The effects of Opioid Substitution Treatment and Highly Active Antiretroviral Therapy on cause-specific risk of mortality among Injection drug using people living with HIV/AIDS

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Background

- Human immunodeficiency virus (HIV) and opioid use disorder carry a substantial public health burden and a high risk of mortality.
- Prior studies indicate that opioid substitution treatment (OST) reduces the risk of mortality and improves the odds of accessing highly active antiretroviral therapy (HAART), however the relative effects of these treatments for injection drug using people living with HIV/AIDS (PLHIV) are unclear.
- We aim to determine the independent and joint effects of OST and HAART on mortality, by cause, within a population of injection drug PLHIV initiating HAART

Methods

- We used a linked population-level administrative database for British Columbia, Canada (1996-2010) to form a cohort of injection drug using PLHIV.
- Our dependent variable was mortality, stratified by cause as follows: drug related, HIV-related, and other cause of death. Key time-variable exposures included OST receipt and HAART receipt.
- We employed time-to-event analytic methods, including competing risks models, proportional hazards models with time-varying covariates, and marginal structural models, to identify the independent and joint effects of OST and HAART on all-cause, as well as drug- and HIV-related mortality, controlling for covariates.

Results

- Among 1,727 injection drug using PLHIV, 493 (28.5%) died during a median 5.1 years (interquartile range:2.1-9.1) of follow-up: 18.7% due to drug-related causes, 55.8% due to HIV-related causes, and 25.6% due to other causes.
- Standardized mortality ratios were 12.2 (95%CI:9.8,15.0) during OST, and 30.0(27.1,33.1) during periods out of OST (**Table 1**).
- Nonparametric estimates of the cumulative hazard of mortality due to OST exposure demonstrated a strong protective effect of OST on the hazard of HIV and other causes of death, but not drug-related death (**Figure 1A**).
- In contrast, HAART had a similarly strong effect on the hazard of HIV-related death and comparable, significant effects on deaths due to drugs and other causes (**Figure 1B**).
- Both the subdistribution PH and marginal structural models demonstrated a similarly large negative effect of OST or HAART on all-cause mortality (**Table 2**).
- We found OST had relatively weaker and not statistically significant results on drug-related deaths compared with those of HIV-related deaths (**Table 2**).
- On the other hand, HAART had a strong and statistically significant negative association with drug-related death (**Table 2**).
- Both OST and HAART had a strong and statistically significant negative association with HIV-related mortality (**Table 2**).
- The risk of death was lowest when individuals were engaged in both forms of treatment (**Table 2**).

Table 1. Standardized Mortality Ratios, by OST and HAART

	No. deaths	Person-years of follow-up	SMR (95% CI)
Overall	493	9,913	23.8 (21.7, 25.9)
Off OST	404	5,934	30.0 (27.1, 33.1)
On OST	89	3,979	12.2 (9.8, 15.0)
Off HAART	306	3,855	45.2 (40.3, 50.6)
On HAART	187	6,058	13.4 (11.5, 15.4)
OST and HAART			
Off OST&HAART	258	2,455	58.4 (51.5, 65.9)
On OST only	48	1,400	20.4 (15.1, 27.1)
On HAART only	146	3,478	16.1 (13.6, 19.0)
On OST&HAART	41	2,580	8.3 (6.0, 11.3)

OST: Opioid substitution treatment; SMR: Standardized Mortality Ratio; 95% CI: 95% confidence interval.

Figure 1. Nelson-Aalen estimates of the cumulative hazard of mortality due to OST and HAART exposure

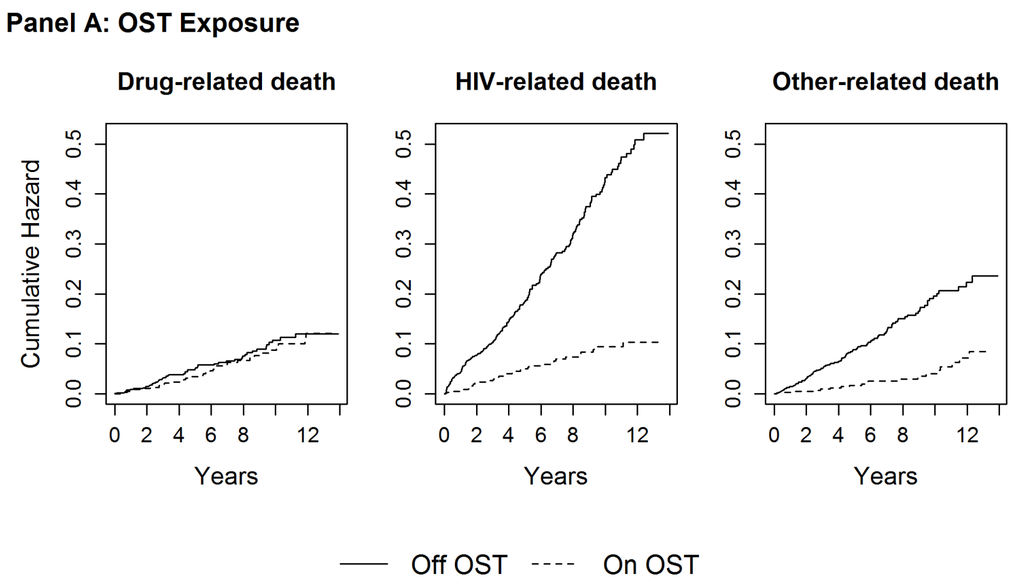

Table 2. Results of multiple regression analysis on the effect of OST and HAART on all-cause and cause-specific mortality

Covariate	All-cause mortality	COD: drug-related	COD: HIV-related
Subdistribution PH model 1[a]			
OST	0.20 (0.15,0.26)	0.65 (0.39,1.09)	0.20 (0.14,0.30)
HAART	0.29 (0.24,0.35)	0.54 (0.35,0.84)	0.31 (0.24,0.40)
Subdistribution PH model 2[a]			
Off OST and HAART	ref	ref	ref
On OST only	0.18 (0.13,0.25)	0.60 (0.32,1.12)	0.21 (0.13,0.35)
On HAART only	0.29 (0.23,0.36)	0.49 (0.28,0.87)	0.31 (0.23,0.42)
On OST and HAART	0.07 (0.05,0.09)	0.37 (0.20,0.70)	0.06 (0.04,0.11)
Marginal structural model 1[b,c]			
OST	0.34 (0.23,0.49)	0.68 (0.42,1.12)	0.33 (0.23,0.48)
Marginal structural model 2[b,d]			
HAART	0.39 (0.31,0.48)	0.49 (0.32,0.75)	0.34 (0.26,0.44)
Marginal structural model 3[b]			
Off OST and HAART	ref	ref	ref
On OST only	0.34 (0.22,0.52)	0.45 (0.22,0.92)	0.35 (0.21,0.56)
On HAART only	0.46 (0.34,0.62)	0.37 (0.21,0.64)	0.35 (0.26,0.46)
On OST and HAART	0.16 (0.10,0.26)	0.40 (0.22,0.73)	0.14 (0.08,0.23)

COD: Cause of death; OST: Opioid substitution treatment; HAART: Highly active antiretroviral therapy; PH: Proportional Hazards; AHR: adjusted hazard ratio; 95% CI: 95% confidence interval; [a] Data are organized into durations on and off OST and HAART. [b] Data is organized in monthly intervals; OST and HAART receipt in at least 95% of days in a given month; estimated parameters are cause-specific hazard ratios. [c] HAART is included as a time-dependent confounder in the model. [d] OST is included as a time-dependent confounder in the model.

Conclusion

- Both HAART and OST are independently negatively associated with mortality in this population; however, the risk of death was lowest when individuals were engaged in both forms of treatment.
- Joint administration of HAART and OST is urgently needed to protect against both drug- and HIV-related mortality.

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