Patterns of transmitted drug resistance and virological response to first-line antiretroviral treatment among HIV-positive people who use illicit drugs in a Canadian setting

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Background

- Transmitted drug resistance (TDR) may compromise response to antiretroviral treatment (ART), with potential negative clinical and public health implications.
- There is limited data on TDR patterns and impacts among people who use illicit drugs (PWUD).
- The objectives of this study were:
  1. to characterize patterns of TDR, and
  2. to assess TDR impacts on first-line ART virological outcomes among PWUD in Vancouver, Canada, between 1996 and 2015.

Methods

Design and setting: Data was drawn from two prospective cohorts of PWUD with harmonized procedures in Vancouver, Canada: the AIDS Care Cohort to Evaluate exposure to Survival Services (ACCESS) study and the Vancouver Injection Drug Users Study (VIDUS) studies.

Study procedures: Semi-annual interview, serological testing (e.g., HIV/HCV) and linkages with the provincial HIV Drug Treatment program (e.g., genotypic tests, CD4, VL, ART dispensation).

Study population: HIV-positive participants enrolled between May 1996 and May 2015 with ≥1 genotypic resistance test while ART naïve.

Measures:

- Transmitted Drug Resistance: The WHO surveillance drug resistance mutations (SDRM) list was used for identification of TDR.
- Other measures: Socio-demographic characteristics (age, sex, self-reported ethnicity), HIV-related variables (recent HIV infection among CD4 count and HIV VL at the time of the genotypic test), HCV co-infection, and history of injection drug use, sex work and incarceration.

Analyses:

1- TDR Patterns

- We calculated the overall (participants with ≥1 SDRM) prevalence of TDR, and for each specific class of ARV (NRTI, NNRTI, PI).
- Trends of prevalence of TDR over time were analyzed using the Cochran-Armitage test and $\chi 2$ test for trend.
- Bivariable and multivariable logistic regression analyses were used to identify the independent correlates of TDR.

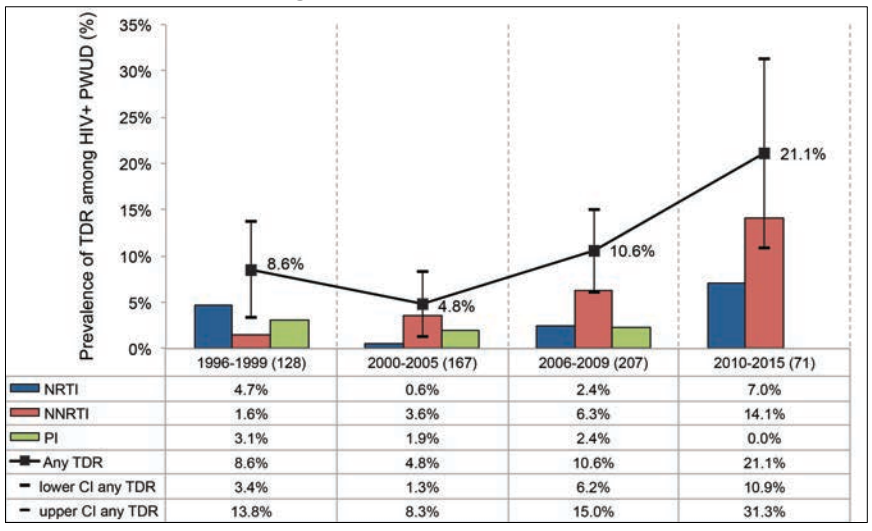
2- TDR impacts on first-line ART regimen

- Analysis restricted to participants who had at least one VL test after 180 days of ART initiation.
- Using the Standford HIVdb algorithm version 8.3, participants were classified as:
  1. no TDR,
  2. TDR with fully active first-line ART (no resistance mutation affecting the prescribed ART), or
  3. TDR with non-fully active ART (≥1 resistance mutation associated with reduced susceptibility to at least one of the drugs of their prescribed ART).
- Kaplan Meier curves we evaluated time to virological failure (2 consecutive VL >50 copies/mL, after 180 days of ART initiation) considering the date of the first VL >50 copies/mL, as failure date.

Results

- 573 HIV-positive PWUD were included
- At baseline:
  - Age, median (IQR): 37 years (31–44)
  - Male: 370 (64.6%)
  - History of injection drug use: 545 (95.1%)
  - Recent HIV infection: 101 (17.6%)
  - CD4 count, median (IQR): 380 cells/μL (230–530)
  - VL, median (IQR): 4.6 $\log_{10}$ copies/mL (IQR 4.0–5.0)
- 496 (86.6%) participants initiated ART
  - Of the 47 participants with TDR, 35 (74.5%) were prescribed a fully active ART
- Overall TDR prevalence: 9.8% (95%CI: 7.3–12.2)
- NRTI SDRM: 3.0% (95%CI 1.5–4.4)
- NNRTI SDRM: 5.4% (95%CI 3.5–7.3)
- PI SDRM: 1.9% (95%CI 0.7–3.1)

Trends in TDR among HIV+ PWUD in Vancouver (1996-2015)



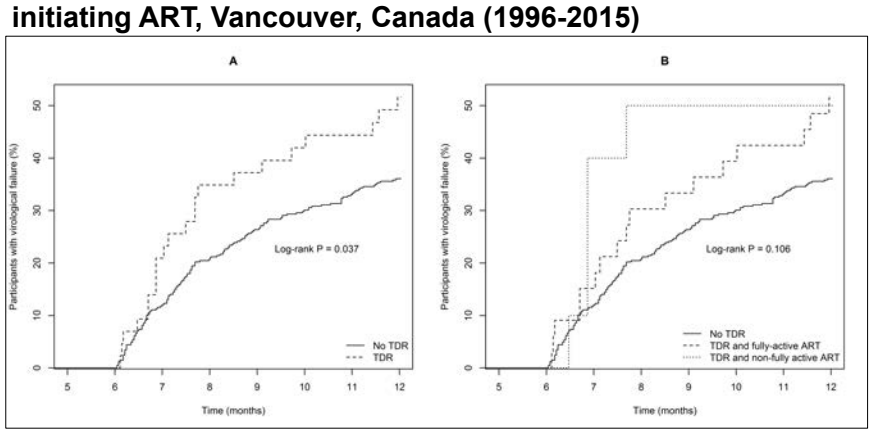
	1996-1999 (128)	2000-2005 (167)	2006-2009 (207)	2010-2015 (71)
NRTI	4.7%	0.6%	2.4%	7.0%
NNRTI	1.6%	3.6%	6.3%	14.1%
PI	3.1%	1.9%	2.4%	0.0%
Any TDR	8.6%	4.8%	10.6%	21.1%
lower CI any TDR	3.4%	1.3%	6.2%	10.9%
upper CI any TDR	13.8%	8.3%	15.0%	31.3%

Unadjusted and adjusted logistic regression analyses of factors associated with TDR

Characteristic	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Age (per 10 years older)¶	1.34 (1.06 – 1.70)†	1.25 (0.98 – 1.61)
Male gender (yes vs. no)	1.73 (1.04 – 3.00)†	1.61 (0.94 – 2.84)
Caucasian ethnicity (yes vs. no)	0.91 (0.57 – 1.46)	
Injection drug use (yes vs. no)*	3.03 (0.77 – 29.42)	
HCV-seropositive (yes vs. no)*	0.71 (0.40 – 1.31)	
Recent HIV infection (yes vs. no)*	0.33 (0.12 – 0.73)†	0.39 (0.15 – 0.87)
CD4 count (ref: <200 cells/μL)¶		
200-349	1.53 (0.69 – 3.57)	
350-499	1.65 (0.77 – 3.76)	
≥500	2.28 (1.11 – 5.04)†	
HIV VL (>5 $\log_{10}$ vs. ≤5 $\log_{10}$ copies/mL)¶	0.49 (0.26 – 0.87)†	0.47 (0.25 – 0.83)
Sex work (yes vs. no)*	0.68 (0.41 – 1.10)	
Incarceration (yes vs. no)*	1.18 (0.63 – 2.39)	

OR, odds ratio. CI, confidence interval. VL, viral load.
¶ At the time of the genotypic resistance test
* Refers to lifetime behavior or exposure
† p<0.10 and considered in the multivariable model selection process

Cumulative incidence of virologic failure among HIV+ PWUD initiating ART, Vancouver, Canada (1996-2015)



Panel A: Risk of virological failure according to presence or not of TDR. Panel B: Risk of virological failure in participants with TDR by predicted susceptibility to first-line ART

Discussion

- We observed moderate overall TDR prevalence (9.8%) among PWUD in Vancouver between 1996-2015.
- TDR prevalence increased significantly over time, largely driven by increases in NNRTI-associated TDR.
- Among participants initiating ART, those with TDR had significantly higher rates of virological failure at 12 months (51.6% vs. 36.1%)
  - Inappropriate ART prescribing?
  - Undetected minority resistant variants?
- Findings support baseline resistance testing early in the course of HIV infection to guide ART selection among PWUD in this setting.

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