

Awareness of fentanyl exposure

Awareness of fentanyl exposure and the associated overdose risks among people who inject drugs in a Canadian setting

Kanna Hayashi, PhD^{1,2}, Evan Wood, MD, PhD^{1,3}, Huiru Dong, MSc^{1,4}, Jane A. Buxton, MBBS, MHSc^{4,5}, Nadia Fairbairn, MD^{1,3}, Kora DeBeck, PhD^{1,6}, M-J Milloy, PhD^{1,3}, Thomas Kerr, PhD^{1,3}

1. British Columbia Centre on Substance Use, 400-1045 Howe Street, Vancouver, BC, Canada, V6Z 2A9
2. Faculty of Health Sciences, Simon Fraser University, 8888 University Drive, Burnaby, BC, CANADA, V5A 1S6
3. Department of Medicine, University of British Columbia, 2775 Laurel Street, 10th Floor, Vancouver, BC, Canada V5Z 1M9
4. School of Population and Public Health, University of British Columbia, 2206 East Mall, Vancouver, BC, Canada, V6T 1Z9
5. British Columbia Centre for Disease Control, 655 West 12th Avenue, Vancouver, BC, Canada, V5Z 4R4
6. School of Public Policy, Simon Fraser University, 515 West Hastings Street, Office 3269, Vancouver, BC, Canada, V6B 5K3

Send correspondence to: Dr. Kanna Hayashi

St. Paul's Hospital Chair in Substance Use Research and
Assistant Professor, Faculty of Health Sciences,
Simon Fraser University
Research Scientist, BC Centre on Substance Use
400-1045 Howe Street, Vancouver BC V6Z 2A9 Canada
Tel: +1 778 945 7616 / Fax: +1 604 428 5183
Email: bccsu-kh@bccsu.ubc.ca

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ABSTRACT

Introduction and Aims: Illicitly-manufactured fentanyl continues to fuel the opioid overdose crisis throughout the United States and Canada. However, little is known about factors associated with knowingly or unknowingly using fentanyl. Therefore, we sought to identify the prevalence and correlates of suspected/known and unknown exposure to fentanyl (excluding the prescribed one) among people who inject drugs (PWID), including associated overdose risks.

Design and Methods: Data were derived from three prospective cohort studies of community-recruited people who use drugs in Vancouver, Canada in 2016–2017. Multivariable logistic regression was used to identify correlates of suspected/known exposure (i.e., urine drug screen positive [UDS+] and self-reporting past three-day exposure) and unknown exposure to fentanyl (i.e., UDS+ and self-reporting no past three-day exposure), respectively.

Results: Among 590 PWID, 296 (50.2%) tested positive for fentanyl. Of those, 143 (48.3%) had suspected/known and 153 (51.7%) had unknown exposure to fentanyl. In multivariable analyses, using supervised injection sites and possessing naloxone were associated with both suspected/known and unknown exposure (all $p < 0.05$). Injecting drugs alone (Adjusted Odds Ratio [AOR]: 3.26; 95% Confidence Interval [CI]: 1.72–6.16) was associated with known exposure, but not with unknown exposure.

Discussion and Conclusions: We found a high prevalence of fentanyl exposure in our sample of PWID, with one half of those exposed consuming fentanyl unknowingly. While those exposed to fentanyl appeared more likely to utilize some overdose prevention services, PWID with suspected/known fentanyl exposure were more likely to inject alone, indicating a need for additional overdose prevention efforts for this group.

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INTRODUCTION

In recent years, there has been an exponential growth in the number of fatal drug overdoses throughout the United States and Canada [1–3]. The Canadian province of British Columbia (BC) experienced a rapid rise in opioid overdoses earlier than many other jurisdictions in North America, with drug overdose mortality rates in 2017 being two- to three-fold higher compared to national averages in Canada and the United States [2,4]. A recent study also estimated that between 2014 and 2016, life expectancy at birth in the province declined by 0.12 years due to drug overdose deaths alone [5]. While a public health emergency was declared in April 2016 [6], and a range of overdose prevention interventions have been implemented since then [7], the province continues to see high numbers of fatal overdoses, though showing some declining trends in 2019 [3].

The key contributor to the overdose crisis is illicitly-manufactured fentanyl (a potent synthetic opioid) and its analogues that have contaminated the illicit drug supply [8,9]. In BC, fentanyl has been attributed to the dramatic increase in overdose mortality since 2012, with fentanyl-detection rates in illicit drug overdose deaths increasing from 4% in 2012 to 86% in 2018 [10]. Fentanyl is commonly added to or sold as heroin [9,11,12], though other street drugs in the unregulated market, including stimulants and counterfeit medications (e.g., benzodiazepine pills), have also been found to contain fentanyl [13,14]. Previous studies reported that people who use drugs struggle to discern

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substances sold as heroin and may be unknowingly exposed to fentanyl [11,15]. A recent qualitative study in Vancouver, BC [16] reported that people who use illicit drugs generally had a high level of trust for their regular drug dealers, who they believed would provide them with accurate information regarding the contents of the drug sold (e.g., whether the drug is cut with fentanyl). However, the extent to which street-level drug dealers possess and convey accurate information on the contents of the drug to their clients is not known. People may also obtain drugs from unfamiliar sources from time to time, and therefore may not always be aware of the contents of the drug they obtain [16].

As fentanyl has increasingly contaminated the illicit drug supply, previous studies also reported that some people who use drugs have adapted their drug-using practices in an effort to prevent an overdose, including reducing the frequency of drug use, using drugs with others, and carrying naloxone [17]. A recent cross-sectional study from three cities in the US reported that approximately 60% of their community-recruited sample of people who use illicit drugs (n=334) had ever suspected fentanyl exposure prior to using their drugs, and the prevalence of engaging in some harm reduction behaviour (e.g., using less of the drug) among those with suspected fentanyl exposure was relatively high at 39% [18]. However, since the self-report data were not corroborated with biological markers of fentanyl exposure, the extent to which those individuals accurately identified their exposure to fentanyl was unknown.

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While knowledge of fentanyl exposure may be an important factor influencing individuals' drug-using behaviour, potential differences in overdose risks associated with known and unknown exposure to fentanyl have not been fully characterized, particularly among people who inject drugs (PWID). A recent survey of 486 people who use drugs across BC documented that about 60% had been recently exposed to fentanyl, with 64% of them reporting known exposure to fentanyl [19]. This study found that those who preferred injection to non-injection drug use were more likely to report known exposure to fentanyl [19]. Building on this previous study and considering that PWID is the population that suffers from extremely high mortality from drug overdoses [20,21], it is important to characterize overdose risks associated with known and unknown exposure to fentanyl among PWID. Therefore, we sought to estimate the prevalence and correlates (including overdose risk behaviour) of suspected/known and unknown exposure to fentanyl (excluding the prescribed one) among PWID in Vancouver.

METHODS

Study setting and design

Data were derived from three ongoing prospective cohort studies of people who use drugs in Vancouver: the Vancouver Injection Drug Users Study (VIDUS), the AIDS Care Cohort to evaluate Exposure to Survival Services (ACCESS), and the At-Risk Youth Study (ARYS). Detailed descriptions of these cohorts have been previously published

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elsewhere [22,23]. In brief, VIDUS enrolls HIV-seronegative adults (≥ 18 years of age) who injected illicit drugs in the month prior to enrolment. ACCESS enrolls HIV-seropositive adults who used an illicit drug in the month prior to enrolment, and ARYS enrolls street-involved youth aged 14 to 26 who used an illicit drug in the month prior to enrolment. The cohorts use harmonized data collection procedures to allow for pooled.

At baseline and semi-annually thereafter, participants complete an interviewer-administered questionnaire, which elicits a range of information including demographic data, substance use, and healthcare access. Since June 2016, a multi-panel qualitative urine drug screen (UDS) using BTNX Rapid Response™ Multi-Drug Test Panel (Markham, ON, Canada) has been added to the data collection procedures. This rapid chromatographic immunoassay qualitatively and simultaneously detected multiple substances in urine within five minutes. As described previously [24], the screened substances (calibrator, cut-off value in ng/mL) included: fentanyl (fentanyl, 100, and norfentanyl, 20); morphine/heroin (morphine, 100); methadone metabolite (2-Ethylidine-1, 5-dimethyl-3, 3-diphenylpyrrolidine, 100); buprenorphine (BUP-3-D-Glucoronide, 10); cocaine (benzoylecgonine, 150); amphetamine/methamphetamine (d-amphetamine, 1000); benzodiazepine (oxazepam, 300). The UDS kit has separate panel strips for each substance. If only one coloured line appears on the strip, it means that it tested positive for the substance. Two lines on the strip indicate a negative result. If no line appears on the strip, the UDS is invalid. While detection times after use of these substances vary

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depending on many factors, including routes of administration, frequencies of use, and doses, the BTNX fentanyl test panel with the aforementioned cut-off values is believed to detect exposure to fentanyl within a maximum of past three days [25]. All three cohorts have received approvals from the University of British Columbia/Providence Health Care Research Ethics Board.

Study sample and measures

Eligibility criteria for the present cross-sectional study included: completing both the interviewer-administered questionnaire and UDS between December 2016 and May 2017, and reporting having injected illicit drugs in the past six months. Additional sample restrictions were made based on the combinations of the UDS and self-report data that were used to derive the primary outcome as described below.

The primary outcome was recent exposure to fentanyl (excluding the prescribed one), which was classified as suspected/known exposure *vs.* unknown exposure *vs.* no exposure. Specifically, we defined suspected/known exposure as having a positive UDS result for fentanyl and self-reporting suspected exposure to fentanyl in the past three days. Suspected exposure to fentanyl was ascertained from a question: “Have you used any drugs that you knew or now believe contained fentanyl? If yes, when was the last time you used such drugs?” In this question, fentanyl referred to non-prescribed fentanyl only. Trained interviewers asked this question either before administering the UDS or without showing or corroborating the results of UDS if UDS had been administered

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before the interview, in order to avoid reporting bias. Unknown exposure to fentanyl was defined as having a positive UDS result for fentanyl and self-reporting no suspected exposure to fentanyl in the past three days. Two participants who were classified as unknown fentanyl exposure but self-reported use of prescribed fentanyl in the last 24 hours were excluded from the analytic sample in order to ensure that this category only includes cases of unknown exposure to non-prescribed fentanyl. No exposure to fentanyl was defined as having a negative UDS result for fentanyl. Among 335 individuals who tested negative for fentanyl, 42 (12.2%) reported suspected exposure to fentanyl in the past three days and were excluded from the analysis. Determination of the analytic study sample is further described in Figure 1.

In order to identify potentially distinct patterns of recent substance use among the three groups of the primary outcome measure, we examined UDS results of six substances (i.e., morphine, methadone metabolite, buprenorphine, cocaine, amphetamine/methamphetamine and benzodiazepine) as well as self-reported patterns of use for eight substance over the past three days, including heroin, non-medical use of prescription opioids (POs), cocaine, crack cocaine, crystal methamphetamine, speedball (i.e., combining an opioid and cocaine) or goofball (i.e., combining an opioid and crystal methamphetamine) injection, exclusive use of stimulants (i.e., either cocaine, crack cocaine or crystal methamphetamine, but no opioids), and benzodiazepine (non-medical use). Non-medical use of POs was defined as using POs when they were not prescribed

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for the participant or that the participant took only for the experience or feeling they caused.

We also considered a range of factors that we hypothesized might be associated with suspected/known and unknown exposure to fentanyl based on previous studies [19,24,26]. Demographic variables included: age (continuous, per year older); sex (female *vs.* male); and ethnicity/ancestry (white *vs.* non-white). For behavioural and social-structural factors, we considered patterns reported in the past six months unless otherwise specified because most of the relevant questions in the questionnaire referred to the past six months. Substance use-related variables included: \geq daily heroin injection, \geq daily non-medical use of PO, \geq daily cocaine injection, \geq daily crack smoking, \geq daily crystal methamphetamine use (either injection or non-injection), \geq daily alcohol use, and non-medical use of benzodiazepine. Variables related to overdose risks and prevention included: experiencing a non-fatal overdose (defined as having a negative reaction from using too much drugs by accident); injecting alone; being enrolled in opioid agonist therapy (OAT); using a supervised injection/overdose prevention site; and currently possessing naloxone. Social and structural exposures in the past six months included: residence in the Downtown Eastside (DTES) neighbourhood in Vancouver, an area with a large open drug market; being homeless; recent incarceration; and inability to access any community health or social services (e.g., food services, housing, counsellor, social

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worker), defined as reporting having been unable to access any of these services when they wanted. Unless otherwise stated, all variables were dichotomized as yes *vs.* no.

Statistical analyses

As a first step, we examined the sample characteristics stratified by recent exposure to fentanyl, using the Pearson's Chi-squared test (for categorical variables) and Kruskal-Wallis test (for continuous variables). Next, in order to identify a set of factors associated with higher odds of suspected/known and unknown exposure to fentanyl, respectively, we built two multivariable logistic regression models: Model 1 compared suspected/known *vs.* no exposure to fentanyl, and Model 2 compared unknown *vs.* no exposure to fentanyl. In addition, we fit Model 3 to compare suspected/known *vs.* unknown exposure to fentanyl. Because of highly skewed distributions (see Table 1), the variables of \geq daily heroin injection and \geq daily non-medical use of PO were removed from the multivariable modelling procedure for each model. For all models, we used an *a priori*-defined backward model selection procedure based on examination of Akaike Information Criterion (AIC) to fit a multivariable model [27]. In brief, we constructed a full model including all variables that were associated with the outcome at $p < 0.10$ in bivariable analyses. After examining the AIC of the model, we removed the variable with the largest p -value and built a reduced model. We continued this iterative process until we reached the lowest AIC score. All p -values were two-sided. All statistical analyses were performed using SAS 9.4 (Cary, North Carolina, USA).

RESULTS

Sample characteristics

In total, 590 participants were eligible for the present study. As shown in Table 1, 225 (38%) were female, 323 (55%) self-identified as white, and the median age was 46 (quartile [Q] 1–3: 35–54) years. A total of 296 (50%) individuals tested positive for fentanyl, of whom 143 (48%) had suspected/known and 153 (52%) had unknown exposure to fentanyl.

Regarding the self-reported substance use in the past three days (see Table 1), there was a significantly higher prevalence of reported stimulant use but no opioid use among those who were not exposed to fentanyl (49%) when compared to those with suspected/known and unknown exposure to fentanyl (0.7% and 12%) ($p<0.001$). However, crystal methamphetamine use was the highest among those with suspected/known exposure to fentanyl (49%), followed by those with unknown exposure (39%) and no exposure to fentanyl (34%) ($p=0.008$). The prevalence of reporting speedball or goofball injection followed a similar pattern.

Also shown in Table 1, the UDS results of the six substances were similar to the findings on self-reported substance use in the past three days. Specifically, the prevalence of positive UDS results for morphine was significantly higher among those with known and unknown exposure to fentanyl (94% and 86%) compared to those with no exposure

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to fentanyl (26%) ($p < 0.001$). The prevalence of positive UDS results for amphetamine was the highest among those with suspected/known exposure to fentanyl (70%), followed by those with unknown exposure (55%) and no exposure to fentanyl (39%) ($p < 0.001$).

Table 2 lists the top five combinations of positive UDS results identified among those with suspected/known and unknown exposure to fentanyl, respectively, accounting for approximately a half of each sub-sample. As shown, among those with suspected/known exposure to fentanyl, all combinations included both morphine and one of the stimulants (amphetamine or cocaine), as did all but one combination (methadone metabolite and morphine) among those with unknown exposure to fentanyl.

Factors associated with suspected/known and unknown exposure to fentanyl

Table 3 presents the results of bivariable and multivariable logistic regression analyses. As shown, in both Model 1 (comparing suspected/known *vs.* no exposure to fentanyl) and Model 2 (comparing unknown *vs.* no exposure to fentanyl), younger age, OAT use, use of supervised injection/overdose prevention sites, and possession of naloxone were independently and positively associated with both suspected/known and unknown fentanyl exposure (all $p < 0.05$). DTES residence (adjusted odds ratio [AOR]: 2.00; 95% confidence interval [CI]: 1.18, 3.39), incarceration (AOR: 3.21; 95% CI: 1.22, 8.46), self-reported inability to access to any community health or social services (AOR: 1.83; 95% CI: 1.08, 3.11), non-fatal overdose (AOR: 2.01; 95% CI: 1.14, 3.54), and injecting alone (AOR: 3.26; 95% CI: 1.72, 6.16) were independently and positively associated with

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suspected/known exposure to fentanyl, but not with unknown exposure to fentanyl. In Model 3 (comparing suspected/known *vs.* unknown exposure to fentanyl), injecting alone was independently and positively associated with suspected/known exposure (AOR: 3.77; 95% CI: 2.04, 6.99).

DISCUSSION

We found that approximately one-half of our community-recruited sample of PWID in Vancouver tested positive for fentanyl, and one-half of these individuals reported being unknowingly exposed to fentanyl. Combined data from UDS and self-reported use of drugs indicated that polysubstance use, most commonly involving illicit opioids and crystal methamphetamine, was prevalent among those exposed to fentanyl, particularly among those with suspected/known exposure. In multivariable analyses, PWID who had recent exposure to fentanyl were more likely to be younger, on OAT, use supervised consumption sites, and carry naloxone regardless of being aware or unaware of fentanyl exposure. Those who suspected their fentanyl exposure were additionally more likely to have recently injected drugs alone, experienced a non-fatal overdose, been incarcerated, and been unable to access health or social services. When comparing PWID who were and were not aware of fentanyl exposure, injecting alone was the only factor that remained independently associated with suspected/known exposure to fentanyl.

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We found a high prevalence of polysubstance use involving illicit opioids and crystal methamphetamine among those with fentanyl exposure, and the prevalence of the past three-day use of crystal methamphetamine was the highest (nearly 50%) among those with suspected/known fentanyl exposure. This is in line with recent reports documenting increasing trends in co-detection of fentanyl and methamphetamine in fatal drug overdose cases in the US [28] and BC [29]. Specifically, in BC, there has been a five-fold increase in the number of illicit drug toxicity deaths involving crystal methamphetamine since 2014, the majority (87%) of which also involved fentanyl [29]. Similarly, several studies in the US have also suggested a marked increase in methamphetamine use among people who use opioids in recent years [30–34]. Qualitative data in an online survey suggested that there might be a range of factors motivating people who use opioids to use methamphetamine, including high-seeking, balancing the effect of opioids, and its easy availability as a substitute for opioids [33]. However, in our multivariable regression analyses, at least daily use of crystal methamphetamine was not significantly associated with either suspected/known or unknown exposure to fentanyl, indicating that those exposed to fentanyl may be engaging in less frequent use of crystal methamphetamine. Future research should investigate motivations for, practices and effects of co-use of street opioids and crystal methamphetamine in more depth.

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The significant association between non-fatal overdose and suspected/known fentanyl exposure could have two possible interpretations. It may be that those individuals with suspected/known fentanyl exposure are simply at a higher risk of overdose. Alternatively, because of the way suspected/known fentanyl exposure was ascertained, it may be that some of those with suspected/known fentanyl exposure might have not necessarily been aware of their fentanyl exposure at the time of their drug use but became aware after they experienced a non-fatal overdose in the past three days. However, unfortunately, our dataset did not allow us to determine how many of the 46 (32% of the suspected/known fentanyl exposure group) individuals reporting both suspected fentanyl exposure in the past three days and non-fatal overdose in the past six months fell into such cases.

Of concern, those who engaged in overdose risk behaviour (i.e., injecting alone) were more likely to report suspected/known exposure to fentanyl. Such behaviour was not as salient among individuals with unknown fentanyl exposure. These findings may suggest that this sub-population of PWID with suspected/known exposure to fentanyl might be at a particularly high risk of experiencing a fatal overdose. While future research needs to establish the temporal relationship between injecting alone and known fentanyl exposure, given the well-known highly toxic illicit drug supply in our study setting [35], it may be that some PWID were injecting alone despite knowingly using drugs that contained fentanyl. In this regard, a large body of literature on HIV/AIDS demonstrates

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that individual-level education about HIV risk behaviour (e.g., syringe sharing) alone would not be sufficient to enable PWID to avoid HIV risk behaviour unless broader social and structural factors that shape risk environments and constrain PWID's ability to exercise harm reduction practices are addressed [36]. A recent rapid ethnographic study from our study setting also reported that some women who use drugs do not utilize housing-based overdose prevention sites (i.e., supervised consumption sites) and intentionally used drugs alone at their home as they considered those overdose prevention sites to be unsafe environments [37]. Taken together, there is an urgent need to understand why some PWID inject alone and address the fatal overdose risk associated with this behaviour.

Further, while PWID exposed to fentanyl appeared more likely to access some key overdose prevention services such as supervised consumption sites, naloxone and OAT, those who were aware of fentanyl exposure were more likely to have recently been incarcerated and report inability to access health/social services. These markers of overdose risk and structural vulnerability did not stand out among PWID with unknown exposure to fentanyl. Collectively, our findings suggest that those with suspected/known exposure to fentanyl may be the ones who particularly suffer from marginalization and bear the greatest overdose risks. Therefore, our study findings indicate a need for structural interventions to address the upstream drivers of overdose risk, in addition to

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individual-level overdose prevention interventions that have been the primary responses to the ongoing opioid overdose crisis in the United States and Canada to date.

This study has some limitations. First, the cross-reactivity of the UDS may have resulted in over- or underestimation of the recent exposure to some substances [38], although a previous study documented that the UDS panel used in the present study had high specificity and sensitivity for fentanyl detection [39]. Also, our UDS panel did not screen 6-monoacetylmorphine (a specific metabolite of heroin) or fentanyl analogues such as carfentanil. Second, self-reported data may be influenced by some reporting bias, although such data have been shown to be mostly valid in studies involving PWID [40]. Third, a non-random sample used in the present study limits the generalizability of our findings.

In sum, we found that a half of PWID in our sample tested positive for fentanyl, with a half of these individuals being unknowingly exposed to fentanyl. Co-use of illicit opioids and crystal methamphetamine appeared highly prevalent among those exposed to fentanyl, particularly those with suspected/known exposure. While those exposed to fentanyl were more likely to access some key overdose prevention services, those who were aware of fentanyl exposure were also more likely to inject drugs alone, experience recent incarceration and report inability to access health or social services, indicating that this sub-population of PWID may be particularly marginalized and at a high risk of fatal overdose. These findings indicate a need for scaling up ongoing overdose prevention

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efforts by addressing not only opioid use but also stimulant use, and the social and structural factors that shape overdose risk behaviour among this population.

Conflict of interest:

EW has a part-time appointment as the Chief Medical Officer with Numinus, a company that operates a testing and research lab facility and works towards potential addiction treatment and other therapeutic applications of psychedelic substances. MJM's institution has received an unstructured gift from NG Biomed, Ltd., to support his research. MJM is the Canopy Growth professor of cannabis science at the University of British Columbia, a position created by unstructured gifts to the university from Canopy Growth, a licensed producer of cannabis, and the Government of British Columbia's Ministry of Mental Health and Addictions. Neither of EW's employer or the funder that supports MJM had any role in study design; collection, analysis, and interpretation of data; writing the report; and the decision to submit the report for publication. All authors declare no conflict of interest.

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Table 1: Sample characteristics stratified by exposure to fentanyl among 590 PWID in Vancouver, Canada, 2016-2017.

Characteristic	Total 590 (100%)	Exposure to fentanyl			P-value
		Suspected/Known 143 (24.2%)	Unknown 153 (25.9%)	No exposure 294 (49.8%)	
Age (median, Q1-Q3)	45.7 (34.6 – 53.7)	38.6 (30.9 – 49.2)	43.3 (34.7 – 50.6)	49.3 (38.9 – 55.4)	<0.001 ^c
Female	225 (38%)	60 (42%)	65 (42%)	100 (34%)	0.129
White	323 (55%)	82 (57%)	85 (56%)	156 (53%)	0.682
DTES residence^a	403 (68%)	106 (74%)	112 (73%)	185 (63%)	0.020
Homeless^a	109 (18%)	38 (27%)	29 (19%)	42 (14%)	0.008
Incarceration^a	40 (7%)	19 (13%)	13 (9%)	8 (3%)	<0.001
Inability to access any community health or social services^a	143 (24%)	44 (31%)	39 (26%)	60 (20%)	0.058
Non-fatal overdose^a	127 (22%)	46 (32%)	36 (24%)	45 (15%)	<0.001
Injecting alone^a	436 (74%)	126 (88%)	101 (66%)	209 (71%)	<0.001
Opioid agonist therapy^a	360 (61%)	99 (69%)	102 (67%)	159 (54%)	0.002
Supervised injection/overdose prevention sites use^a	283 (48%)	91 (64%)	85 (56%)	107 (36%)	<0.001
Currently possessing naloxone	397 (67%)	106 (74%)	117 (77%)	174 (59%)	<0.001
Self-reported substance use in the past 6 months^a					
≥ Daily heroin injection ^{a, b}	182 (31%)	100 (70%)	67 (44%)	15 (5%)	<0.001
≥ Daily non-medical PO use ^a	19 (3%)	9 (6%)	2 (1%)	8 (3%)	0.050 ^d
≥ Daily cocaine injection ^a	33 (6%)	8 (6%)	5 (3%)	20 (7%)	0.304
≥ Daily crack smoking ^a	42 (7%)	11 (8%)	13 (9%)	18 (6.1%)	0.621
≥ Daily crystal methamphetamine use ^a	112 (19%)	34 (24%)	29 (19%)	49 (17%)	0.206
≥ Daily alcohol use ^a	44 (7%)	5 (4%)	15 (10%)	24 (8%)	0.096
Non-medical use of benzodiazepine ^a	36 (6%)	9 (6%)	8 (5%)	19 (7%)	0.870
Self-reported substance use in the past 3 days					
Heroin	285 (48%)	132 (92%)	110 (72%)	43 (15%)	<0.001

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Non-medical use of PO	41 (7%)	16 (11%)	7 (5%)	18 (6%)	0.060
Cocaine	88 (15%)	18 (13%)	17 (11%)	53 (18%)	0.100
Crack cocaine	108 (18%)	20 (14%)	28 (18%)	60 (20%)	0.265
Crystal methamphetamine	229 (39%)	70 (49%)	60 (39%)	99 (34%)	0.008
Speedball or goofball injection	74 (13%)	34 (24%)	28 (18%)	12 (4%)	<0.001
Using stimulants but no opioids ^b	162 (27%)	1 (1%)	18 (12%)	143 (49%)	<0.001 ^d
Non-medical use of benzodiazepine	13 (2%)	4 (3%)	3 (2%)	6 (2%)	0.873 ^d
UDS positive for:					
Morphine	343 (58%)	135 (94%)	131 (86%)	77 (26%)	<0.001
Methadone metabolite	318 (54%)	83 (58%)	96 (63%)	139 (47%)	0.004
Buprenorphine	34 (6%)	7 (5%)	6 (4%)	21 (7%)	0.336
Cocaine	313 (53%)	73 (51%)	95 (62%)	145 (49%)	0.032
Amphetamine	299 (51%)	100 (70%)	84 (55%)	115 (39%)	<0.001
Benzodiazepine	118 (20%)	42 (29%)	26 (17%)	50 (17%)	0.006
Cohort designation					
VIDUS	302 (51%)	79 (55%)	76 (50%)	147 (50%)	
ACCESS	204 (35%)	35 (25%)	56 (36%)	113 (38%)	
ARYS	84 (14%)	29 (20%)	21 (14%)	34 (12%)	

ACCESS: AIDS Care Cohort to evaluate Exposure to Survival Services. ARYS: At-Risk Youth Study. DTES: Downtown Eastside. PO: prescription opioid. PWID: people who inject drugs. Q: quartile. UDS: urine drug screen. VIDUS: Vancouver Injection Drug Users Study.

^a Denotes behaviors/events in the past six months.

^b Stimulants include any of cocaine, crack cocaine or crystal methamphetamine.

^c Denotes that p-value was obtained from the Kruskal-Wallis test.

^d Denotes that p-value was obtained from the Fisher's exact test.

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Table 2: The top five combinations of positive UDS results among PWID with suspected/known and unknown exposure to fentanyl in Vancouver, Canada, 2016-2017.

Combination	n	%
<i>Among PWID with suspected/known exposure to fentanyl (n = 143)</i>		
Amphetamine + Methadone metabolite + Morphine	23	16
Amphetamine + Cocaine + Methadone metabolite + Morphine	17	12
Amphetamine + Morphine	14	10
Amphetamine + Cocaine + Morphine	10	7
Cocaine + Methadone metabolite + Morphine	9	6
<i>Among PWID with unknown exposure to fentanyl (n = 155)</i>		
Amphetamine + Cocaine + Methadone metabolite + Morphine	26	17
Cocaine + Methadone metabolite + Morphine	21	14
Amphetamine + Morphine	15	10
Methadone metabolite + Morphine	13	8
Amphetamine + Methadone metabolite + Morphine	12	8
PWID: people who inject drugs. UDS: urine drug screen.		

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Table 3: Bivariable and multivariable logistic regression analyses of factors associated with suspected/known and unknown exposure to fentanyl among 590 PWID in Vancouver, Canada, 2016-2017.

Variable	Model 1 (Suspected/Known vs. no exposure)				Model 2 (Unknown vs. no exposure)				Model 3 (Suspected/Known vs. unknown exposure)			
	OR (95% CI)	p- value	AOR (95% CI)	p- value	OR (95% CI)	p- value	AOR (95% CI)	p- value	OR (95% CI)	p- value	AOR (95% CI)	p- value
	Age (per year increase)	0.95 (0.93, 0.97)	<0.001	0.95 (0.93, 0.97)	<0.001	0.97 (0.95, 0.99)	<0.001	0.97 (0.95, 0.99)	0.001	0.98 (0.96, 1.00)	0.021	0.98 (0.96, 1.00)
Female	1.41 (0.93, 2.12)	0.105			1.42 (0.95, 2.12)	0.088			0.99 (0.62, 1.57)	0.968		
White	1.19 (0.80, 1.78)	0.399			1.11 (0.75, 1.64)	0.616			1.08 (0.68, 1.70)	0.757		
DTES residence ^a	1.69 (1.08, 2.63)	0.021	2.00 (1.18, 3.39)	0.010	1.61 (1.05, 2.47)	0.030	1.56 (0.98, 2.48)	0.060	1.05 (0.62, 1.76)	0.857		
Homeless ^a	2.17 (1.32, 3.56)	0.002			1.40 (0.83, 2.36)	0.201			1.55 (0.89, 2.68)	0.119		
Incarceration ^a	5.48 (2.34, 12.85)	<0.001	3.21 (1.22, 8.46)	0.018	3.32 (1.34, 8.19)	0.009	2.45 (0.94, 6.36)	0.065	1.65 (0.78, 3.48)	0.188		
Inability to access any health or social services ^a	1.73 (1.10, 2.72)	0.019	1.83 (1.08, 3.11)	0.026	1.33 (0.84, 2.11)	0.227			1.30 (0.78, 2.16)	0.313		
Non-fatal overdose ^a	2.61 (1.63, 4.20)	<0.001	2.01 (1.14, 3.54)	0.015	1.70 (1.04, 2.77)	0.035	1.52 (0.89, 2.60)	0.129	1.54 (0.92, 2.57)	0.098	1.49 (0.86, 2.56)	0.154
Injecting alone ^a	3.01 (1.71, 5.31)	<0.001	3.26 (1.72, 6.16)	<0.001	0.79 (0.52, 1.20)	0.270			3.82 (2.08, 7.00)	<0.001	3.77 (2.04, 6.99)	<0.001
Opioid agonist therapy ^a	1.91 (1.25, 2.92)	0.003	1.82 (1.10, 3.00)	0.020	1.70 (1.13, 2.55)	0.011	1.82 (1.16, 2.85)	0.010	1.12 (0.69, 1.83)	0.637		
Supervised injection/overdose prevention sites use ^a	3.06 (2.02, 4.63)	<0.001	2.01 (1.25, 3.25)	0.004	2.18 (1.47, 3.25)	<0.001	1.94 (1.27, 2.96)	0.002	1.40 (0.88, 2.23)	0.158		
Currently possessing naloxone	1.98 (1.27, 3.07)	0.003	1.72 (1.02, 2.90)	0.041	2.24 (1.44, 3.48)	<0.001	1.81 (1.13, 2.92)	0.015	0.88 (0.52, 1.50)	0.640		
Self-reported substance use in the past 6 months^a												
≥ Daily cocaine injection ^a	0.81 (0.35, 1.89)	0.629			0.46 (0.17, 1.26)	0.131			1.75 (0.56, 5.49)	0.335		
≥ Daily crack smoking ^a	1.28 (0.59, 2.78)	0.537			1.42 (0.68, 2.99)	0.351			0.90 (0.39, 2.07)	0.801		
≥ Daily crystal methamphetamine use ^a	1.56 (0.95, 2.55)	0.077			1.17 (0.70, 1.94)	0.546			1.33 (0.76, 2.33)	0.312		

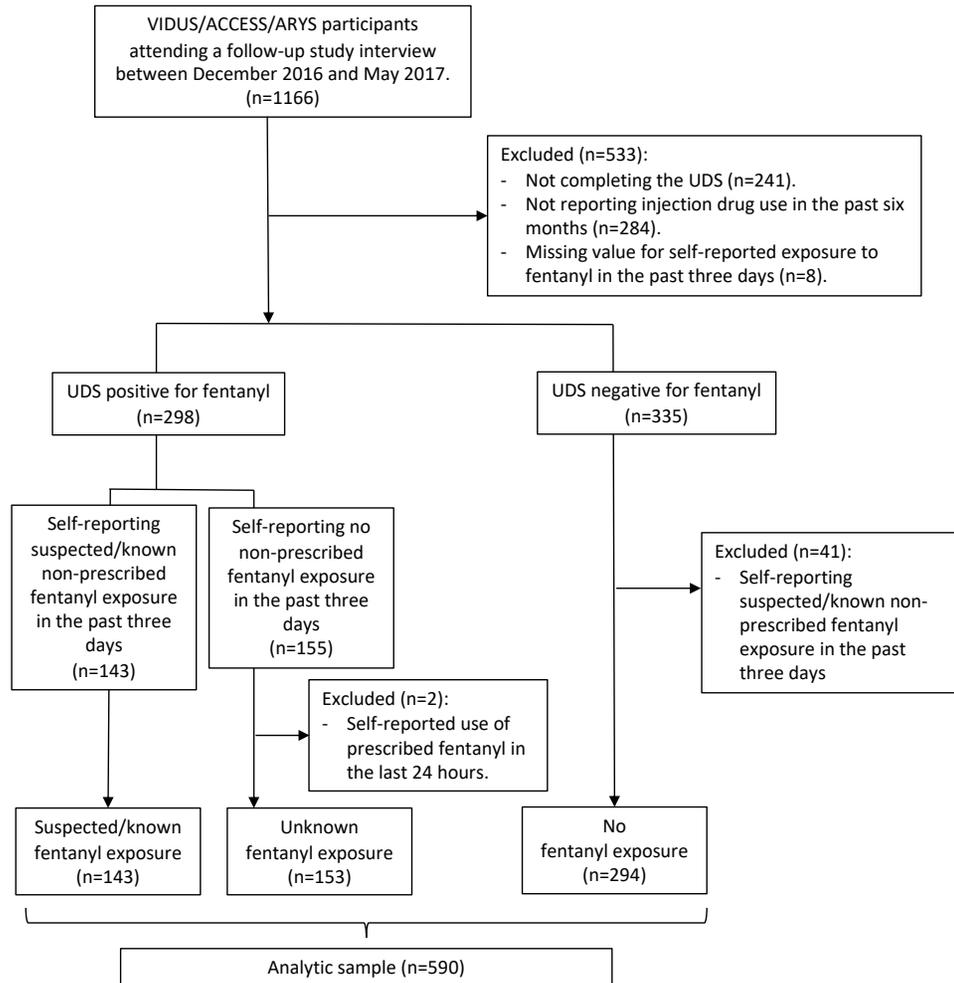
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≥ Daily alcohol use ^a	0.41 (0.15, 1.09)	0.074	0.34 (0.11, 1.04)	0.058	1.22 (0.62, 2.41)	0.560	0.33 (0.12, 0.94)	0.038	0.39 (0.13, 1.15)	0.088
Non-medical use of benzodiazepine ^a	0.97 (0.43, 2.21)	0.946			0.80 (0.34, 1.87)	0.604	1.22 (0.46, 3.25)	0.694		
Cohort designation										
ACCESS (vs. VIDUS)	0.58 (0.36, 0.92)	0.021			0.96 (0.63, 1.46)	0.845	0.60 (0.36, 1.02)	0.058		
ARYS (vs. VIDUS)	1.59 (0.90, 2.80)	0.110			1.19 (0.65, 2.20)	0.568	1.33 (0.70, 2.53)	0.387		

ACCESS: AIDS Care Cohort to evaluate Exposure to Survival Services. AOR: adjusted odds ratio. ARYS: At-Risk Youth Study. CI: confidence interval. DTES: Downtown Eastside. OR: odds ratio. PO: prescription opioid. PWID: people who inject drugs. VIDUS: Vancouver Injection Drug Users Study.

^a Denotes behaviors/events in the past six months.

Figure 1: Determination of the analytic sample.



UDS: urine drug screen.