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# The Impact of Opioid Substitution Treatment on Highly Active Antiretroviral Treatment Adherence


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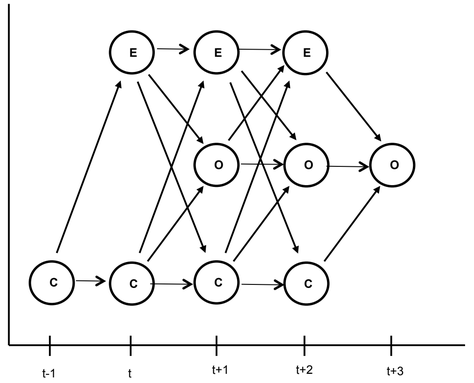
## Background

- Injection drug users 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 highly-active antiretroviral therapy (HAART), yet sparse evidence is available to support this hypothesis.
- Our objective is to determine the causal impact of OST exposure on adherence to HAART among HIV-positive opioid dependent individuals in a Canadian setting.

## Methods

- We selected all identified HAART-eligible HIV-positive individuals ever accessing OST, as indicated by methadone or buprenorphine dispensation records in the BC PharmaNet database, from July 1st, 1996 to March 31st, 2010.
- The dependent variable in the study was 95% HAART adherence, according to pharmacy refill compliance records, measured on a monthly basis.
- Exposure to OST, defined by ≥21 days of OST dispensed in a calendar month was the key independent variable considered.
- Past HAART adherence can be considered a time-dependent confounder for the effect of OST on future HAART adherence, since it may be hypothesized to not only predict future HAART adherence, but also subsequent initiation of OST, and past OST history is an independent predictor of subsequent HAART adherence. The hypothesized relationship is characterized in the directed acyclic graph illustrated in **Figure 1**.
- To control for time-varying confounding in the exposure-outcome relationship, a marginal structural model was used with monthly-updated inverse probability of treatment weights (IPTW).
- We controlled for fixed and time-varying covariates, including age, gender, ethnicity, geographic area of residence, calendar year, OST history at HAART eligibility, AIDS status, CD4 and prior HAART exposure in estimated IPTW.

**Figure 1. Directed acyclic graph illustrating the hypothesized causal relationship between time-varying OST and HAART exposure**




## Results

- Among 12,349 HIV-positive individuals observed in BC between 1996 and 2010, 1,811(14.7%) accessed OST, with 1,337(73.8%) eligible for our study.
- Subjects were 39% female, were of median age 35 (interquartile range:29-41) at HAART eligibility, and had a median of 6.8 years (2.9-11.1) of follow-up.
- During OST, individuals spent a median 55%(20%-84%) of the time on HAART, while out of OST individuals spent only 26%(7%-56%) of the time on HAART (**Table 1**).
- The unadjusted odds of HAART adherence during OST exposure was 2.27 (95% confidence interval: 2.01-2.55), while the adjusted odds, estimated within the marginal structural model, was 1.95 (1.71-2.23) (**Table 2**).
- We considered three changes in the classification of OST exposure: (i) using a 95% adherence threshold to indicate exposure, (ii) requiring treatment at the minimum effective dose, and (iii) requiring that individuals be at a stable maintenance dose to be classified as exposed. In each case, adjusted odds ratios in the structural model decreased, but remained statistically significantly positive (**Table 2**).
- We also considered subgroups of individuals becoming eligible in the modern HAART era, and those with no OST experience at HAART eligibility. In each case, odds ratios were higher than in the baseline model formulation (**Table 2**).

**Table 1. Summary statistics on exposure to OST and HAART throughout study follow-up**

| Variable | Median (IQR) |
|---|---|
| Total years of follow-up | 6.8 (2.9 – 11.1) |
| Total time on HAART / Total follow-up (%) | 44 (20 – 68) |
| Total time on OST / Total follow-up (%) | 52 (14 – 87) |
| Total time on HAART only / Total follow-up (%) | 7 (1 – 24) |
| Total time on OST only / Total follow-up (%) | 14 (2 – 37) |
| Total time on HAART and OST / Total follow-up (%) | 18 (0 – 50) |
| Total time off HAART and OST / Total follow-up (%) | 27 (5 - 53) |
| Total time on HAART during OST / Total time on OST (%) | 55 (20 – 84) |
| Total time on HAART outside OST / Total time outside OST (%) | 26 (7 – 56) |
| Time to HAART initiation following HAART eligibility (years) | 0.3 (0.0 – 1.3) |
| Time to OST initiation following HAART eligibility (years) | 0.4 (0.0 – 2.3) |

**Table 2. Sensitivity analysis on the effect of OST on HAART**

| Model Specification | N | Measure of effect (OR (95% CI)) | Mean (SE) of IPTWs* |
|---|---|---|---|
| **Unweighted estimates** | | | |
| Unadjusted, GEE | 1337 | 2.27 (2.01,2.55) | - |
| Baseline adjusted, GEE | 1337 | 2.11 (1.85,2.39) | - |
| Baseline + time-dependent adjusted, GEE | 1337 | 2.12 (1.86,2.41) | - |
| **Weighted estimates** | | | |
| Baseline model specification | 1337 | 1.95 (1.71,2.23) | 1.01 (0.23) |
| Baseline model with truncated IPTW | 1337 | 1.97 (1.72,2.25) | 1.01 (0.19) |
| Initiating treatment with modern-era HAART (ITT) | 441 | 2.22 (1.74,2.83) | 1.01 (0.23) |
| No OST experience prior to HAART eligibility | 649 | 2.21 (1.87,2.61) | 1.00 (0.19) |
| 95% OST adherence | 1337 | 1.66 (1.48,1.86) | 1.04 (0.85) |
| OST with minimum effective dose | 1337 | 1.41 (1.22,1.63) | 1.02 (0.49) |
| OST during maintenance treatment | 1337 | 1.37 (1.20,1.56) | 1.02 (0.40) |

GEE: Generalized Estimating Equations; OR (95% CI): Odds Ratio (95% Confidence interval); ITT: Intent-to-treat; SE: standard error; IPTW: Inverse probability of treatment weights. *For the assumption of positivity or no misspecification to hold, the mean of IPTWs should be approximately equal to one.

## Conclusions

- In a setting characterized by universal healthcare and widespread access to both office-based OST and HAART, we found that accessing OST nearly doubles the odds of HAART adherence among opioid-dependent individuals with HIV.
- The results were robust to a number of sensitivity analyses focusing on the assumptions of correct model specification inherent in the selected modeling approach.
- These findings underline the need to address barriers to OST globally to reduce the disease burden of both opioid dependence and HIV/AIDS.

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