Clinical Infectious Diseases

MAJOR ARTICLE

Patterns of Transmitted Drug Resistance and Virological Response to First-line Antiretroviral Treatment Among Human Immunodeficiency Virus–Infected People Who Use Illicit Drugs in a Canadian Setting

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Background. Transmitted drug resistance (TDR) may compromise response to antiretroviral therapy (ART). However, there are limited data on TDR patterns and impacts among people who use illicit drugs (PWUD).

Methods. Data were drawn from 2 prospective cohorts of PWUD in Vancouver, Canada. We characterized patterns of TDR among human immunodeficiency virus (HIV)–infected PWUD, and assessed its impacts on first-line ART virological outcomes.

Results. Between 1996 and 2015, among 573 ART-naive PWUD (18% with recent HIV infection), the overall TDR prevalence was 9.8% (95% confidence interval [CI], 7.3%–12.2%), with an increasing trend over time, from 8.5% in 1996–1999 to 21.1% in 2010–2015 ($P = .003$), mainly driven by resistance to nonnucleoside reverse transcriptase inhibitors (NNRTIs). TDR-associated mutations were more common for NNRTIs (5.4%), followed by nucleoside reverse transcriptase inhibitors (3.0%) and protease inhibitors (1.9%). TDR prevalence was lower among recently infected PWUD (adjusted odds ratio, 0.39 [95% CI, .15–.87]). Participants with TDR had higher risk of virological failure than those without TDR (log-rank $P = .037$) in the first year of ART.

Conclusions. Between 1996 and 2015, TDR prevalence increased significantly among PWUD in Vancouver. Higher risk of virological failure among PWUD with TDR may be explained by some inappropriate ART prescribing, as well as undetected minority resistant variants in participants with chronic HIV infection. Our findings support baseline resistance testing early in the course of HIV infection to guide ART selection among PWUD in our setting.

Keywords. transmitted drug resistance; people who use drugs; HIV; North America; antiretroviral treatment.

Global scale-up of antiretroviral therapy (ART) coverage has led to remarkable declines in human immunodeficiency virus (HIV)–related morbidity and mortality, as well as reductions in new infections [1]. In addition, increasing availability of more potent, safer, and fixed-dosed ART regimens has resulted in improved tolerability and adherence, and consequently reduced the risk of virologic failure among people living with HIV (PLHIV) [2]. Thus, in recent years, rates of acquired drug resistance have declined sharply in most developed countries [3–5]. On the contrary, a similar declining trend has not been observed for transmitted drug resistance (TDR) [3, 6, 7].

Prevalence of TDR varies widely across geographic settings, populations, and calendar time [6]. For example, whereas studies in Europe have documented stable trends in TDR at around 8% for the period 2008–2010 [7, 8], studies conducted in the United States have shown higher and increasing rates of TDR of approximately 17% for the same period [9]. Surveillance data from Canada indicates an overall prevalence of TDR of around 10% for the period 1999–2008 (with higher rates in more recent years) [10].

TDR has important clinical and public health implications. At the individual level, the presence of TDR may limit first-line ART options and, if undetected, increase the risk of virologic failure, which in turn may compromise both the individual- and population-level effectiveness of standardized first-line ART regimens [11]. Thus, surveillance of TDR is critical to inform HIV-related policies and clinical guidelines, particularly with respect to recommended first-line ART regimens and the need of baseline genotypic resistance testing.

Although people who use illicit drugs (PWUD) represent a key population within the HIV pandemic, there is relatively less

Received 6 February 2017; editorial decision 19 April 2017; accepted 3 May 2017; published online May 6, 2017.

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Clinical Infectious Diseases® 2017;65(5):796–802

DOI: 10.1093/cid/cix428

information on TDR patterns and impacts among this group compared to other key populations (eg, men who have sex with men [MSM]) [7]. While existing estimates indicate an overall TDR prevalence between 8% and 10% among people who inject drugs in North America [7, 12, 13], more updated estimates (ie, after 2010) are currently lacking. This represents a critical knowledge gap, particularly in the context of recent outbreaks of HIV infection driven by opioid injection in many North American settings [14]. Therefore, the objective of this study was to evaluate the prevalence, correlates, and trends of TDR, and secondarily to assess its impacts on virological outcomes of first-line ART among HIV-infected PWUD in Vancouver, Canada, from 1996 to 2015.

METHODS

Study Design and Population

Data for this study were drawn from 2 open prospective cohorts of PWUD with harmonized study procedures in Vancouver, Canada: the AIDS Care Cohort to evaluate Exposure to Survival Services (ACCESS) and the Vancouver Injection Drug Users Study (VIDUS) studies. Eligibility and study procedures have been described in detail previously [15, 16]. In brief, individuals are recruited through extensive street outreach and snowball sampling in the greater Vancouver region with a focus on the Downtown Eastside neighborhood, an area with an open drug market and high levels of illicit drug use, poverty, and HIV infection. VIDUS consists of HIV-negative adults (≥18 years) who injected drugs in the month prior to enrollment, and ACCESS of HIV-infected adults who used illicit drugs (other than cannabis) in the month prior to enrollment. VIDUS participants were considered for inclusion in the present analysis if they seroconverted to HIV during follow-up.

After providing written informed consent, at baseline and semiannually thereafter, participants complete an interviewer-administered questionnaire that collects information on sociodemographic characteristics, drug use patterns, and healthcare access and utilization, including HIV and addiction care as well as other relevant exposures. At each of these visits, participants provide blood samples for hepatitis C virus (HCV) and HIV serological testing and HIV disease monitoring as appropriate, and are examined by a study nurse, who provides basic medical care and referrals to additional health services when needed. As has been described elsewhere [15], information gathered at each visit is augmented by confidential data linkages with the British Columbia Centre for Excellence in HIV/AIDS Drug Treatment Program, which provides HIV care, including free ART and HIV clinical monitoring to all PLHIV in the province of British Columbia. Through these linkages, we are able to build a complete retrospective longitudinal HIV clinical and laboratory profile for each participant, including data on all CD4 counts, HIV viral load (VL), and genotypic tests conducted either through the aegis of the study or in the course of regular clinical care, as well as data on all ART dispensations (eg, dates, regimen, quantities). Of relevance to the present analysis, baseline genotypic testing was increasingly requested as part of regular clinical care in British Columbia after the year 2000, formally becoming standard of care in 2005. In addition, for participants enrolled before these years, genotypic testing was done retrospectively using archived samples when available; however, these retrospective test results were not available to clinicians to inform selection of first-line ART. Participants receive a stipend of 30 Canadian dollars at each study visit. Both cohort studies have received ethical approval by the University of British Columbia/Providence Health Care Research Ethics Board.

For the present analysis, we included HIV-infected participants who were recruited between 1 May 1996 and 31 May 2015 who had 1 or more genotypic resistance tests while ART naive. For participants with >1 test while ART naive, only the earliest available test was considered.

Transmitted Drug Resistance

Population-based nucleotide sequencing of the HIV reverse transcriptase and protease genes were performed at the British Columbia Centre for Excellence in HIV/AIDS following previously described laboratory and analytic protocols [13, 17]. The World Health Organization surveillance drug resistance mutation (SDRM) list was used for identification of TDR [18]. The overall prevalence of TDR was estimated as the percentage of participants with ≥1 SDRM. We also calculated the prevalence of TDR for each specific class of antiretroviral drugs: nucleoside reverse transcriptase inhibitors (NRTIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs), and protease inhibitors (PIs).

Other Measures

We considered various factors that we hypothesized might be associated with TDR among PWUD, including sociodemographic characteristics (age, sex, self-reported ethnicity), HIV-related variables (recent HIV infection among VIDUS seroconverters [ie, <12 months between the last documented negative and the first documented positive HIV test], CD4 count and HIV plasma RNA VL at the time of the genotypic test), HCV coinfection, and history of injection drug use, sex work, and incarceration.

Statistical Analysis

As a first step, we examined baseline characteristics of the sample, stratified by presence of TDR. We compared categorical variables using the χ^2 test or the Fisher exact test, as appropriate; continuous variable were compared using the Mann-Whitney test. Next, we used bivariable and multivariable logistic regression to identify the independent correlates of TDR. Starting with a full multivariable model containing all variables associated

with the outcome at $P < .10$ in bivariable analysis, we used an a priori–defined backward stepwise procedure to select the final model with the best fit (ie, model with the lowest Akaike information criterion value).

Overall TDR prevalence values and 95% confidence intervals (CIs) were calculated based on the normal approximation method with continuity correction factor. Trends of prevalence of TDR over time were analyzed using the Cochran-Armitage test and χ^2 test for trend. For this analysis, observations were grouped into periods based on ART availability in British Columbia: 1996–1999 (introduction of combination ART); 2000–2005 (steady state of ART use); 2006–2009 (second expansion of ART distribution); and 2010–2015 (aggressive scale-up of ART among key populations as part of treatment-as-prevention efforts), using data presented previously [19]. A similar analysis was conducted for each specific class of antiretroviral.

As a subanalysis, we assessed first-line ART regimens among the study sample and the impact of TDR on virological response to first-line ART. The latter was restricted to participants who had at least 1 VL test after 180 days of ART initiation. First, using the Stanford HIVdb algorithm version 8.3 [20], 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 1 of the drugs of their prescribed ART) [11]. Then, using Kaplan-Meier curves, we evaluated time to virological failure, defined as 2 consecutive VLs >50 copies/mL, after 180 days of ART initiation, considering the date of the first VL >50 copies/mL as failure date. Participants were censored if they died, stopped ART, or were lost to follow-up, or at their last VL test date in the 9- to 15-month window period after ART initiation. All analyses were conducted using R studio software (version 0.99.892) [21], and all P values are 2-sided.

Table 1. Baseline Characteristics of 573 Human Immunodeficiency Virus–Infected People Who Use Illicit Drugs, Stratified by Presence of Transmitted Drug Resistance, Vancouver, Canada, 1996–2015

Characteristic	Total, No. (%) (N = 573)	Transmitted Drug Resistance, No. (%)		*P* Value
		Yes (n = 56)	No (n = 517)	
Individual-level factors				
Age, y, median (IQR)[a]	37 (31–44)	41 (34–47)	37 (30–43)	.003[b]
Male sex	370 (64.6)	42 (75.0)	328 (63.4)	.086
White race	329 (57.4)	31 (55.4)	298 (57.6)	.743
Injection drug use[c]	545 (95.1)	55 (98.2)	490 (94.8)	.508[d]
HCV seropositive[c]	485 (84.6)	45 (80.4)	440 (85.1)	.331
HIV-related factors				
Recent HIV infection	101 (17.6)	4 (7.1)	97 (18.8)	.027[d]
CD4 count, cells/μL[a]				
Median (IQR)	380 (230–530)	430 (290–560)	380 (230–530)	.088[b]
Categories				
<200	114 (19.9)	7 (12.5)	107 (20.7)	.303
200–349	132 (23.0)	12 (21.4)	120 (23.2)	
350–499	154 (26.9)	15 (26.8)	139 (26.9)	
≥500	162 (28.3)	21 (37.5)	141 (27.3)	
Viral load, $\log_{10}$ copies/mL[a]				
Median (IQR)	4.6 (4.0–5.0)	4.2 (3.8–4.7)	4.6 (4.0–5.0)	.012[b]
>5	168 (29.3)	10 (17.9)	158 (30.6)	.047
Year of resistance test				
1996–1999	128 (22.3)	11 (19.6)	117 (22.6)	.004
2000–2005	167 (29.1)	8 (14.3)	159 (30.8)	
2006–2009	207(36.1)	22 (39.3)	185 (36.8)	
2010–2015	71 (12.4)	15 (26.8)	56 (10.9)	
Structural-level factors				
Sex work[c]	241 (42.1)	19 (33.9)	222 (42.9)	.194
Incarceration[c]	480 (83.8)	48 (85.7)	432 (83.6)	.678

Abbreviations: HCV, hepatitis C virus; HIV, human immunodeficiency virus; IQR, interquartile range.

[a]At the time of the genotypic resistance test.

[b]Wilcoxon rank-sum test.

[c]Refers to lifetime behavior or exposure.

[d]Fisher exact test.

RESULTS

Of 1125 participants recruited into ACCESS and completing ≥1 study interview between May 1996 and May 2015, 573 (50.9%) HIV-infected PWUD had at least 1 genotypic test while ART naive and were included in the present study. In comparison to the 552 participants who were excluded owing to lack of genotypic testing while ART-naive, participants included in these analyses were younger (median age, 37 vs 39 years, $P = .028$) and less likely to be coinfected with HCV (85% vs 89%; $P = .003$), with no other significant differences. Baseline characteristics of included participants, stratified by presence of TDR, are presented in Table 1. The median age was 37 years (interquartile range [IQR], 31–44 years), 370 (64.6%) were male, the majority (545 [95.1%]) had a history of injection drug use, and 101 (17.6%) had documented recent HIV infection. Median CD4 count and VL at the time of the genotypic test were 380 cells/μL (IQR, 230–530 cells/μL) and 4.6 $\log_{10}$ copies/mL (IQR, 4.0–5.0 $\log_{10}$ copies/mL), respectively.

The overall prevalence of TDR in the study sample was 9.8% (95% CI, 7.3%–12.2%), with only 3 (0.5% [95% CI, .0–1.2%]) participants harboring dual-class TDR. SDRMs were more common for NNRTIs (5.4% [95% CI, 3.5%–7.3%]), followed by NRTIs (3.0% [95% CI, 1.5%–4.4%]) and PIs (1.9% [95% CI, .7%–3.1%]). The most prevalent SDRM was the K103N (NNRTI-associated mutation) found in 3.7% of the participants (37.5% of those with TDR), followed by the M46I/L (PI-associated mutation) present in 1.2%. The most frequent NRTI-SDRMs were the thymidine analogue mutations D67N, K219Q, and T215 revertants T215S/C/E, each found in 1.0% of individuals.

The final multivariable model of correlates of TDR is presented in Table 2. The prevalence of TDR was significantly

Table 2. Unadjusted and Adjusted Logistic Regression Analyses of Factors Associated With Transmitted Drug Resistance Among Human Immunodeficiency Virus–Infected People Who Use Illicit Drugs, Vancouver, Canada, 1996–2015

Characteristic	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Age (per 10 years older)[a]	1.34 (1.06–1.70)[b]	1.25 (.98–1.61)
Male sex (yes vs no)	1.73 (1.04–3.00)[b]	1.61 (.94–2.84)
White race (yes vs no)	0.91 (.57–1.46)	
Injection drug use (yes vs no)[c]	3.03 (.77–29.42)	
HCV-seropositive (yes vs no)[c]	0.71 (.40–1.31)	
Recent HIV infection (yes vs no)[c]	0.33 (.12–.73)[b]	0.39 (.15–.87)
CD4 count (ref: <200 cells/μL)[a]		
200–349	1.53 (.69–3.57)	
350–499	1.65 (.77–3.76)	
≥500	2.28 (1.11–5.04)[b]	
HIV VL (>5 $\log_{10}$ vs ≤5 $\log_{10}$ copies/mL)[a]	0.49 (.26–.87)[b]	0.47 (.25–.83)
Sex work (yes vs no)[c]	0.68 (.41–1.10)	
Incarceration (yes vs no)[c]	1.18 (.63–2.39)	

Abbreviations: CI, confidence interval; HCV, hepatitis C virus; HIV, human immunodeficiency virus; OR, odds ratio; VL, viral load.

[a]At the time of the genotypic resistance test.

[b]$P < .10$ and considered in the multivariable model selection process.

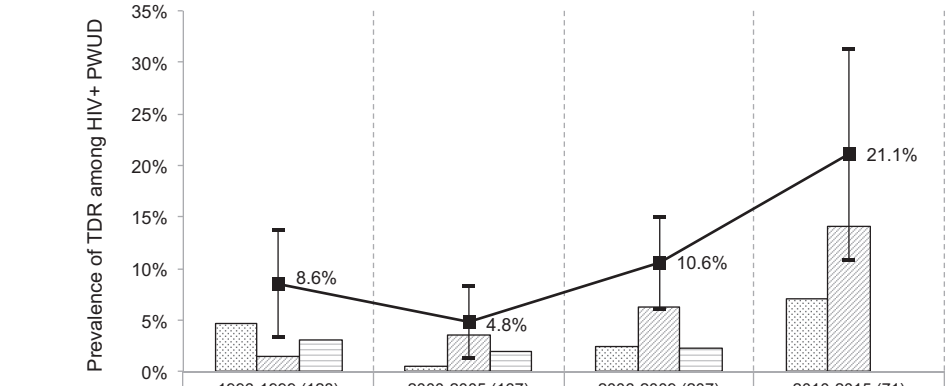
[c]Refers to lifetime behavior or exposure.

lower among PWUD with recent HIV infection (adjusted odds ratio [aOR], 0.39 [95% CI, .15–.87]) and those with high VL (>5 $\log_{10}$ copies/mL; aOR, 0.47 [95% CI, .25–.83]).

Figure 1 depicts the prevalence of TDR in the 4 time periods. As shown, after an initial decline in TDR, there was a significant increase in TDR prevalence over time, from 8.5% (95% CI, 3.4%–13.8%) in 1996–1999 to 21.1% (95% CI, 10.9%–31.3%) in 2010–2015 ($P = .003$), which remained even after adjusting for factors independently associated with TDR (ie, chronic HIV infection and low VL; $P = .031$). The increase in TDR prevalence over time was driven largely by an increase in NNRTI TDR from 1.6% (95% CI, .0–4.2%) in 1996–1999 to 14.1% (95% CI, 5.3%–22.9%) in 2010–2015 ($P < .001$). Prevalence of PI and NRTI TDR showed no significant changes over time ($P = .270$ and $P = .410$, respectively).

Of the 573 included participants, 496 (86.6%) initiated ART, with no significant differences between those with or without TDR (83.9% vs 86.8%; $P = .688$). The most common first-line ART regimens in both groups were PI-based regimens. However, PWUD with TDR were more likely to be prescribed PI-based regimens (72.3% vs 51.2%; $P = .006$) and integrase strand transfer inhibitor (INSTI)–based regimens (8.5% vs 1.1%; $P = .006$), and less likely to receive NNRTI-based regimens (17.0% vs 41.2%; $P = .001$). Of the 47 participants with TDR, 35 (74.5%) were prescribed a fully active ART regimen, and 12 (25.5%) non–fully active regimens, half of whom had PI-associated TDR.

Of the 496 participants who initiated ART during the study period, 454 (91.5%) met the inclusion criteria for the analysis of virological outcomes: 409 (90.1%) with no TDR, 33 (7.3%) with TDR and fully active regimen, and 12 (2.6%) with TDR and non–fully active regimen. As indicated in Figure 2A, cumulative incidence of virological failure at 12 months of ART initiation was significantly higher among participants with TDR compared to those with no TDR (51.6% [95% CI, 34.0%–64.6%] and 36.1% [95% CI, 31.2%–40.6%], respectively; log-rank $P = .037$). However, when the TDR group was stratified according to predicted susceptibility of first-line ART, this association was no



	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%

Figure 1. Trends in transmitted drug resistance among human immunodeficiency virus–infected people who use illicit drugs, Vancouver, Canada, 1996–2015. Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; PWUD, people who use drugs; TDR, transmitted drug resistance.

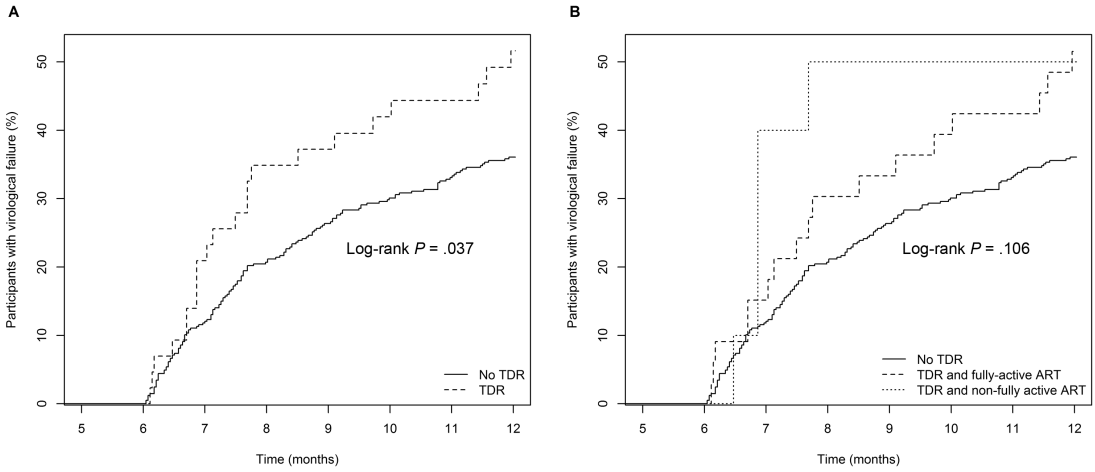


Figure 2. Cumulative incidence of virologic failure among human immunodeficiency virus–infected people who use illicit drugs initiating antiretroviral therapy (ART) in Vancouver, Canada, 1996–2015. *A*, Risk of virological failure according to presence or not of transmitted drug resistance (TDR). *B*, Risk of virological failure in participants with TDR by predicted susceptibility to first-line ART.

longer significant, likely due to the small number of cases in each of the subgroups (Figure 2B; log-rank $P = .657$).

DISCUSSION

To our knowledge, the present study is among the largest studies assessing trends of TDR over time in a community-recruited cohort of ART-naive, HIV-infected PWUD. Over a 20-year period, spanning from 1996 (coinciding with the introduction of combination ART) to 2015 (during a community-wide treatment as prevention–based ART scale-up initiative), we observed moderate prevalence rates (9.8% overall) of TDR among PWUD in Vancouver [22]. However, given that most of our study participants had HIV infection of unknown duration, this figure may be an underestimation of real TDR prevalence in our setting. In addition—and of concern—prevalence of TDR increased substantially over time, reaching values of 21.1% for the period 2010–2015, and largely driven by increases in NNRTI-associated TDR.

The overall TDR prevalence found in this study is in line with findings reported in a recent systematic review that found pooled TDR estimates for PWID in North America from 1996 to 2011 ranging between 8.0% and 10.2% [7]. However, our results are in contrast with the findings that TDR prevalence rates have stabilized among PWID in high-income settings [7]. This disagreement may be explained by the fact that the aforementioned review included aggregated TDR prevalence estimates from both North America and Western Europe, potentially obscuring regional differences. Indeed, previous research has documented lower and fairly stable TDR prevalence trends among PWID in Europe in recent years [6–8]. Alternatively, it might reflect differences in the sampling frames, as the largest rise in TDR prevalence in our study was observed in the period 2010–2015, a time period not covered by the systematic review [7].

Consistent with most studies conducted in the combination ART era (ie, after 1996), SDRMs to NNRTIs were the most frequent SDRMs observed in our analysis, driving also the temporal increasing trend in global TDR [6, 7, 23]. Specifically, more than one-third of participants in our study with TDR harbored the K103N mutation. Also similar to previous studies, TDR to PIs remained low throughout the study period [6, 7, 23]. The high prevalence of NNRTI-associated TDR may be explained by a lower genetic barrier and increasing use of efavirenz-based regimens as first-line ART in British Columbia, as well as the minimal fitness costs associated with the K103N mutation [24]. It is worth noting that research has demonstrated that ART-naive PLHIV (including those undiagnosed, out of care, and PLHIV on pre-ART care) are a significant source of TDR (especially of low-fitness-cost SDRMs) in many settings [3, 25, 26]. The observed TDR pattern (ie, high prevalence of K103N, and extremely low prevalence or absence of high-fitness-cost SDRMs, such as M184V or K65R) suggests similar TDR transmission dynamics among PWUD in Vancouver. Future phylogenetic studies may help to better characterize sources of TDR in our setting. Collectively, these findings highlight the importance of expanding and sustaining efforts for earlier HIV diagnosis and effective treatment to achieve durable viral suppression and, consequently, prevent onward transmission of drug-resistant viruses. Importantly, the risk of cross-transmission of HIV drug resistance through sexual contact to other subpopulations (eg, MSM, heterosexual men and women) should not be overlooked [27].

Unexpectedly and in contrast to prior literature [28], we found that TDR prevalence rates were lower among recently infected PWUD compared to those with chronic or unknown duration of HIV infection. A possible explanation may be that almost half of PWUD with documented recent HIV infection

were enrolled before the year 2000, when limited numbers of PWUD accessed ART due to multiple barriers [13, 16], thus contributing to limited population-level ART exposure among this group.

Our subanalysis revealed that three-quarters of HIV-infected PWUD with TDR were prescribed fully active first-line ART, underscoring the important role of baseline genotypic testing to guide clinical decisions. Some of the balance of inappropriate ART prescribing may be further accounted by the fact that, for some participants, genotypic testing was done retrospectively. Finally, overall participants with TDR had higher risk of virological failure compared with participants with no TDR. Among participants with fully active ART, a possible explanation for this finding may relate to the presence of minority resistant variants not detected with standard genotypic resistance testing, particularly among chronically infected participants [11, 29, 30].

Results from this study should be interpreted in light of a number of limitations. First, given the absence of official registries of PWUD in Vancouver and hidden nature of this population, we employed a nonrandom sampling strategy to recruit participants into our cohorts. Thus, findings of this analysis may not necessarily be representative of the larger population of HIV-infected PWUD in Vancouver or other settings. Second, the lack of phylogenetic analysis precludes the possibility of reliably identifying the source of TDR. However, the TDR pattern observed in our study suggest that ART-naive PWUD may be a significant reservoir of drug-resistant HIV in Vancouver. Third, although at the time of the analysis, INSTI resistance data were not available and thus we were not able to assess its prevalence and potential impact on first-line ART, epidemiological studies suggest that the prevalence of INSTI TDR is still minimal [31]. Finally, as reflected by the wide CI, the relatively small sample size for the period 2010–2015 may affect the accuracy of the TDR prevalence estimate. That said, recent studies in North America have documented a similarly high prevalence of TDR [9, 32, 33].

In summary, this study found overall moderate levels of TDR among ART-naive PWUD in Vancouver, Canada, over a 20-year period, but with a significant temporal rise in TDR, mainly driven by NNRTI-related TDR, reaching high levels of TDR in more recent years. Additionally, participants with TDR had increased risk of virological failure in the first year of ART initiation. These results support current recommendations for resistance testing among newly diagnosed PLHIV to guide individual clinical management [34], as well as the need for ongoing monitoring of TDR among PWUD and other subpopulations of PLHIV to inform HIV treatment guidelines [22]. Moreover, our findings underscore the importance of universal HIV testing and rapid linkage to care and ART initiation among newly diagnosed HIV-infected PWUD to limit the spread of TDR.

Notes

Acknowledgments. The authors thank the study participants for their contributions to the research, as well as current and past researchers and staff. We specifically thank Evan Wood, Deborah Graham, Tricia Collingham, Jennifer Matthews, Steve Kain, Sarah Sheridan, and Paul Sereda for their research and administrative assistance.

Financial support. This work was supported by the US National Institute on Drug Abuse (NIDA) at the US National Institutes of Health (NIH) (grant numbers U01-DA038886 and R01-DA021525). M. E. S. is supported by a Michael Smith Foundation for Health Research (MSFHR) postdoctoral fellowship award and a Canada Addiction Medicine Research Fellowship from NIDA (R25-DA037756). M.-J. M. is supported in part by the NIH (grant number R01-DA021525), a Scholar Award from MSFHR, and a New Investigator award from the Canadian Institutes of Health Research (CIHR). P. R. H. is supported by a CIHR/GlaxoSmithKline Research Chair in clinical virology. J. M. is supported by the British Columbia Ministry of Health and through an Avant-Garde Award from NIDA at the NIH (1DP1DA026182). K. H. is supported by a CIHR New Investigator Award (MSH-141971).

Potential conflicts of interest. The University of British Columbia has received unstructured funding from NG Biomed, Ltd, an applicant to the Canadian federal government, for a license to produce medical cannabis, to support M.-J. M.'s research. J. M. has received limited unrestricted funding, paid to his institution, from AbbVie, Bristol-Myers Squibb, Gilead Sciences, Janssen, Merck, and ViiV Healthcare. P. R. H. has received grants from, served as an ad hoc advisor to, or spoke at various events sponsored by Pfizer, GlaxoSmithKline, Abbott, Merck, Virco, and Monogram. All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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