refill adherence on OST through the use of IPTW, the marginal structural model yielded an AOR of 1.68 (95% CI 1.48–1.92). The time-varying effect of prior HAARTadherence thus inflated the estimated odds ratio by a magnitude of 0.23 vs. the fully adjusted GEE model. The intermediate results of models estimated to construct the IPTW were presented in the supplementary appendix, <http://links.lww.com/QAD/A670>.

Sensitivity analysis on the effect of opioid substitution treatment on HAART

Baseline results indicating a positive and statistically significant effect of OST on HAART were supported by the results of our sensitivity analyses. We considered two changes in the classification of OST exposure: requiring treatment at the minimum effective dose, and requiring that individuals be at a stable maintenance dose to be classified as exposed. In each case, AORs in the structural model decreased compared with the baseline model formulation with truncated IPTW, but remained statistically significantly positive. Further, models with alternate adherence thresholds for both HAART and OST adherence had similar results

compared with the baseline model. We also considered subgroups of individuals beginning follow-up at HAART initiation, and individuals with and without prior OST exposure at HAART eligibility. Odds ratios were higher than in the baseline model formulation for those with no prior exposure to OST.

Discussion

Using a linked population-level database capturing HIV-positive PWID in a Canadian province, this study has demonstrated a 68% increase in the odds of HAART medication refill adherence due to OST exposure. The results were robust to a number of sensitivity analyses focusing on the assumptions of correct model specification inherent in the selected modelling approach.

These results largely confirm prior studies showing a positive association between OST and HAART adherence (measured within the same time period) in settings in which office-based OST is available; however the role of continuing injection drug use (in particular heroin use) was unclear [10,11,13]. Specifically, Palepu *et al.* [11] controlled for time-varying heroin use and found that OST was independently positively associated with adherence, with an AOR of 1.52 (95% CI 1.16–2.00). In contrast, Roux *et al.* [13] found that the odds of nonadherence for those engaged in OST and not injecting were no different from those currently opioid-abstinent, but patients reporting drug injection during OST had a two-fold risk of nonadherence compared with those currently abstinent.

These analyses were executed through prospective cohort studies that were able to ascertain self-reported drug use alongside time-varying measures of OST exposure and HAART medication refill adherence. However, in both studies, their measurement of OST exposure was coarse, capturing ‘ever accessing OST in the past 6 months’. Although we did not observe time-varying measures of the use of opioids, given the specificity with which we measured OST exposure, the high threshold for OST adherence and the blockade effect of methadone and buprenorphine against illicit opioid use, periods of OST exposure likely featured limited, to no illicit opioid use. Inclusion of this covariate would therefore constitute a violation of the assumption of positivity in this context [25].

Adjusting for the effect of prior HAART on OST resulted in a difference of 0.23 in the magnitude of the odds ratio, or 14% compared with unweighted (GEE) models. We believe this approximates the effect of healthcare system linkage through HAART on OST receipt. Although the remaining positive effect of OST on HAART cannot be separated into its hypothesized explanations (‘stabilized lifestyle’ and ‘linkage to the healthcare system’), we expect that healthcare system linkage through OST had a larger effect than the contrary. As opposed to antiretrovirals, certification is required to prescribe methadone or buprenorphine, making linkage to HIV care through OST prescribers perhaps more plausible than the contrary, as HAART prescribers with no OST exemption would have to refer clients elsewhere. The complex case-mix of this patient population, featuring a high prevalence of comorbid HIV, hepatitis C virus (HCV), mental health conditions and pain [31,32], is just one of the factors that challenge access and physician participation in the treatment of this patient population [33]. Comprehensive and integrated healthcare, incorporating addiction

treatment in primary care [34], is clearly critical for the successful treatment of HIV-positive individuals with opioid dependence. In this regard, integrated ‘directly observed therapy’ programmes, combining OST and HAART medication pickups, have shown mixed results, but continue to be assessed [35,36].

Our findings also have important implications for healthcare resource allocation decisions. The benefits in HAART medication refill adherence caused by exposure to OST lead directly to improved disease progression profiles [37], as well as reductions in infectivity through viral suppression [4–7]; these secondary benefits of OST should be incorporated directly into simulation models developed to determine the long-term cost-effectiveness of competing OST modalities [38] and population-level OST uptake [39,40].

We note that although maintenance-oriented treatment is recommended both federally and provincially in British Columbia, Canada, in some cases, patterns of medication dispensation resembling detoxification treatment have been observed [30]. In the baseline model, we did not distinguish between these two modalities because there is no explicit indication within our health administrative databases to differentiate them. Nonetheless, we considered an alternate definition of reaching a minimum effective dose of 60 mg/day as an indirect measure of maintenance treatment receipt in sensitivity analysis. Furthermore, buprenorphine is not commonly used in BC, with the medication only gaining approval as a second-line treatment in 2010, initially only under special authority [33]. As such, buprenorphine was only observed in only one patient month of follow-up within the study sample.

Our study offers the advantages of a complete population of HIV-positive PWID accessing OST and specific measurement of exposure and outcome, allowing for narrow repeated observation periods and a clear temporal ordering in cause and effect. Nonetheless, several limitations require careful consideration. First, although the study was population-based and featured complete follow-up data with precise measurement of exposure and outcome, the underlying policies and clinical practice in BC – specifically, maintenance-oriented OST with available office-based prescription and community pharmacy-based dispensation, and universal and comprehensive coverage for HIV medications and care – may differ substantially from other settings. Second, those identified as PWID at HIV diagnosis may have injected substances other than opioids exclusively, thus precluding indication for OST. Although we suspect the proportion of such individuals to be small, their inclusion may have attenuated the estimated effect of OST on HAART. Otherwise, although we judge the measurement of exposure and outcome to be at a high level, HAART adherence was measured according to pharmacy refill compliance records, which may overestimate true adherence, albeit equally during periods of OST exposure and nonexposure (nondifferential outcome misclassification), thus resulting in perhaps attenuated odds ratios. Finally, although we have tested the potential effects of model misspecification extensively, there remains potential unmeasured confounding due to depressive symptoms, alcohol use and potentially other drug use, previously identified as factors independently negatively associated with HAART adherence [13]. The population under study likely included individuals with these behaviours; therefore, our results can be interpreted as a weighted average effect; samples with high levels of mental health comorbidity and/or polydrug use

may have an attenuated effect, whereas nonexposed samples may have a larger effect. Otherwise, the causal interpretation of the results of marginal structural model relate to the affirmation of temporal ordering and control for key time-varying confounders; other interpretations of causal inferences consider a number of additional criteria, including repeated observation of the effect in different populations and study settings [41,42]. Cautious interpretations of the results are therefore recommended.

This study demonstrates the substantial benefits of OST in linking HIV-positive opioid-dependent individuals into HAART in a universal healthcare setting with freely available HAART. There is a priority to expand access to OST particularly within HIV-positive populations, to optimize HIV treatment uptake and adherence and its subsequent individual and population health and economic benefits.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We gratefully acknowledge the critical revisions suggested by Miguel Hernan on a previous draft of this article. We acknowledge BCMoH and Vancouver Coastal Health Decision Support Staff involved in data access and procurement, including Monika Lindegger, Clinical Prevention Services, BC Centre for Disease Control; Elsie Wong, Public Health Agency of Canada; Al Cassidy, BC Ministry of Health Registries and Joleen Wright and Karen Luers, Vancouver Coastal Health decision support. This study was funded by the National Institutes of Health/National Institute on Drug Abuse grant no. R01-DA032551 and the BC Ministry of Health-funded 'Seek and treat for optimal prevention of HIV & AIDS' pilot project.

B.N. and V.L. are Michael Smith Foundation for Health Research Scholars. J.S.G.M. has received grants from Abbott, Biolytical, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead Sciences, Janssen, Merck and ViiV Healthcare. He is also supported by the Ministry of Health Services and the Ministry of Healthy Living and Sport, from the Province of British Columbia; through a Knowledge Translation Award from the Canadian Institutes of Health Research (CIHR); and through an Avant-Garde Award (No. 1DP1DA026182) from the National Institute of Drug Abuse, at the US National Institutes of Health. He has also received support from the International AIDS Society, United Nations AIDS Program, WHO, National Institute on Drug Abuse, National Institutes of Health Research-Office of AIDS Research, National Institute of Allergy & Infectious Diseases, The United States President's Emergency Plan for AIDS Relief (PEPFAR), Bill & Melinda Gates Foundation, French National Agency for Research on AIDS & Viral Hepatitis (ANRS), Public Health Agency of Canada.

The STOP HIV/AIDS Study Group is composed of the following: Rolando Barrios, MD, FRCPC, Senior Medical Director, VCH; Adjunct Professor, School of Population and Public Health, UBC; Patty Daly, MD, and Reka Gustafson, MD, Vancouver Coastal Health Authority; Mark Gilbert, Clinical Prevention Services, BC Centre for Disease Control; School of Population & Public Health, University of British Columbia; Perry R.W. Kendall, OBC, MBBS, MSc, FRCPC, Provincial Health Officer, British Columbia Ministry of Health; Clinical Professor, Faculty of Medicine UBC; Ciro Panessa, Gina McGowan and Nancy South, British Columbia Ministry of Health; Kate Heath, Julio S.G. Montaner, Robert S. Hogg and Bohdan Nosyk, BC Centre for Excellence in HIV/AIDS.

B.N. designed the study, assisted with analysis and wrote the first draft of the article. J.M. led the analysis and assisted with study design and interpretation of results. G.C. and B.Y. assisted with the analysis and study design. V.D.L., M.J.M., E.W. and J.S.G.M. aided in study design, interpretation of results and provided critical revisions to the article. J.S.G.M. led the procurement of the database. All authors approved the final draft.

The lead author (B.N.) affirms that the manuscript is an honest, accurate and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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Fig. 1. Directed acyclic graph illustrating the hypothesized causal relationship between time-varying opioid substitution treatment and HAART exposure
 C, confounding factors, including time-invariant and time-varying covariates; E, exposure to OST; O, outcome, HAART adherence.

Fig. 2. Study sample selection

OST, opioid substitution treatment; PWID, people who inject drugs.

Table 1

Characteristics of HIV-positive people who inject drugs meeting study eligibility criteria: British Columbia, Canada, 1996–2010.

Variable	N(%) /Median (IQR)
Number of HIV-positive clients in OST	1852
Age (years)	35 (29–41)
<30	371 (20%)
30–39	729 (39%)
40–49	553 (30%)
50+	199 (11%)
Female sex	629 (34%)
Aboriginal	
Yes	492 (27%)
No	1360 (73%)
Place of residence (HA) at baseline	
Interior	118 (6%)
Fraser	445 (24%)
Vancouver Coastal	908 (49%)
Vancouver Island	294 (16%)
Northern	87 (5%)
On HAART at baseline ^a	966 (52%)
On OST at baseline ^a	372 (20%)
On HAART and OST at baseline ^a	98 (5%)
CD4 ⁺ cell count at baseline (cells/μl)	
Missing	89 (5%)
<200	570 (31%)
200–499	806 (44%)
500	387 (21%)
OST medication dosage at baseline	
Titration	102 (6%)
Taper	153 (8%)
Minimum (max dosage 60 mg)	208 (11%)
Low (max dosage <60 mg)	56 (3%)
Off therapy	1333 (72%)
Number of prior OST episodes at baseline	0 (0–1)
0	1133 (61%)
1	423 (23%)
2	296 (16%)
CCI (>0) at baseline	585 (32%)
AIDS at baseline	318 (17%)
Calendar year at baseline	
1996–1999	853 (46%)

Variable	N(%) /Median (IQR)
2000–2003	364 (20%)
2004–2007	635 (34%)
Number of deaths during follow-up	465 (25%)
Ever accessed HAART during follow-up	1640 (89%)
Ever accessed OST during follow-up	932 (50%)

CCI, Charlson comorbidity index; IQR, interquartile range; OST, opioid substitution treatment.

^aOn HAART/OST (95% medication refill adherence in a month)

Table 2

Summary statistics on exposure to opioid substitution treatment and HAART throughout study follow-up.

Variable	Median (IQR)
Total years of follow-up	(2.2–10.1)
Total time on HAART ^a /Total follow-up (%)	44 (14–71)
Total time on OST ^a /Total follow-up (%)	0 (0–45)
Total time on HAART only/Total follow-up (%)	21 (5–55)
Total time on OST only/Total follow-up (%)	0 (0–13)
Total time on HAART and OST/Total follow-up (%)	0 (0–16)
Total time off HAART and OST/Total follow-up (%)	41 (15–73)
Total time on HAART during OST/Total time on OST ^b (%)	56 (14–86)
Total time on HAART outside OST/Total time outside OST ^c (%)	38 (11–69)
Time to HAART initiation following HAART eligibility ^d (years)	0.3 (0.1–1.3)
Time to OST initiation following HAART eligibility ^d (years)	1.6 (0.0–5.6)

Statistics were based on a monthly data set. IQR, interquartile range; OST, opioid substitution treatment.

^aOn HAART/OST: 95% medication refill adherence in a month.

^bAmong 856 patients who were on OST for at least 1 month (95% adherent) during follow-up.

^cAmong 1828 individuals who had at least 1 month out of OST (<95% adherent) during follow-up.

^dIf never accessed HAART or OST during follow-up, the last observation was used.

Table 3

Multiple regression analysis on the effect of opioid substitution treatment on HAART medication refill adherence.

Model specification	N	Measure of effect [OR (95% CI)]	Mean (SD) of IPTWs ^a
Unweighted estimates			
Unadjusted, GEE	1852	1.54 (1.36–1.75)	–
Baseline adjusted, GEE	1852	1.96 (1.72–2.24)	–
Baseline +time-dependent adjusted, GEE	1852	1.91 (1.68–2.19)	–
Weighted estimates			
Baseline model with truncated IPTW	1852	1.68 (1.48–1.92)	1.01 (0.34)
Sensitivity analyses			
80% HAART adherence	1852	1.69 (1.48–1.93)	1.01 (0.34)
50% HAART adherence	1852	1.67 (1.46–1.90)	1.01 (0.35)
80% OST adherence	1852	1.80 (1.56–2.07)	0.99 (0.22)
50% OST adherence	1852	1.84 (1.58–2.15)	0.98 (0.18)
No OST prior to HAART eligibility	1133	2.10 (1.69–2.60)	0.99 (0.26)
OST prior to HAART eligibility	719	1.49 (1.26–1.75)	1.05 (0.56)
OST with minimum effective dose ^b	1852	1.41 (1.22–1.63)	1.02 (0.49)
OST during maintenance treatment	1852	1.52 (1.12–2.07)	1.50 (3.52)
Cohort started from initial HAART	1821	1.60 (1.39–1.86)	1.00 (0.29)

95% CI, 95% confidence interval; GEE, generalized estimating equations; IPTW, inverse probability of treatment weights; OR, odds ratio; OST, opioid substitution treatment; SD, standard deviation.

^aFor the assumption of positivity or no misspecification to hold, the mean of IPTWs should be approximately equal to one.

^bDefined as at least 60 mg/day at some point during the OST episode.