Reductions in Mortality Rates among HIV-Positive People Who Inject Drugs in Vancouver, Canada, during a Treatment-as-Prevention-Based HAART Scale-up Initiative: A Gender-Based Analysis

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Background

- HIV/AIDS remains a major cause of death among people who inject drugs (PWID).
- However, little is known about the impact of recent efforts to expand access to antiretroviral therapy (ART) on mortality in this population, including how such impacts might vary by gender.
- Therefore, we conducted a gender-based analysis to identify rates and predictors of death among HIV-positive PWID in Vancouver, Canada, where an HIV Treatment-as-Prevention (TasP) initiative has been greatly scaled up since 2010.

Methods

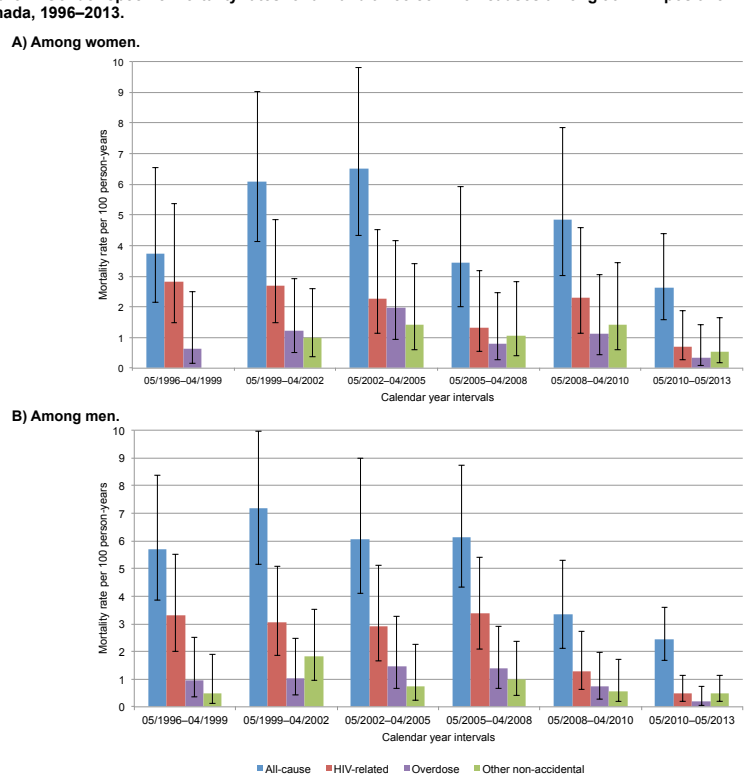
- Data were derived from the AIDS Care Cohort to evaluate Exposure to Survival Services (ACCESS), an open prospective cohort study of HIV-positive people who use illicit drugs in Vancouver, Canada, beginning in May 1996.
- Through self-referral and street-based outreach, ACCESS has enrolled HIV-positive individuals who were aged ≥18 years, had used illicit drugs other than cannabis in the previous month, resided in the Greater Vancouver area, and provided informed consent.
- At baseline and semi-annually thereafter, participants complete an interviewer-administered questionnaire soliciting data on socio-demographics, drug use patterns, and other exposures, and underwent hepatitis C virus testing. Participants were compensated $30 CAD at each visit.
- ACCESS data were confidentially linked to a province-wide centralized HIV treatment dispensation program database, through which a complete HIV-related clinical profile of each participant was obtained. ACCESS data were also confidentially linked to the British Columbia Vital Statistics database to ascertain rates and causes of death.
- For the present analysis, the sample was restricted to those who completed the baseline and at least one follow-up visit between May 1996 and May 2013 and reported a history of injection drug use at baseline.
- Causes of death were classified into the following six categories: HIV-related, overdose, liver-related, other accidental, other non-accidental, and unknown causes.
- We fit multivariable Poisson regression models including age and gender as independent variables to calculate age-adjusted relative risk of death from each specific cause among women compared to men.
- We also used multivariable Poisson regression including age and calendar year intervals before and after the wide-scale implementation of the TasP initiative (2010–2013 *vs.* 1996–2009) to examine changes in mortality rates among men and women, respectively.
- We fit multivariable extended Cox regression models to identify predictors of all-cause mortality among men and women, respectively. We considered a range of demographic, behavioural, clinical and social/structural variables that might be associated with all-cause mortality, as presented in Table 2.

Table 1: Baseline Characteristics of 961 HIV-positive PWID in Vancouver, Canada, 1996–2013.

Characteristic	Total *n* (%)	Female 353 (36.7%)	Male 608 (63.3%)	*P* - value
Calendar year of enrolment (median [IQR])	2006 (1996–2009)	1999 (1996–2007)	2006 (1996–2009)	<0.001
Age (median [IQR])	39.4 (32.2–45.6)	35.0 (28.1–42.8)	41.3 (34.8–46.7)	<0.001
Years since first injection (median [IQR])	15.9 (8.1–24.2)	13.5 (6.5–22.0)	17.6 (9.2–25.4)	<0.001
Caucasian	537 (55.9%)	159 (45.0%)	378 (62.2%)	<0.001
≥ Daily heroin injection[a]	252 (26.2%)	136 (38.5%)	116 (19.1%)	<0.001
≥ Daily cocaine injection[a]	286 (29.8%)	122 (34.6%)	164 (27.0%)	0.010
≥ Daily methamphetamine injection[a]	24 (2.5%)	8 (2.3%)	16 (2.6%)	0.729
≥ Daily PO injection or non-injection use[a]	89 (9.3%)	34 (9.6%)	55 (9.0%)	0.667
≥ Daily crack smoking[a]	244 (25.4%)	109 (30.9%)	135 (22.2%)	0.002
Cannabis use[a]	513 (53.4%)	159 (45.0%)	354 (58.2%)	<0.001
≥ Daily alcohol use[a]	149 (15.5%)	59 (16.7%)	90 (14.8%)	0.443
Unstable housing[a]	688 (71.6%)	243 (68.8%)	445 (73.2%)	0.242
Sex work[a]	227 (23.6%)	177 (50.1%)	50 (8.2%)	<0.001
Incarceration[a]	250 (26.0%)	95 (26.9%)	155 (25.5%)	0.601
Enrolled in MMT[a]	288 (30.0%)	125 (35.4%)	163 (26.8%)	0.005
Enrolled in addiction treatment other than MMT[a]	374 (38.9%)	149 (42.2%)	225 (37.0%)	0.112
Access and adherence to ART[a]				0.042
CD4 cell count of ≥200 cells/mm^3 at ART initiation and ≥95% ART adherence in the first year	154 (16.0%)	41 (11.6%)	113 (18.6%)	
CD4 cell count of <200 cells/mm^3 at ART initiation or <95% ART adherence in the first year	651 (67.7%)	251 (71.1%)	400 (65.8%)	
Never accessed ART	154 (16.0%)	60 (17.0%)	94 (15.5%)	
Years since HAART initiation (median [IQR])	0.0 (0.0–3.0)	0.0 (0.0–1.0)	0.0 (0.0–4.0)	<0.001
Plasma HIV-1 RNA viral load[a] (log10, median [IQR])	4.1 (2.0–4.8)	4.1 (2.8–4.8)	4.0 (1.8–4.8)	0.243
HCV seropositivity	874 (90.9%)	331 (93.8%)	543 (89.3%)	0.003

ART, antiretroviral therapy; CI, Confidence Interval; HAART, highly-active antiretroviral therapy; HCV, hepatitis C virus; IQR, interquartile range; MMT, methadone maintenance therapy; PO, prescription opioid; PWID, people who inject drugs.
[a] denotes activities/events in the past 6 months.

Figure 1: Gender-specific mortality rates for all- and three common causes among 961 HIV-positive PWID in Vancouver, Canada, 1996–2013.



Results

- In total, 961 HIV-positive PWID were eligible for the present analysis, including 353 (36.7%) women. Baseline sample characteristics are presented in Table 1.
- There were 264 deaths during follow-up, resulting in a mortality rate among men of 4.64 (95% confidence interval [CI]: 3.98 – 5.40) and 4.41 (95% CI: 3.65 – 5.32) deaths per 100 person-years among women.
- As shown in Table 2, there was no gender-based difference in age-adjusted all-cause mortality rates (adjusted rate ratio [ARR]: 1.02; 95% CI: 0.79 – 1.31). The only significant gender-based difference in age-adjusted mortality rates was detected in liver-related mortality (ARR: 0.12; 95% CI: 0.02 – 0.96).
- Figure 1 shows gender-specific mortality rates for all- and three common causes over time. In multivariable Poisson regression analyses, HIV-related mortality rates have significantly declined since 2010 among both men (ARR: 0.11; 95% CI: 0.04 – 0.28) and women (ARR: 0.20; 95% CI: 0.07 – 0.55).
- In multivariable Cox regression analyses (Table 3), those who initiated ART at a CD4 cell count ≥200 cells/mm^3 and had ≥95% adherence to ART in the first year of treatment had a significantly lower hazard of death compared to those who never accessed ART among both men (adjusted hazard ratio [AHR]: 0.18; 95% CI: 0.09 – 0.34) and women (AHR: 0.35; 95% CI: 0.17 – 0.72).
- Daily prescription opioid use was independently and positively associated with mortality among men only (AHR: 2.07; 95% CI: 1.35 – 3.17).

Table 2: Causes of death and gender-specific mortality rates among HIV-positive PWID in Vancouver, Canada, 1996–2013.

Causes of death	Total sample (*n* = 961)		Females (*n* = 353)		Males (*n* = 608)		Age-adjusted rate ratio (ARR)
	n (%)	Rate[a] (95% CI)	*n (%)*	Rate[a] (95% CI)	*n (%)*	Rate[a] (95% CI)	ARR[b] (95% CI)
All causes	264 (100)	4.5 (4.0, 5.1)	105 (100)	4.4 (3.7, 5.3)	159 (100)	4.6 (4.0, 5.4)	1.02 (0.79, 1.31)
HIV-related	115 (43.6)	2.0 (1.7, 2.4)	45 (42.9)	1.9 (1.4, 2.5)	70 (44.0)	2.0 (1.6, 2.6)	0.93 (0.63, 1.36)
Overdose	51 (19.3)	0.9 (0.7, 1.2)	23 (21.9)	1.0 (0.6, 1.5)	28 (17.6)	0.8 (0.6, 1.2)	1.29 (0.72, 2.32)
Liver-related	14 (5.3)	0.2 (0.1, 0.4)	1 (1.0)	0.04 (0.01, 0.3)	13 (8.2)	0.4 (0.2, 0.7)	0.12 (0.02, 0.96)
Other accidental[c]	15 (5.7)	0.3 (0.2, 0.4)	7 (6.7)	0.3 (0.1, 0.6)	8 (5.0)	0.2 (0.1, 0.5)	1.03 (0.35, 2.97)
Other non-accidental[d]	48 (18.2)	0.8 (0.6, 1.1)	21 (20.0)	0.9 (0.6, 1.4)	27 (17.0)	0.8 (0.5, 1.2)	1.52 (0.85, 2.73)
Ill-defined/unknown	21 (7.9)	0.4 (0.2, 0.6)	8 (7.5)	0.3 (0.2, 0.7)	13 (8.2)	0.4 (0.2, 0.7)	0.88 (0.38, 2.06)

PWID, people who inject drugs; CI, confidence interval.
[a] Rates are per 100 person-years.
[b] Females *vs.* males.
[c] Includes: homicide, suicide, transport accidents, accidental falls, etc.
[d] Includes: circulatory disease, respiratory disease, neoplasms, etc.

Table 3: Univariable and multivariable Cox regression analyses of factors associated with all-cause mortality among HIV-positive PWID in Vancouver, Canada, 1996–2013.

Characteristic	Females (*n* = 353)		Males (*n* = 608)	
	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
Calendar year of study enrolment				
(per year later)	0.94 (0.89, 0.99)		0.91 (0.88, 0.95)	0.95 (0.91, 1.00)
Age[a]				
(per 10 years older)	1.22 (0.99, 1.51)	1.35 (1.09, 1.68)	1.15 (0.95, 1.38)	
Ancestry				
(Caucasian *vs.* other)	0.91 (0.62, 1.35)		1.33 (0.96, 1.84)	1.35 (0.95, 1.92)
Years since first injection at baseline				
(per year longer)	1.01 (0.99, 1.04)		1.01 (1.00, 1.03)	
Heroin injection[a,b]				
(≥ daily *vs.* < daily)	0.78 (0.48, 1.26)		1.13 (0.73, 1.75)	
Cocaine injection[a,b]				
(≥ daily *vs.* < daily)	0.79 (0.46, 1.34)		1.11 (0.74, 1.66)	
Methamphetamine injection[a,b]				
(≥ daily *vs.* < daily)	0.85 (0.11, 6.52)		0.29 (0.04, 2.09)	
PO injection or non-injection use[a,b]				
(≥ daily *vs.* < daily)	0.98 (0.42, 2.29)		2.00 (1.23, 3.24)	2.07 (1.35, 3.17)
Crack cocaine smoking[a,b]				
(≥ daily *vs.* < daily)	1.02 (0.68, 1.53)		1.06 (0.73, 1.55)	
Cannabis use[a,b]				
(yes *vs.* no)	1.08 (0.73, 1.61)		0.87 (0.64, 1.17)	
Alcohol use[a,b]				
(≥ daily *vs.* < daily)	1.03 (0.56, 1.89)		1.58 (1.04, 2.41)	
Unstable housing[a,b]				
(yes *vs.* no)	1.27 (0.85, 1.89)		1.16 (0.84, 1.60)	
Sex work[a,b]				
(yes *vs.* no)	0.85 (0.53, 1.35)		1.13 (0.52, 2.46)	
Cumulative incarceration events[a]				
(1–2 times *vs.* never)	1.05 (0.66, 1.67)		1.23 (0.83, 1.83)	
(3–5 times *vs.* never)	0.77 (0.44, 1.35)		1.28 (0.83, 2.00)	
(> 5 times *vs.* never)	1.05 (0.49, 2.25)		0.90 (0.51, 1.57)	
Enrolled in MMT[a,b]				
(yes *vs.* no)	0.79 (0.54, 1.16)		0.71 (0.52, 0.98)	
Enrolled in addiction treatment other than MMT[a,b]				
(yes *vs.* no)	0.72 (0.49, 1.05)		0.86 (0.63, 1.16)	
Access and adherence to ART[a]				
(CD4 cell count of ≥200 cells/mm^3 at ART initiation and ≥95% ART adherence in the first year *vs.* never accessed)	0.27 (0.12, 0.59)	0.35 (0.17, 0.72)	0.13 (0.07, 0.25)	0.18 (0.09, 0.34)
(CD4 cell count of <200 cells/mm^3 at ART initiation or <95% ART adherence in the first year *vs.* never accessed)	0.33 (0.21, 0.52)	0.35 (0.22, 0.55)	0.25 (0.17, 0.37)	0.27 (0.17, 0.43)
Years since HAART initiation[a]				
(per year longer)	0.96 (0.90, 1.01)		0.92 (0.88, 0.96)	1.04 (0.99, 1.10)
Plasma HIV-1 RNA viral load[a,b]				
(per year log10 increase)	1.36 (1.17, 1.59)	1.43 (1.22, 1.67)	1.48 (1.32, 1.66)	1.32 (1.14, 1.53)
HCV serostatus[a]				
(positive *vs.* negative)	1.37 (0.34, 5.43)		1.80 (0.64, 5.05)	

ART, antiretroviral therapy; CI, Confidence Interval; HAART, highly-active antiretroviral therapy; HCV, hepatitis C virus; HR, hazard ratio; MMT, methadone maintenance therapy; PO, prescription opioid; PWID, people who inject drugs.
[a] denotes time-updated variables.
[b] denotes activities/events in the past 6 months.

Conclusions

- In this 18-year cohort study of community-recruited HIV-positive PWID, mortality rates were similar between male and female participants.
- HIV-related mortality rates have significantly declined since the beginning of efforts to expand access and adherence to ART, suggesting that TasP-based efforts to scale-up ART among PWID have been associated with sharp declines in HIV/AIDS-related mortality among this population.
- High-intensity prescription opioid use independently predicted mortality among men, indicating a need to identify factors shaping harms from prescription opioid use among this population.

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