The relevance of polydrug use in HIV risk and associated injecting and sexual risk behaviours among people who inject drugs

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Declaration of originality:

I declare that the work presented in this thesis is my own research and is referenced or acknowledged otherwise. It includes original work conducted during my PhD at Imperial College, London from 2011 to 2016.

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Abstract

HIV transmission has effectively been reduced in many countries by focusing on high transmission foci with interventions tailored to key populations groups and high risk behaviours. However people who inject drugs (PWID) still accounted for significant proportions of new HIV and Hepatitis C infections in several regions in 2014[1]. Among PWID, as in other populations, risk behaviours are not distributed equally. Polydrug use (using multiple drugs) in particular has increasingly been cited as a source of harm and possibly greater HIV infection risk but remains under-researched.

In this thesis, I assessed the epidemiological significance of polydrug use on HIV and HCV risk behaviours among PWID, using several methods, and data sources from different settings. Multiple methodological challenges were faced, related to inherent difficulties in studying PWID, including stigmatised behaviours, comparatively small sample sizes and the absence of sampling frame for PWID.

I established that polydrug use was frequent among PWID, in contrast with the common assumption that PWID mainly inject heroin, and considerable proportions of injectors across locations had recently injected or used multiple drugs (chapter 2). I generated new evidence on the biological and behavioural risks associated with injecting certain drugs and drug combinations in three stages. First, in the meta-analysis, HIV incidence rates were consistently higher among PWID injecting cocaine, amphetamine (ATS) or combinations of heroin and stimulants, compared to those not injecting or not injecting the drug(s). Wide confidence intervals and inconsistent reference categories however, limited conclusions (chapter 3). Second, I identified differences in injecting risk and HIV status between ATS and opiate injectors (chapter 5), and greater injecting and sexual risk among polydrug- than single-drug injectors in Russia and Estonia (chapter 6). Finally, using a generic polydrug typology developed in latent variable modelling, I found significant differences in HIV-related injecting and sexual risk behaviours between polydrug classes (chapter 7).

The results of this work fill important research gaps by establishing that polydrug use is frequent and associated with substantial heterogeneity in HIV risk among PWID. My thesis examines the implications of these findings and proposes a polydrug use typology to help tailor drug and HIV prevention and treatment interventions to high risk PWID sub-groups to prevent the spread of new HIV and HCV infections.

[1] (i.e. Eastern Europe and central Asia, the Middle East and North Africa and Asia and the Pacific)

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List of abbreviations

AIC	Akaike information criterion
AIDS	Acquired Immune Deficiency Syndrome
aOR	adjusted odds ratio
M/ATS	Amphetamine/ Methamphetamine Type Substances
BBV	Blood-borne viruses
BIC	Bayesian information criterion
CI	Confidence interval
CNS	Central Nervous System
ECDC	European Centre for Disease Prevention and Control
EMCDDA	European Monitoring Centre for Drugs and Drug Addiction
GHB	Gamma-hydroxybutyric acid
HAART	Highly active anti-retroviral therapy
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HSV	Herpes Simplex Virus
IBBS	Integrated Biological Behavioural Survey
IDU	Injecting Drug User (superseded by PWID)
LRT	Log likelihood ratio test
MDMA	3,4-methylenedioxy-methamphetamine (“ecstasy”)
MMT	Methadone maintenance treatment
MSM	Men Who Have Sex with Men
NGO	Non-governmental organization
NSP	Needle/syringe programme/
OR	Odds Ratio
OST	Opioid substitution treatment
PLHA	People living with HIV/AIDS
PWID	People who inject drugs
PY	Person/years
RDS	Respondent-driven sampling
RDSAT	RDS Analysis Tool
RDS-I	Respondent-driven sampling estimator 1 (Salganick-Heckathorn)
RDS-II	Respondent-driven sampling estimator 2 (Volz-Heckathorn)
SD	Standard deviation
STI	Sexually transmitted infection
TLS	Time–location sampling
UNAIDS	United Nations Joint Programme on HIV and AIDS
UNODC	United Nations Office on Drugs and Crime
WHO	World Health Organisation

Chapter 1: Overview:
HIV, Hepatitis C and drug injection

Chapter 1 Overview: HIV, Hepatitis C and drug injection

1.1 Synopsis – injection and poly-injection are major health issue

Human Immunodeficiency (HIV) and Hepatitis C (HCV) infections among people who inject drugs (PWID) often overlap and have become global epidemics, with outbreaks of infection occurring in countries and populations previously unaffected, as well as those with existing drug or HIV epidemics. More drugs have become available to sizeable PWID populations with sub-optimal HIV prevention; polydrug use (using multiple drugs) in particular has been associated with HIV risk and may hinder efforts and progress in reducing new HIV infections [1-3].

The non-medical injection of drugs is responsible for a high burden of infection and disease globally. People who inject drugs (PWID) are exposed to multiple risks, including the transmission of blood-borne viral infections such as Human Immunodeficiency Virus (HIV), hepatitis C (HCV) and hepatitis B (HBV), but also drug overdose and death [4-8]. Globally, 13.5% of an estimated 12.2 million PWID were living with HIV and more than half were infected with HCV (~6.3 million) in 2013 [9]. In addition to being a major contributor to HIV and HCV infections, parenteral transmission through unsafe injecting is recognised to have a significant impact on the course of HIV epidemics and can be a sustaining factor in their evolution [10, 11].

The consumption of illicit drugs has expanded in contexts of rapid social and economic transition, particularly in countries of Eastern Europe, Central Asia and Southeast Asia. An estimated 16.5 million people globally, or 0.4% of the world population aged 15-64 years, used opiates in 2013, through injection or non-injection [9]. Although the use of illicit drugs such as heroin and cocaine has remained stable in parts of the world, drug markets have expanded to emerging economies in Asia and Africa and the abuse of substances such as meth/amphetamine type stimulants (M/ATS), prescription drugs and new psychoactive substances (e.g. synthetic cannabinoids) has increased [1, 9, 12-14].

Drug patterns have evolved and polydrug use has developed with the growing availability of psychoactive drugs in locations where their transit and/or production and that of their precursors have increased [9, 14-16]. While drug injection is a major risk factor for HIV and HCV, combining multiple substances and routes of administration has also been shown to be associated with significant health risks, not least overdose [2, 9]. However less is known on the specific HIV-related risks associated with polydrug use among

PWID, and even less on how different patterns of polydrug use may contribute to the risk of HIV and HCV infection among PWID, especially in resource-limited settings.

There is some evidence that polydrug drug use patterns are associated with HIV and HCV related risks. If this is the case, understanding heterogeneity in risk within PWID populations could assist programmes in reaching particularly vulnerable sub-groups at even greater risk in this marginalised and stigmatised population [17, 18].

The United Nations General Assembly Special Session on Drugs 2016 reaffirmed its commitment to evidence-based HIV interventions that target the specific needs of drug-affected populations [19]**.** If polydrug use is frequent and associated with increased risk of HIV infection, focusing efforts on polydrug practices may help to prevent more infections; it could also potentially provide a marker of risk for interventions to adapt to the prevention and treatment needs of different PWID sub-groups, thus maximising resources in contexts where funding is constrained [20].

The overarching aim of my thesis was to examine the epidemiological and public health significance of polydrug use in HIV and HCV risk, and associated risk behaviours, drawing on different epidemiological methods, sources of evidence and PWID populations to triangulate the findings.

My specific aims and the structure of my thesis are elaborated on at the end of this chapter, following a brief introduction to drug injection, burden of HIV and HCV infections and polydrug use.

1.2 The double burden of drug use: HIV and Hepatitis C infections

Drug injection

An estimated 12.2 million people globally had recently injected drugs in 2013 (IQR[2]: 8.5–21.5 million), corresponding to 0.26% (IQR: 0.2-0.5%) of the adult population aged 15-64 years [9, 21, 22][3]. Past-year drug injection was reported in 158 countries globally in 2014, including several African countries previously not reporting drug use [9, 23-25]. The prevalence of drug injecting in the general population was highest in Eastern and South-Eastern Europe, where as many as 1.27% of the population aged 15-64 were estimated to be injecting illicit substances. However the largest numbers of PWID were in East and

[2] IQR=Interquartile range

[3] WHO/UNAIDS/World Bank estimates based on reporting from 93 countries which together represent 84% of the population aged 15-64.

Southeast Asia where 3.15 million, or one in four, PWID live [9]. The Russian federation, China and the United States accounted for almost half of the number of PWID worldwide.

Burden of HIV and Hepatitis C

HIV and HCV are blood borne infections which disproportionately affect PWID. HIV, also transmitted sexually, is the retrovirus that causes AIDS[4]. Untreated, HIV infection leads to a lifelong severe illness and chronic inflammatory process that may cause cardiac, renal, neurologic and other comorbidities, and after a long incubation period, can lead to death [26]. HCV infects the liver and can cause acute and chronic infection which in approximately 20% (15%-45%) of cases, is cleared spontaneously by the immune system within 6 months [27]. A fifth of those who remain chronically infected with HCV are likely to develop liver cirrhosis and hepatocellular carcinoma within 20 years, and if untreated, to die prematurely [27-30].

Antiretroviral treatment (ART) for HIV reduces viral load to undetectable levels, thereby decreasing individuals' infectivity but not curing HIV. Despite its proven effectiveness and global scale-up, few HIV-positive PWID receive ART [31-33]. Similarly, Direct Acting Antiretroviral Agents (DAA) treatment can cure most HCV infections. However DAA prices are high and access to HCV treatment is low among PWID. There is currently no vaccine for HIV or Hepatitis C.

PWID are at greater risk of bacterial and viral infections, cognitive impairment, overdose and premature death than the general population while HIV and overdose were the lead causes of mortality among PWID in recent burden of disease studies [4, 8]. Globally, 1.7 million PWID (13.5%) were estimated to be living with HIV in 2013 (range: 0.9–4.4 million) with the greatest burden of HIV infection attributed to drug use concentrated in three regions: Southwest Asia (29.0%), Eastern and South-Eastern Europe (22.8%) and East and South east Asia (10.5%)[9]. Non-medical injection has been a major entry point for HIV in countries of South and South-East Asia, the Middle East, North Africa and Latin America and is responsible for as many as 80% of HIV infections in Eastern Europe and Central Asia [34]. PWID accounted for 30% of new HIV infections outside sub-Saharan Africa in 2013 and constituted a majority of the estimated 5 million new annual

[4] AIDS is defined as HIV infection associated with either a serum CD4+ T-lymphocyte level of less than 200 cells/μL or with an opportunistic infections or "AIDS defining illness".

HIV infections in Asia (3.7–6.0 million) and 1.4 million HIV infections in Eastern Europe and Central Asia (1.1–1.8 million) [9, 35].

Both hepatitis C and HIV may be acquired by percutaneous exposure but the per exposure transmission probability of HCV infection is 10 times higher than it is for HIV due to the greater efficiency of transmission and longer survival time of the HCV virus [36, 37]. Among PWID, HCV infection is generally more prevalent than HIV and worldwide 52% of PWID were estimated to be infected with HCV in 2013, with wide variations between countries [9, 38, 39] (table 1.1). Countries with large PWID populations such as China, the US and Russian Federation had the largest numbers of HCV infections and HCV prevalence among PWID was substantially higher than in the general population [9, 40].

Table 1.1: Estimated Hepatitis C burden among PWID in 88 countries with prevalence data

	Countries reporting	**HCV prevalence**	**HCV infections among PWID** (estimates)
Total	88 countries	52%	6.30 million
of which	29 countries, *including China*	> 60%	*1.93 million (China)*
	19 countries, *including the US*	> 70%	*1.52 million (United States)*
	10 countries, *including Russia*	> 80%	*1.30 million (Russian Federation*)

Table 1.1: sources: World Drug Report, 2015, Wiessing, 2014. Estimates were based on reports from 88 countries where HCV serology testing was not widespread and generally carried out in treatment or hospital settings. HCV testing may or not be offered to individuals who are part of a population with high HCV prevalence or who have a history of HCV risk exposure/ behaviour. PWID= People Who Inject Drugs. HCV=Hepatitis C. US=United States.

Although untreated HIV and HCV infection cause disease, disability and death, harm reduction interventions which provide sterile needles and syringes, and opiate substitution treatment to PWID can contribute to reducing injecting risk, infection and transmission of HIV and HCV [41-44]. Drug substitution therapy has also shown to improve adherence to antiretroviral therapy among HIV-infected PWID [45-48]. However the coverage of these harm reduction interventions remains insufficient and out of reach for PWID in many settings where resources are limited or drug substitution treatment is illegal [20, 32, 33].

1.3 Polydrug use

Polydrug use, defined as using multiple drugs over a short period of time, has been associated with greater risk of infection, injury, overdose and drug-induced deaths than non-polydrug use, and has garnered increasing attention in drug research [1, 2]. Drugs differ in their physiological and psychoactive properties and while PWID typically have a preferred drug, some elect to potentiate, counteract or replicate these effects using other substances [1, 2, 9]. However, while drug and routes of administration combined by PWID may generate intended effects, less is known of the interactions and unintended

consequences on HIV risk behaviours and immunity to infection. The properties and effects of major drugs are reviewed briefly below to inform my analyses and interpretation of results in the subsequent chapters. The major drugs injected include opiates and prescription opioids (central nervous system depressants) and cocaine and M/ATS (central nervous system stimulants), combinations of which are expected to compound the behavioural and infection risks of injecting one drug. Details of the drugs reported in PWID studies are presented in Table 1.2 [12, 13, 49, 50].

Opiates are derived from the opium poppy and can induce analgesia, euphoria and in higher doses, stupor, coma, and respiratory depression [51-53]. Heroin is a semi-synthetic opiate derived from morphine which generates a sense of well-being, reduced tension and anxiety and in large doses produces euphoria. The effects of heroin can last 3–5 hours depending on purity, dose and administration route [51, 54]. It can be smoked, ingested or injected, is highly addictive and withdrawal can be severe.

Opioids are synthetic analogues to opiates with similar effects. These pharmaceutical preparations, developed for medical use, to manage acute and chronic pain (e.g. Fentanyl, Oxycodone) or opioid dependence (e.g. buprenorphine, methadone), vary in potency and acting duration [51, 55]. Reports of prescription opioids intended for pain management or sedation being injected for non-medical purposes have increased in several countries but quantifying the prevalence of their use remains a challenge [12, 13, 50].

At the other end of the spectrum, stimulants such as cocaine and meth/amphetamine-type stimulants (M/ATS) stimulate the central nervous system with effects such as increased alertness, energy and stamina, euphoria and decreased appetite [51-53].

Cocaine is a powerful central nervous system stimulant used non-medically to produce euphoria or wakefulness; repeated use produces dependence. Cocaine hydrochloride has been used as a local anaesthetic in ophthalmology, ear, nose and throat surgery and dentistry for its vasoconstrictive action which help to reduce bleeding [55]. Cocaine increases energy and feelings of well-being with its effects lasting from 1-3 hours due to a short half-life; this can lead to frequent injections (up to 10 or 20 injections a day) [56].

Methamphetamine (MDMA) is an amphetamine-type substance discovered in Japan in 1919 and widely prescribed in the 1950s and 1960s as a medication for depression and obesity [53, 57]. The current prescription of ATS is limited to the treatment of narcolepsy and attention-deficit hyperactivity disorder [52, 53, 55]. M/ATS have a potent stimulant action on the central nervous system and can be smoked, snorted, ingested orally or injected. M/ATS have been used by a variety of populations groups such as soldiers, lorry

and taxi drivers, hospital workers, students, sex workers, clubbers and heroin users for their stimulant effects including increased energy, alertness, concentration, sexual libido and decreased social or sexual inhibitions [58, 59]. Several studies have examined the growing use of ATS by sex workers and clients and by groups of men who have sex with men (MSM) to increase sexual pleasure and facilitate prolonged sexual intercourse and greater numbers of partners [60, 61]. However, prolonged use of ATS at high levels can lead to dependence, and chronic use commonly induces personality and behaviour changes including impulsivity, aggressive behaviour, irritability, impaired judgement, suspiciousness and paranoid psychosis as well as cognitive impairment [5, 53, 59, 62]. Withdrawal reactions can occur after cessation following prolonged or heavy use and may result in depressed mood, fatigue, hyperphagia and sleep disturbance.

Polydrug use among PWID involves combining drugs and routes of administration for a desired effect, which may also produce unintended consequences including impaired judgment, increased risk behaviours, reduced immunity to infection and interactions when consumed close together [2]. Polydrug use has been associated with risk of infection, injury, overdose and drug-induced deaths and though recognised as a possible risk factor in HIV, the evidence on polydrug use and HIV and HCV risk is still scarce [1, 2, 17].

Challenges in studying polydrug use

Studying polydrug use presents three key challenges. Firstly, while certain drugs have been associated with HIV and HCV infection, studies have either examined associations with a main drug injected (compared to no drug or another drug) or associations with polydrug use (compared to a single main drug). Most studies have not accounted for the influence of a second drug, thus precluding the ability to differentiate the influence of the main drug from that of drug combinations, thus possible interactions between substances [1, 2, 63, 64]. If additional drugs are injected or used with the main drug, associations with this main drug may be weakened in an unmeasured way; conversely, associations between polydrug use and HIV risk could be confounded by a main drug as well as by the range or number of other drugs [65]. A second challenge is that the range and availability of psychoactive substances used across different social, economic and geographical settings has increased in recent years resulting in large numbers of possible combinations; as is the case with pharmaceutical drugs, combinations tend to increase adverse health risks [12, 50, 66, 67].

Table 1.2: Summary of drugs reported in PWID studies, medical use, properties and effects

Drug group	Opioids			Benzodiazepines	Sedating antihistamines	Amphetamines		Cocaine
Medical use	Medical use: Narcotic analgesics			Hypnotic, anxiolytic, neuroleptic, anaesthesia	Anticholinergic,	Cough decongestant	**A**DHD, narcolepsy	Medical use: local anaesthesia
Sub-group	**Opiates** naturally occurring	**Opioids** Semi-synthetic	**Opioids** Synthetic			Sympatho-mimetics	Vaso-constrictor	vaso-constrictor
Medical name, *tradename*	**Morphine** Diacetyl-morphine *Roxanol™ Duramorph™* **Codeine** *Robitussin A-C™ Tylenol™ with Codeine*	**Heroin** Diamorphine hydrochloride (heroin hydro-chloride) **Oxycodone** (hydrochloride) *OxyNorm™ Oxycotin™* **Buprenorphine** *Subutex™ Temgesic™*	**Meperidine** meperidine hydrochloride *Demerol™)* **Methadone** Methadone hydrochloride *Methadose™, Dolophine™* **Fentanyl** *Fentanyl™, Sublimaze™ Duragesic™, Actiq™* **Dextropropoxyphene** *Spasmo-proxyvon™* **Pentazocine,** *Fortral™, Sosegon™,* **Nalbuphine** hydrochloride *Nubain™* **Tramadol** hydrochloride *Zamadol™, Zydol™, Dromadol™, Larapam™, Mabron™*	**Diazepam** (oral mild sedation, long-acting, also rectal solution) **Alprazolam** oral tablet, anxyolitic *Xanax™* **Temazepam** (oral, rapid onset, short duration: +/- 90 mins) **Lorazepam** (prolonged sedation) **Midazolam** injected, profound sedation, fast recovery *Midazolam™ Hypnovel™*	**Promethazine Hydrochloride** *Phenergan™* **Pherniramine maleate** *Avil™* **Dyphenhydramine hydrochloride**, *Dimedrol™ Benadryl™* **Other CNS depressant** **Ketamine** (dissociative general anesthetic) **GHB** *(Gamma Hydroxy-butyrate)*	**Ephedrine** hydro-chloride Pseudo-ephedrine *Sudafed™*	**Amphetamine**s Dextro-amphetamine **Methamphetamines** MDMA (Ecstasy) methylenedioxy-methamphetamine *chemically similar to amphetamine, produced w/ Ephedrine* Methcathinone "Jeff, Vint" MDA (3,4 methylene-dioxyamphetamine MDEA=methylenedi-oxyethylamphetamine	**Synthetic forms:** .Lidocaine hydrochloride .Prilocaine hydrochloride .Procaine hydrochloride
Effects	Central Nervous System depressants					Central Nervous System stimulants		

Table 1.2 note: Non-exhaustive selection of drugs reported in studies among people who inject drugs. Drugs were categorised using standard classifications from the World Health Organisation, British National Formulary and National Institute for Drug Abuse [51, 52, 54, 55]. Drug names are in bold, generic chemical names in non-bold and known trade names are in italics. ADHD: Attention Deficit Hyperactive Disorder. Anticholinergic: inhibits parasympathetic nerve impulses by selectively blocking involuntary muscle movements associated with certain disease (eg. asthma, incontinence, gastrointestinal cramps and muscular spasms).

Thirdly, despite greatly improved consistency in measuring behavioural risk variables among PWID, the methods used to measure illicit drug use and polydrug use differ across studies, with no current standard or defined timeframe to measure polydrug use in PWID.

Our understanding of the pharmacological, neurological, immunological, cognitive and behavioural effects of the main drugs above has increased and can inform the study HIV risk and behaviours associated with specific polydrug combinations among PWID. More consistent assessments of polydrug use and clearer definitions could therefore further understanding of its link with HIV and HCV risks to inform prevention and treatment implementation, as well as policy development and research.

1.4 Global trends and geographical distribution of illicit drugs

Polydrug practices are largely determined by the drugs available; though markets have expanded in recent years, the geographical distribution of illicit drugs is not uniform across regions [9]. In many countries, heroin has replaced other poppy-derived opiates and become a dominant drug, as have certain stimulants such as cocaine, M/ATS and prescription drugs; reports of new psychoactive substances (NPS) have also increased since 2009, mostly in urban settings [68-71]. The dominant drugs used and injected in different regions are shown in Table 1.3 [50]**.**

Table 1.3: Illicit drugs most commonly used and injected by geographical region

	Americas	Africa	Europe	Eastern Europe, Central Asia	Southeast Asia	Oceania
Dominant drug reported	Cocaine, Heroin,	Heroin	Heroin, Cocaine, ATS	Heroin (black tar, pure), ATS, Ephedrine	Heroin, Prescription opioids, MATS	Heroin, MATS,
Other drugs	Prescription opioids, ATS	Cocaine	MATS NPS	ATS, Prescription opioids	Benzodiazepine, Cocaine, NPS	Cocaine, Benzodiazepines, NPS.

Table 1.3: ATS and MATS are differentiated in this table: ATS= Amphetamine Type Stimulant. MATS= Methamphetamine Type Stimulant. NPS= New Psychoactive Substances. Source UNODC, 2015; published studies.

According to the United Nations Office on Drugs and Crime (UNODC), opiate use (heroin and opium) remained stable globally in the past five years but the non-medical use of pharmaceutical opioids has increased [9]. Global estimates suggest there were 32.4 million opioid users (0.7% of the adult population[5]) and 16.5 million opiates users (0.4%) worldwide in 2013 [9]. Stimulant-dependant individuals were estimated at 24.1 million globally, of whom 6.3 million were dependent on cocaine or 0.1% of the adult population in 2010 (95% CI: 0.09% - 0.11%)[4, 9]. Cocaine use is reported to have declined in the

[5] aged 15–64 years old

past five years with 14-21 million users worldwide (0·3–0·5% of adults) and although rarely seen in Africa or Asia until recently, cocaine now transits through and is consumed in West Africa and Hong Kong [2, 9, 50]. ATS have become a global health problem with several sub-regions reporting increases in methamphetamine use. Methamphetamine is probably the most widely used synthetic stimulant worldwide, but ATS historically has been, and remains the most produced, trafficked and used synthetic stimulant in Europe [9, 72]. M/ATS injection has recently been reported in heroin-producing countries in Asia [73]. There were an estimated 14-56 million ATS users in the adult population worldwide in 2013 (0.3–1.3%), of whom 0.25% were dependant (0.22% - 0.28%) [4, 9, 74-77]. The non-medical use and injection of pharmaceuticals opioids prescribed for pain management, sedation or opiate substitution has increased in several geographical regions with reports of injection of buprenorphine preparations and lower potency opioids, such as codeine, nalbuphine and dextropropoxyphene and tranquilisers or sedatives in Canada, Afghanistan, Iran, Georgia, India, Nepal, Bangladesh [12, 13, 78].

With increased drug availability, polydrug use appears to have expanded and while possibly associated with HIV risk, polydrug use is also difficult to treat and poses challenges to drug and HIV responses [2, 9, 79, 80]. Better understanding its different forms and their association with HIV risk could usefully inform HIV prevention and treatment services in increasingly complex and dynamic drug use environments. With this in mind, my thesis aims to fill the research gaps summarised below.

1.5 Aim and objectives

The overarching aim of this thesis is to assess the epidemiological significance of polydrug use and associated HIV and HCV risk among PWID. The specific objectives of my research were (1) to determine the magnitude of the problem by examining the frequency and type of polydrug use across programme and geographical settings; (2) to review the state of the evidence on HIV infection risk associated with the injection of different drugs and drug combinations among PWID across countries; (3) to compare HIV-related risk associated with the injection of ATS or opiates in two PWID populations experiencing significant HIV epidemics in Estonia and the Russian Federation; (4) to characterise polydrug use and compare HIV-related risk associated with poly-injection among primary ATS and opiate injectors in the same two settings; and finally, to develop polydrug classifications and determine associations between polydrug class and HIV risks in the same two PWID samples. The results of this work have potentially important

implications for drug and HIV prevention and treatment, surveillance and research among PWID.

These objectives are addressed in seven chapters. Following the brief overview presented in this chapter, chapter 2 develops the theoretical frame for my research and examines the evidence on HIV risk and polydrug use. The following questions have guided my analyses and are grouped into three broad categories:

(i)* Determine the magnitude of the problem: frequency *of polydrug use

- Is polydrug use among PWID frequent? Are patterns of polydrug use common across different settings?
- Is there evidence of HIV-related risks associated with polydrug use among PWID?
    - These questions are addressed in a comprehensive review of literature in Chapter 2 (and throughout the thesis).

***(ii)* Determine what is currently known on HIV infection risk among PWID injecting different drugs or drug combinations**

- How does the risk of HIV (and HCV) infection vary between type of drug or drug combinations (polydrug use) injected among PWID?

This question is addressed:

- in a comprehensive review of literature in Chapter 2,
- in a systematic review and meta-analysis of HIV incidence among PWID in Chapter 3.

(iii) HIV, injecting and sexual risks in polydrug-using populations in two high HIV prevalence settings

- Is injecting amphetamine-type stimulants (ATS) associated with different injecting or sexual risk behaviours and, prevalence of HIV or HCV infection, as compared to injecting opiates?
- Is polydrug use prevalent in PWID populations? If so, can it be better characterised?
- Are specific polydrug combinations associated with greater HIV-related injecting and sexual risk behaviours, as compared to exclusively injecting a main drug?
    - These questions are covered in chapters 4 to 6 in the analysis of two PWID surveys in Kohtla-Järve in Estonia and St Petersburg in the Russian Federation.

- Can pragmatic polydrug classifications be developed to inform programmes, and are specific polydrug classes associated with HIV risk, unsafe injecting and sexual risk practices?
    - Polydrug classes are developed using latent class analysis of the two PWID surveys from Estonia and Russia in Chapter 7 and HIV risk compared among classes in multinomial regression.

Chapter 2

Polydrug use and HIV risk: evidence from the literature, definitions and conceptual framework

Chapter 2 Polydrug use and HIV risk: evidence from a literature review, definitions and conceptual framework

2.1 Background

Unsafe injecting is a recognised factor in the transmission of blood-borne infections among people who inject drugs (PWID) [81-83]. Comparatively less attention, however, has been given to heterogeneity in risk and to the potential role of polydrug patterns in determining HIV and HCV infection risk among PWID. The introduction of the thesis highlighted some challenges in the study of polydrug use and HIV risk and the aim of this chapter is to lay the theoretical foundation and evidence base for my subsequent analyses. The specific objectives of this chapter were to (i) examine the frequency of polydrug use by PWID across countries and review polydrug use concepts and definitions, to (ii) review the evidence on the behavioural, HCV and HIV risks associated with different drugs or drug combinations globally and finally, to (iii) develop a new conceptual framework for my analyses of polydrug use and HIV infection risk among PWID.

2.2 Literature review

The conceptual and evidence base which ground my analysis were developed in three stages in this chapter. The first was to map the prevalence of polydrug use among PWID from published reports either studying or reporting the use of multiple drugs among PWID in different regions and study settings, and to review polydrug definitions and drug combinations reported (section 2.3). In the second stage, epidemiological and drug research studies reporting biological markers (HIV or HCV infection) or behavioural outcomes (injecting and sexual risk behaviours), or both, among PWID injecting different drugs or drug combinations were reviewed and gaps identified (section 2.3.2). HCV was also included as it shares the parenteral route of transmission with HIV and may provide a marker of injecting risk among PWID, among whom HCV prevalence is extremely high [84-86]. In the third stage, theoretical frameworks used in epidemiology, population health and drug research were searched in the literature to inform my conceptual framework for the analysis of polydrug use (section 2.3.3). Details of the methods used for the searches are described in Box 1.

Box 1: Literature review: search strategy

The first two stages were based on a comprehensive but non-systematic review, for which database searches were conducted in Ovid, Medline and Embase using a simple search strategy, with additional searches in Google Scholar. The search used key terms to capture studies reporting drug combinations and practices among PWID, even when polydrug use was not the main outcome or explicitly mentioned. The search terms were: ("opiate addiction" OR "drug abuse" OR "substance abuse" OR "psychoactive" OR "inject$ adj2 drug" OR "intravenous drug abuse" OR "polydrug") AND ("HIV" or "Human immunodeficiency virus" OR "hepatitis C" OR "infection risk") AND ("risk and behaviour$" OR "risk factor$"). The population of interest were people who had injected one or more illicit drugs (i.e. heroin, prescription opioids, cocaine and meth/amphetamines (M/ATS)) in the past 1 to 6 months. Studies published between 1990 and 2013 were eligible, with no a-priori limitation on language. Research among PWID in recent epidemics in Asia and Africa, and where drug use and HIV and HCV epidemics persist were actively sought. Studies of polydrug use that focused on alcohol, cannabis, the general population, adolescents and school surveys were excluded, as were those only reporting lifetime polydrug use. Duplicate reports from the same PWID sample were prioritised by relevance to the outcome of interest, recent publication and amount of detail on drugs reported.

Examining polydrug use and HIV risk required a framework that conceptualised and structured hierarchically complex connections between exposure variables and events [87, 88]. Most of those used in drug and dependence research presented broad hierarchies of factors contributing to drug and behavioural risks but no linear risk structure that could be applied to polydrug use; equally, epidemiological frameworks conceptualising HIV and HCV transmission in other populations included sexual risk but no parenteral risk. Frameworks were appraised for their ability (i) to help articulate linear connections, ii) to identify determinants of risk (injecting and sexual) on the pathway to infection (which interventions may then target), iii) to highlight gaps in the evidence, and finally iv) to help structure the research needed to answer questions.

Box 2: Literature review: search results

From 3,490 records returned by the search, 400 reported at least one biological (HIV, HCV) or behavioural outcome of interest (injecting and/or sexual risk behaviours) in the title or abstract and 212 of these reported PWID as the population of interest. Among these, 65 full text studies reported on one or more primary drug(s) injected, namely: heroin, cocaine, M/ATS, prescription opioids, new psychoactive substances or their combinations. After removing duplicate reports, 15 studies reported *HIV prevalence* among cocaine and heroin injectors (n=6) or ATS and heroin injectors (n=9), and 5 studies reported *HCV prevalence* among heroin and opiate with stimulant co-injectors (i.e. heroin with cocaine or heroin with ATS). Of 40 studies of injecting and/or sexual behaviours among PWID, 21 compared *injecting risk* between PWID injecting M/ATS (n=13), cocaine (n=3), fentanyl (n=1), heroin with cocaine (n=6), heroin with M/ATS (n=3) or heroin with sedatives (n=1), and those injecting heroin or not injecting the drug.

Box 2 Literature review: search results (continued)

Sexual risk behaviours were reported by 23 studies among PWID injecting M/ATS (n=8), cocaine (n=11), benzodiazepines (n=1), heroin (n=1) or heroin with cocaine (n=3) compared with those injecting heroin or not injecting the drug (The number of studies exceeds 40 as some reported on several drugs). Two relevant studies were translated from Russian and Chinese.

A total of 61 studies reporting polydrug use in PWID were identified, of which 54 studies in the main search on polydrug use and 7 from references cited in other papers. After removing duplicate reports from the same PWID sample, 42 studies conducted in 19 countries and five continents reported some form of polydrug among PWID with timeframes ranging from 30 days to a lifetime [89-97]. Study details are shown in appendix 2, Table S2.1.

2.3 Literature review results

2.3.1 Polydrug use prevalence, definitions and limitations

Extent and prevalence of polydrug use in people who inject drugs

Research from countries with established drug and HIV epidemics (e.g. Canada, United States, United Kingdom and Australia) and from regions where drug use and injecting have emerged more recently and evolved rapidly (e.g. Eastern Europe, Asia and Africa), suggested that using multiple drugs was widespread among PWID [73, 92, 98-100]. Figure 2.1 shows the prevalence of recent polydrug use among PWID, based on 42 published reports with samples ranging from 45 to 2,469 PWID, the majority of whom were male, street-recruited and out-of-treatment. Past month polydrug use prevalence in young PWID out-of-treatment ranged from 21% in California in 1998 to 78% in Australia in 2007, [18, 101-104]. In more recent drug epidemics, 21% of PWID in Yunnan province (China), 53% in Tallinn (Estonia), 70% in Northern India (2008) and 90% in Russia (2006), had used other drugs in addition to heroin injection in the last 1-3 months [93, 98, 105-107]. PWID in-treatment settings reported lower levels of polydrug use, conceivably resulting from the limited effectiveness of opiate pharmacotherapy in individuals dependent on multiple drugs; 15% of PWID on methadone in the United Kingdom (2005) and 25% in Israel (1999) reported multiple drugs in the last month and year, respectively [94, 97, 108].

Defining polydrug use

Although some PWID studies recognised polydrug use as an important factor in drug research, few epidemiological reports studied the practice which was mostly cited along with other behaviours [1, 2, 9, 64]. The main and consistent feature of polydrug use across studies was the use of more than one drug or type of drug by an individual over a period

of time [2, 53, 63, 109, 110]. That said, definitions across studies reviewed differed in (i) the number and type of substances included, investigating illicit as well as licit substances such as alcohol and cannabis, in (ii) the population of interest, including the general population, young people, homeless individuals or illicit substance users, and in (iii) the timeframe used to define polydrug use or examine associated risks [2, 63, 101, 110-112].

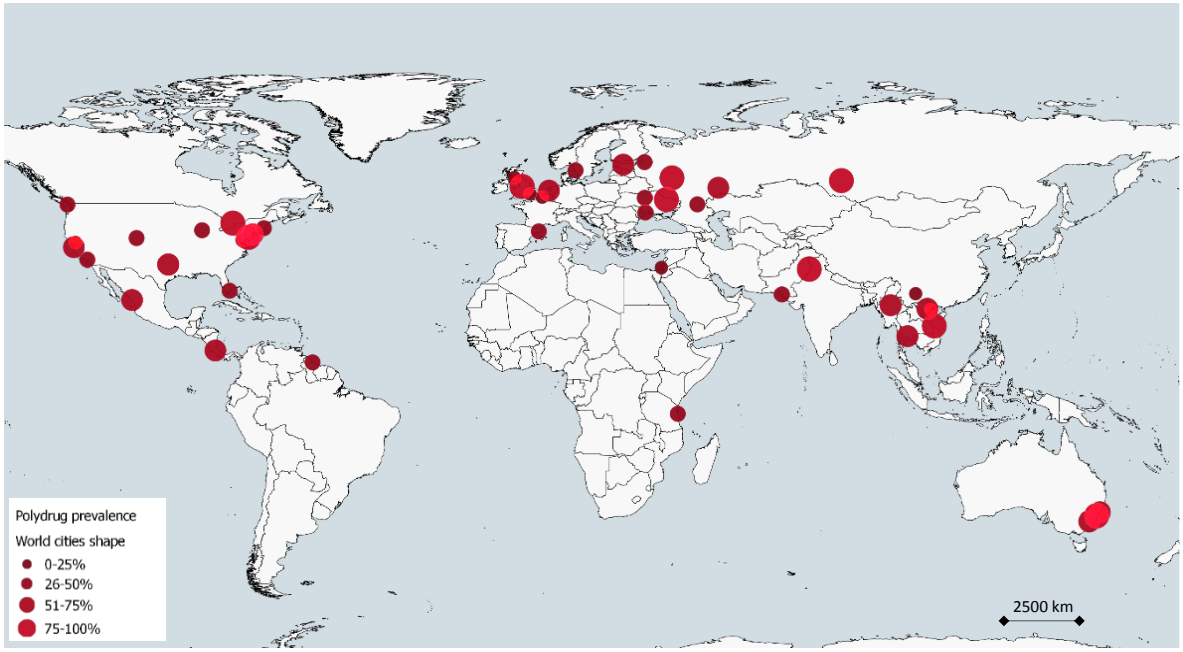


Figure 2.1: Polydrug use prevalence among people who inject drugs - compiled from the most recent among 61 published study reports conducted between 1993 and 2015 in 40 cities and 19 countries.

Some researchers have attempted to define the timeframe in which different drugs are administered and differentiated *sequential* from *simultaneous* polydrug use but to date few studies of HIV risk associated with polydrug use in PWID have used these definitions [109, 110].

Polydrug use patterns may differ in drug combinations, PWID groups and study context and may provide imperfect generalisations of results due to the lack of consistent measurement criteria. Schensul *et al* attempted to differentiate patterns of polydrug use using three key measures including the (i) *time period within which use of different drugs* occurred (concurrency), (ii) *intention* behind the combination and (iii) individuals' *agency* or capacity to intervene to *produce a particular effect* [109]. Similar criteria were used by Leri and Bruneau in a review of polydrug use among heroin and cocaine users, to elucidate drug combinations as a function of the *time of administration* of each drug, the *intention* and experience or *effect sought* by the user [113]. They concluded that the *effect sought* can be (i) to enhance a feeling through a combination, (ii) to self-medicate and/or

manage withdrawal, or (iii) to potentiate the effects of one drug with another, testifying to the awareness of pharmacology among experienced drug users [110, 113, 114]. *Timing* is a critical factor that determines possible drug interactions, as are the intention and agency, whether users *proactively* seek to produce desired effects or *reactively* adapt to external events such as drug price increases or drug shortage [109, 110].

The World Health Organisation (WHO) elaborated on earlier definitions of polydrug use in 2013, by adding the notion of intention to differentiate polydrug patterns and combinations: "the use of more than one drug or type of drug by an individual, often at the same time or sequentially, and usually with the intention of enhancing, potentiating, or counteracting the effects of another drug" [53]. In summary, three broad polydrug use categories described the diverse combinations found in my review: *sequential, alternate (or replacement)* and *combined (or simultaneous)* polydrug use, shown in Figure 2.2.

- *Sequential polydrug use* (Figure 2.2a) refers to the injection of one type of drug after another in a short space of time – usually with the aim of counteracting the effects of the first drug. Injecting stimulants followed by central nervous system (CNS) depressants to offset CNS stimulating effects is a common practice among cocaine and some ATS injectors [65, 113].
- *Alternate (replacement) polydrug use* (Figure 2.2b) occurs when a drug is injected to "substitute" a preferred or usual drug – it often results from external factors, such as high drug prices, low availability or supply of a drug. PWID engaging in this type of polydrug use, typically switch to a drug with similar psychoactive properties but this is not always the case. Following heroin shortages, PWID injected cocaine or ATS in Australia, prescription opioids in Canada, and fentanyl in Estonia [93, 100, 102, 115, 116]. One study found injecting methadone syrup instead of heroin to be associated with greater heroin dependence among PWID [117].
- *Combined (simultaneous) polydrug use* (Figure 2.2c) is the injection of two or more substances at the same time, to enhance or potentiate the effects of a main drug [109].

In *combined polydrug use*, the effects may be *additive* as in the injection of prescription opioids or benzodiazepines with hypnotics or sedatives (or antihistamines) to potentiate/ complement the effects of heroin [118-120] while in *sequential polydrug use* they may be *interactive* as in using gamma-hydroxy butrate (GHB) after ecstasy (MDMA) to counteract the stimulant effects of ecstasy [121]. These three definitions were applied to polydrug use practices reported in PWID studies in Table 2.1, illustrating both the range of polydrug patterns and their potential for classification.

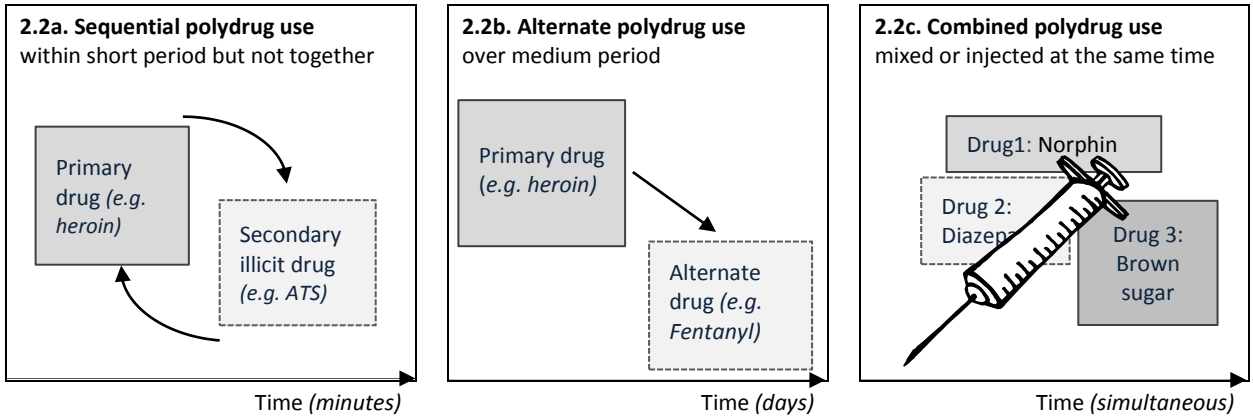


Figure 2.2: Polydrug use by timeframe, intention and drug combination

Table 2.1: Polydrug use type reported in studies of HIV-related risk among people who inject drugs

Type	Intention	Drug combination(s) reported and findings	Study type	Author, year
Sequential	**to counteract effects of a drug with another** (CNS depressant after stimulant) **to "self-medicate" or manage withdrawal**	e.g. Heroin after cocaine e.g. GHB after Ecstasy e.g. Ketamine after Ecstasy e.g. Methadone and heroin	Pharmaco-logical, Ethno-graphic	Leri, 2003 [113] Uys, 2005 [121] Lankenau, 2005 [65]
Alternate/replacement	**to replace a drug by another as a result of external factors**	*Estonia*: Heroin replaced by Fentanyl, led to greater injecting risks: sharing needles, and situational risk factors.	Cross-sectional	Talu, 2010 [93]
		Australia: heroin shortage led to use of cocaine. Cocaine injection associated with injection risk, maybe determined by drug practices different from those of heroin users.	Cross-sectional	Maher, 2007 [102]
		Italy, East Europe: Heroin alternated with Tropicamide (eye drops)	Case report	Spagnolo, 2013 [116]
Combined/Simultaneous	**to potentiate effect of opiate or opioid drug with a sedative or hypnotic** (e.g. buprenorphine with benzodiazepines to potentiate effects)	*India*: Lower potency mixture led to greater *frequency of injection*.	Cross-sectional	Mahanta, 2008[120]
		High levels of dependency may lead to *more frequent injection* if substitute drug is less potent (e.g. PO).	Cross-sectional	Bruce 2009; Yokell, 2011 [13]
		Malaysia: more frequent injecting and syringe/needle sharing	Cross-sectional	Jones,2012 [122]Otiashvili, 2010 [123]; Larance,2011 [12]
		Also reported in USA, Afghanistan, Pakistan Bangladesh, Nepal, Thailand	Review	
	(e.g. heroin with sedatives and/or prescription opioids)	*China, Ukraine, Russia:* Mixing drugs in collective preparations –infection risk from *sharing injection equipment*	Cross-sectional	Zhang, 2006
	to induce effects of both drugs simultaneously (e.g. PO and cocaine) **to "self-medicate" or manage withdrawal**	*Montreal:* PO-Cocaine injectors more likely to inject frequently, share used syringes and inject in public places than non-PO injectors.	Longitudinal study	Bruneau, 2011 [115]; Roy, 2013 [18]

Table 2.1. PWID= people who inject drugs. CNS= Central Nervous System. GHB= gamma-hydroxy butrate. ATS= Amphetamine Type Stimulant. PO=Prescription Opioid.

Although recognised as a possible factor in HIV risk, studies reviewed lacked consistent measurement timeframes to usefully inform drug combinations and interactions; recall periods for drug use questions varied from 30 days to a lifetime across studies.

Shorter timeframes have been used in service delivery settings using assessment tools and a 7-day recall period in the timeline follow-back technique (TFBT), a self-reported, retrospective, calendar-based measure to assess drug use over time [124]. However short periods maximize recall but may not capture meaningful patterns in cross-sectional surveys. Questions on drug use and injecting behaviours in recent PWID surveys have used a 30-day recall period which captures drug practices over timeframes short enough to maximise accurate recall yet long enough for patterns to emerge [125].

In addition to measurement issues, the pharmacological interactions, behavioural and HIV infection risk resulting from different polydrug use combinations are not well understood [64, 65, 122, 126]. However the definitions outlined above may be particularly relevant when studying the impact of polydrug use on the risk of HIV and HCV infection.

2.3.2 HIV and HCV prevalence: associations with specific drugs and combinations

This second part of the review examined HIV and HCV prevalence among cocaine or ATS stimulant injectors compared to opiate injectors; several trends emerged from the seemingly mixed results, presented in Figure 2.3 and Figure 2.4 for HIV and Figure 2.5 for HCV prevalence. Overall HIV prevalence among PWID samples ranged from 2.1% to 76%. Within each study, HIV prevalence tended to be associated with cocaine compared to opiate injection in studies where the PWID sample was older, had injected longer, also injected other drugs and where needle/syringe, and drug treatment programmes were developed (Baltimore, USA; Montreal, Canada and Paris, France) (Figure 2.3; [127-129]). By contrast HIV prevalence was significantly lower among cocaine injectors compared to heroin injectors in studies enrolling PWID who were younger, street-recruited and who reported a main drug (Spain, United States)[130, 131]. Similar differences were found between ATS and opiate injectors; HIV prevalence was higher among ATS injectors compared to opiate injectors in PWID who also injected other drugs, were older and recruited from established harm reduction services (USA, Australia) or in drug treatment (Russia) (Figure 2.4; [127, 132]). HIV prevalence was significantly lower among young street-recruited PWID mainly injecting ATS (compared to heroin), where injecting was recent and NSP services less established (Estonia, Myanmar) [93, 133] while no differences were found between drugs among PWID in Ukraine, Georgia and Russia [92, 99, 134, 135].

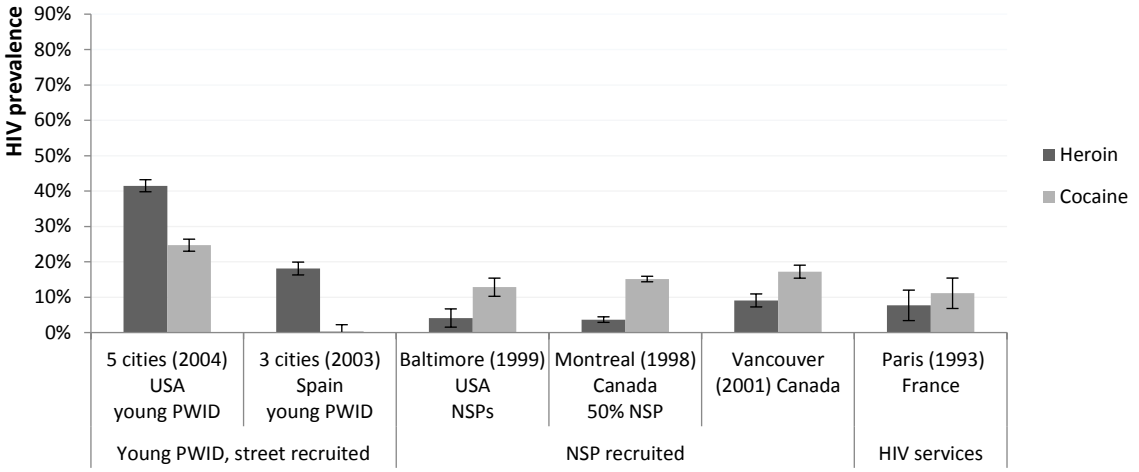


Figure 2.3: HIV prevalence in PWID injecting heroin or cocaine. Error bar=95% confidence interval.

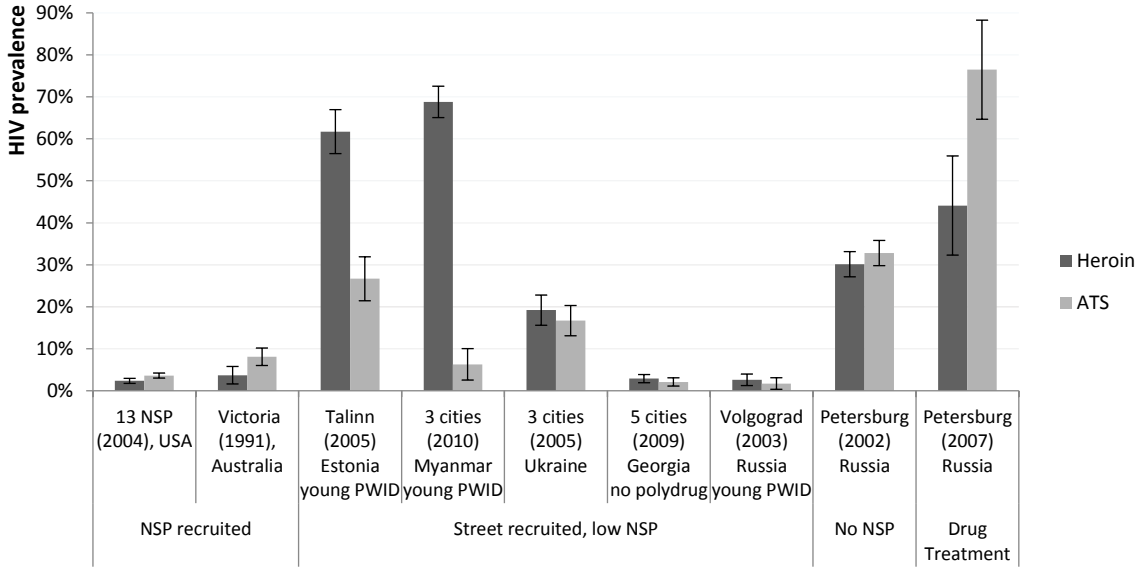


Figure 2.4: HIV prevalence in PWID injecting heroin or ATS. Error bar= 95% confidence interval.

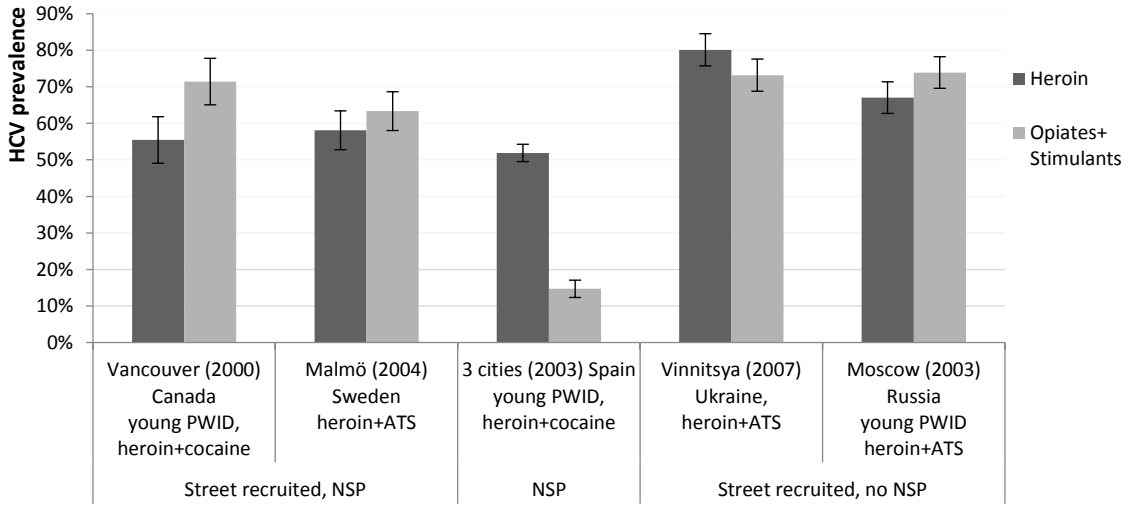


Figure 2.5: HCV prevalence in PWID injecting heroin or opiates with stimulants. Error bar= 95% confidence interval. NSP=Needle and syringe programme, PWID=people who inject drugs. ATS=Amphetamine-Type Stimulants.

HCV prevalence was above 50% in all but one PWID drug group across the studies, consistent with its greater efficiency of transmission than HIV and elevated risk among PWID [28, 37, 84, 85, 136]. HCV prevalence was higher among injectors combining opiates and stimulants (cocaine or ATS) compared to those injecting opiates in three studies but only significantly so among street-recruited young PWID in Vancouver (Figure 2.5) [98, 137, 138]. HCV prevalence was lower among young PWID combining stimulants with opiates (cocaine and heroin), compared to heroin alone, in a sample of educated, employed and less frequent injectors in Spain [89, 130].

Associations between drug "switching" in response to drug shortages, and HIV and HCV infection have also been reported in studies; HCV incidence was associated with increased risk behaviours among PWID who switched to prescription opioids in Canada, and with increases in cocaine injection following the reduced availability of heroin in Australia [102, 139]. Similarly, incident HIV infection was associated with cocaine compared to not injecting cocaine in Montreal [115, 140]. Although most studies adjusted for key demographic, contextual and behavioural variables, several factors seemed to account for differences in the results, not least how drugs were defined (i.e. primary drug, most frequently used or last drug used) and the reference categories reported, and whether polydrug use was accounted for in the analysis. These are discussed in section 2.4.

Injecting risks associated with specific drug use patterns

Injecting ATS, cocaine or combinations thereof was associated with unsafe sharing and injecting practices in several epidemiological studies; Table 2.2 summarises the direction of associations, and their strength if reported [89, 115, 141]. Cocaine or M/ATS stimulant injection (rather than opiate) seemed to be associated with sharing and lending needles and syringes among PWID out-of-treatment, who also injected other drugs; however the review found no evidence that self-identified primary stimulant compared to opiate injectors were more likely to share needles and syringes [142-144]. ATS injection in particular, was associated with sharing and lending needles and syringes, compared to those not injecting ATS, among PWID who co-injected opiates and cocaine [92, 145-148] and M/ATS was associated with lending needle and syringes among PWID who also injected midazolam in Thailand [70]. Receptive sharing of needles and syringes was also positively associated with opiates and ATS injection (compared to opiate) in Ukraine, while PWID injecting opiates and sedatives had higher odds of front/back-loading [92]. Combining heroin and stimulants was predictive of unsafe injecting, and particularly of

sharing injecting equipment in the past month, when compared to injecting an opiate (heroin) among PWID in Australia, the United Kingdom and United States [17, 91, 149]. By contrast, primary ATS injection (ATS reported as main drug) was negatively or not associated with sharing needles/syringes compared to opiate injection, after adjusting for other factors (i.e. age and injecting frequency) in Estonia and the United States [93, 150].

Table 2.2 Associations between primary drug and injecting risk behaviours in published studies

Drug injected	Injecting risk variables	Association (†)	(a)**OR*** (95% CI)	Author, year
M/ATS vs. opiates	Frequent injecting	↓	-	Kaye 2000;
		↓	-	Gleghorn, 1998
		↑	-	Titova 2009‡;
		=	-	Booth 2008 (Ukraine);
	Shared needles/syringes *(= receptive sharing)*	↑	1.61 (1.22-2.13)	Fairbairn 2007;
		↑	-	Booth 2008;
		↑	-	Friedman, 1993;
		↑	-	Copeland, 2001;
		=	ns	Kaye 2000;
		=	ns	Klee, 1993
		↓	-	Kall 1990;
		↓	-	Zule, 1999;
		↓	-	Titova 2009‡;
	Lent used needles/syringes *(= distributive sharing)*	↑	1.90 (1.40-2.60)	Kral, 2011 (+her/coc)
		↑	1.38 (1.02-1.86)	Fairbairn 2007;
		↑	OR=10.2 (2.1-53)[β]	Voon, 2015[β]
	Shared drug solution	↑	-	Booth 2008 (Ukraine);
Cocaine vs opiates	Frequent injecting	↑	-	Booth,1993;
		↑	-	Hankins,2001
		↑	-	Tyndall, 2003
Fentanyl (opioid) vs ATS	Frequent injecting (≥ daily)	↑	4.30 (2.09-8.97)	Talu, 2010;
	Shared used needle/syringe	↑	1.60 (0.84–3.08)	Talu, 2010;
	Shared needle/syringe w/sex partner	↑	1.50 (0.72–3.14)	Talu, 2010
Polydrug users* opiate/cocaine vs. opiate	Frequent injecting	↑	-	Bleich,1990;
	Shared needles/syringes	↑	-	Darke, 1990;
		↑	2.5 (1.22-5.13)	Gleghorn,1998;
		↑	OR=2.7 (1.5-4.8)	Harrell, 2012;
		↑	-	Klee, 1999;
		↑	-	Folch,2006;
opiate/MATS vs opiate	Shared needles/syringe	↑	2.10 (1.50-2.80)	Kral, 2011 (+her/coc)
		↑	2.86 (1.59-5.15)	Hayashi, 2011 (Mid/he)
		↑	-	Braine, 2005
opiate/sedatives vs. opiate	Front or back-loaded syringe	↑	aOR=16.6 (95%CI)	Booth, 2008 (Ukr)
		↑	aOR=1.31 (95%CI)	Booth, 2008 (Ukr)
	Frequent injecting	↑	-	Darke, 1992
	Shared needles and syringes	↑	-	Darke, 1992

Note table 2.2. †The symbols "↑", "↓" and "=" indicate positive, negative or no association, reported by studies as odds ratios (OR), adjusted odds ratio (aOR) or X^2 test. *Study p-values were not included for legibility. ‡ PWID in treatment. [β] Self-reported HIV positive PWID. PWID = people who inject drugs. M/ATS= Meth/ amphetamine type stimulants. vs = comparison group.

Injecting frequency also appeared to vary depending on whether stimulants were injected alone or in combination with opiates. In studies comparing primary drug injectors, ATS injection was associated with less frequent (but as intense) injecting compared to opiates [101, 146, 150]. PWID who co-injected heroin and stimulants in US studies reported more frequent injections and filling syringes from another, as compared to primary heroin-only or stimulant-only injectors [101, 131, 151]. Cocaine has a short half-life which may explain its association with frequent and intense bursts of injecting among PWID in Canada and the US [56, 142, 143]; at the same time, levels of heroin use and polydrug use were factors predictive of injecting risk among out-of-treatment injectors in Sydney (as was sexual relationship with an IDU) [152]. The combination of stimulants with addictive opiates may therefore explain the greater injecting risks reported among PWID combining two drug classes. One treatment-based study found more frequent injecting and polydrug use among primary ATS- compared to opiate- injectors. However, the study was treatment-based, did not specify the type of drug treatment and findings may have resulted from poorer treatment outcomes associated with stimulant- and polydrug use [99]. There is currently no pharmacology for stimulant dependency and poorer treatment outcomes have been reported among PWID injecting cocaine with an opiate [74, 75, 99]. More generally, several studies have also found polydrug use to be associated with progression to regular and addictive drug use and was predictive of transition to injecting in young adults [109, 153, 154].

Sexual risk associated with specific drug use patterns

Comparisons of sexual risk behaviours between stimulants injectors and those not injecting stimulants are presented in Table 2.3, with the direction of associations and their strength, when reported. Several studies found that stimulant injectors were more likely to report multiple sex partners, unprotected sex, selling sex for drugs or money, and sexually transmitted infections (non HIV) compared to those not injecting stimulants. Injecting cocaine or crack-cocaine was consistently associated with increased sexual risk taking, including multiple sex partners and unprotected sex [142-144]. ATS use among PWID was also independently associated with greater numbers of sex partners in young sex workers in Cambodia, while PWID injecting stimulants in Ukraine had the highest average number of injecting and sexual risk behaviours, when compared to PWID injecting opiates [92, 155]. Among primary ATS users in China, sexual risk after using ATS was associated with HIV infection as was history of sex with STI-positive persons,

polydrug use and HCV infection [69]. Hallucinogen use[6] and sexual relationship with an injector were also found to be predictive of sexual risk-taking among PWID in Sydney [152]. Several studies in North America found HIV infection in young stimulant injectors associated with sexual risk such as having multiple sex partners; two early studies found crack-cocaine use among women associated with multiple sex partners and selling sex [131, 142, 156]. Using multiple substances (including Temazepam) was also associated with sexual risk behaviour that may increase exposure to HIV infection among PWID in the UK [91] while in Tanzania, heroin injection with other substances were common and associated with binge injecting and multiple sex partners among women [24]. More generally, high levels of sexual risk were reported among PWID in several settings and HIV seroconversions linked to unprotected heterosexual contacts, despite reductions in injection risks such as needle sharing (i.e. Amsterdam and San Francisco) [157-159].

In addition to the behavioural risks highlighted, immunological factors may also account for the risk of HIV seroconversion among cocaine and ATS injectors. Immunological studies in animals and humans have shown that stimulants such as cocaine and ATS contribute to increasing biological susceptibility to infection by modulating the immune response to HIV infection [160-162]. Cocaine, in particular was found to increase susceptibility to infectious diseases in humans by increasing the pool of infection-susceptible T-cells, thus altering the immune function and increasing viral replication of HIV [160, 161, 163]. Results from studies on the effect of ATS on immunity were less conclusive [162, 164]. Research investigating the effects of cocaine on immunity and HIV also suggested that cocaine increased HIV disease severity and progression [163, 165].

[6] Drug Use Scale employed in study includes LSD, Ecstasy (MDMA) and psilocybin as hallucinogens (Darke, 1991a)

Table 2.3 Associations between primary drug and sexual risk behaviours in published studies

Drug injected	Sexual risk variables	Association (†)	(a)OR (95% CI)	Author, year
M/ATS vs. opiates	Multiple sex partners	↑	OR: 2.2 (1.6-3.1)	Gleghorn, 1998;
		↑	-	Klee,1993;
		↑	-	Booth, 2008;
		↑	-	Zule, 1999;
		↑	-	Baker, 1994;
		↑	-	Bao, 2012;
		↑	-	Molitor, 1998
	Unprotected sex	↑	-	Klee, 1990;
		↑	-	Klee,1993;
		↑	-	Zule, 1999;
		↑	-	Molitor, 1998;
		↑	-	Booth, 2008
	Exchanged drugs for sex	↑	OR: 1.9 (1.2–3.0)	Gleghorn, 1998;
		↑	-	Molitor, 1998;
	Sexually Transmitted Infection (HIV)	↑	-	Crofts, 1994;
		↑	-	Molitor, 1998;
		↑	-	Bao, 2012;
Cocaine, crack vs. opiates	Multiple sex partners	↑	1.82 (1.16-2.85)	Hudgins, 1995;
		↑	-	Booth, 1993;
		↑	-	Somlai, 2003;
		↑	-	Wilson, 1998;
		↑	-	Kral, 1998;
		↑	-	Larrat, 1994;
		↑	-	Strathdee, 2003 (f);
			-	Harrell, 2012;
			-	Hoffman, 2000
	Unprotected sex	↑	1.29 (0.67-2.49)	Hudgins, 1995;
		↑	-	Booth, 1993;
			-	Somlai, 2003;
			-	Larrat, 1994
	Exchanged drugs for sex	↑	3.32 (1.63-6.73)	Hudgins, 1995;
		↑	1.47 (1.21-1.89)	Booth, 1993;
		↑	OR: 3.1 (1.9-5.1)	Kral, 1998;
		↑	-	Hoffman, 2000 (f);
		↑	-	Edlin, 1994 (f)
	Sexually Transmitted Infections	↑	-	Booth, 1993;
		↑	-	Edlin, 1994
Benzodiazepines vs. "other"	Being paid for sex	↑	-	Darke, 1992
Heroin vs. stimulants	Multiple sex partners	↓	-	Hudgins, 1995;
		↓	-	Booth, 2008;
Polydrug users heroin/cocaine	Multiple sex partners	↑	OR: 2.7 (1.9-3.7)	Gleghorn, 1998;
		↑	2.30 (1.80-2.94)	Hudgins, 1995;
vs. opiates	Exchanged drugs for sex	↑	OR: 2.4 (1.6–3.8)	Gleghorn, 1998;
		↑	2.97 (1.07–8.21)	Harrell, 2012;
		↑	3.49 (2.28-5.34)	Hudgins, 1995

Note table 2.3. †The symbols "↑", "↓" and "=" indicate positive, negative or no association, reported as odds ratios (OR), adjusted odds ratio (aOR) or X^2 test. *Study p-values were not included for legibility. PWID = people who inject drugs. (f) Female PWID. ‡ PWID in treatment. ᵝ Self-reported HIV positive PWID. M/ATS= Meth/ amphetamine type stimulants. vs = comparison group.

2.3.3 Conceptual framework for polydrug use and HIV risk

Brief critical review of existing frameworks in the literature

Several frameworks were originally developed to conceptualise factors influencing, sexual risk and HIV transmission in the general population but few have conceptualised the determinants of HIV in the context of injecting and none to date have integrated polydrug use. Of eleven frameworks identified to conceptualise the analysis of polydrug use, five met the conditions outlined in section 2.2 and were appraised [87, 166-171]. They included: 1) Victora's hierarchical framework of risk factors for infectious diseases in developing countries [87]; 2) Boerma and Weir and Zaba's proximate-determinants framework for HIV [166, 167]; 3) Poundstone social epidemiology of HIV risk [168]; 4) Galea and Vlahov social determinants of drug use and health risks [169] and 5) Rhodes's risk environment [170, 171].

The proximate-determinant framework (2) was originally developed for demographic studies of the determinants of fertility and has been widely used in studies of HIV [172]. It was adapted to the study of child survival and subsequently modified by Boerma and Weir to study the distribution and determinants of HIV infection [87, 166, 173]. The proximate-determinants framework for HIV, links factors in the social and environmental system with the biological factors which determine the rate of new infections, leading to disease and death in the absence of treatment [166, 167]. Although the focus of this framework was on sexual transmission in contexts of generalised HIV epidemics, the authors suggested its applicability to other modes of transmission such as blood transfusion, unsafe injections in healthcare settings and needle-sharing among injecting drug users. The framework specifies a multilevel hierarchy consisting of (i) three levels of determinants (i.e. underlying, proximate and biological) and (ii) two levels of outcome (i.e. health and demographic). The underlying determinants include social, economic and environmental factors. The proximate determinants include behavioural factors (e.g. unprotected sex) which combined with biological factors (e.g. viral load) determine susceptibility to infection and the rate at which an epidemic is transmitted [87, 166, 168]. This structured sequence of determinants leading to exposure, transmission of infection, disease and death provides a useful framework for study design and for the analysis and interpretation of risk factors.

An evaluation of the proximate-determinants framework above in a population of adults in Zimbabwe found that most individual-level variation in HIV risk could be explained through proximate-determinants of which many underlying determinants were predictors

[174]. However the study also suggested that wider community and structural factors should be included. The proximate-determinants framework was subsequently used by Zaba *et al* to identify the most relevant determinants influencing biological outcomes in different populations and types of HIV epidemics [167]. It also contributed to prioritising behavioural data requirements for HIV surveillance in different epidemic contexts and to differentiating data collection needs for generalised HIV epidemics from those for epidemics concentrated in high risk population groups [125, 175].

Galea and Vlahov proposed a framework (4) emphasising the *social determinants of drug use* and health risks in disadvantaged populations in the United States [176]. The focus of the framework was on the role of income disparities, homelessness and incarceration as vulnerability factors which determine drug-related risks and disease. The framework has supported advocacy for public health interventions addressing social factors which increase vulnerability and exacerbate the health impacts of drug use.

The *risk environment* framework (5) has also been used by social epidemiologists and harm reduction programmes to assess risk and reduce PWID vulnerability to HIV [177-179]. In this context vulnerability was defined as *"features of a social or economic entity that make it more or less likely that excess morbidity and mortality associated with disease will have deleterious impacts"* [180]. The risk environment framework describes the underlying physical, social, economic and political factors that influence the pathway and causal links to HIV infection among PWID. The framework is comprehensive in highlighting factors that influence vulnerability to infection, including factors in the environment of PWID which contributed to increasing injecting risk for example; it did not however offer a sequential structure where determinants influenced individual susceptibility to blood-borne infections and HIV transmission.

Social epidemiology frameworks have adopted a broad approach, outlining a hierarchy of individual (e.g. demographics, behaviours), social (e.g. social capital) and structural (e.g. legal, policy and cultural) determinants of transmission [168, 181, 182].

These frameworks bring different perspectives to the study of determinants of HIV infection and are useful tools in conceptualizing levels at which determinants operate. The *social determinants of drug use* (4) and *risk environment* (5) in particular have improved our understanding of how policies may contribute to increasing PWID vulnerability to infection. While these frameworks highlight important factors in the study of HIV and HCV in populations with stigmatised behaviours, they lack a rigorous sequence of events to design and analyze studies of HIV, HCV risk and risk behaviours among PWID.

Proposed conceptual framework for polydrug use and HIV risk

My proposed framework builds on the proximate-determinant hierarchy to incorporate injecting risk that increases PWID susceptibility to infection; it also integrates important underlying factors from the risk environment known to contribute to PWID vulnerability to HIV infection (Figure 2.6). The proximate determinants which have a direct impact on HIV transmission dynamics among PWID are factors which influence (i) exposure to risk by contacts with HIV-infected partners, (ii) efficiency of transmission (which depends on biological, genetic, and immunological risk factors in the host and virus) and (iii) duration of infectiousness (proximate determinants in Figure 2.6) [166, 167]. The underlying determinants recognised to have an influence on the risk of acquisition among PWID are those that increase or decrease individual or population vulnerability to HIV and HCV infection.

In this framework, the drug and drug combinations (polydrug use) injected by PWID are expected to impact HIV infection risk through behavioural and biological pathways (e.g. greater risk behaviours and/or decreased immunity, section 2.3.2). The next section details the relevant proximate (injecting and sexual) and underlying determinants which expose PWID to HIV and HCV and determine the likelihood of infection and disease.

Proximate determinants of risk: Injecting and sexual risk behaviours

Exposure to HIV risk through parenteral transmission and contact with an HIV-infected partner through the sharing of needles and syringes is estimated to be 8-15 times greater than with heterosexual sexual transmission [81-83, 183]. Injecting drugs can be an elaborate process involving individual or collective preparation with several steps, all of which have potential to transmit infections through contact with contaminated equipment or fluids [184, 185]. Several key behavioural risk variables in the framework capture exposure to contaminated blood or liquids among PWID (Table 2.4). The number of injections in the last month (*injecting frequency*) and number of injections on the last day injected (*intensity of injecting*) provide a measure of the frequency of exposure to injecting equipment and fluids. *Sharing* or *lending needles and syringes* and *sharing injection paraphernalia* indicate the number (or proportion) of unsafe contacts with contaminated equipment/fluids. Practices such as *front- or back-loading* (filling a syringe from working syringe) have potential to transmit infections and consist of either, mixing drugs with blood in a syringe then sharing it among users or, filling a syringe from another donor syringe to inject oneself, either by removing the needle (front-loading) or plunger (back-loading) from the receiving syringe [89, 186-188]. The *duration of*

injecting provides a measure of cumulative exposure to contaminated equipment and blood over time and has been associated with HCV and HIV status [189]. The background HIV prevalence in a PWID population provides a proxy-measure of the probability that an individual injecting in a given population will be exposed to the virus (assuming random mixing) [190-192].

Evidence of sexual risk and HIV transmission among PWID and their partners, improved survey methods and more resources, have contributed to better reporting of sexual behaviours in studies that previously overlooked or reported only one or two sexual activity variables [193, 194]. Variables for which there is evidence of elevated risk of HIV transmission through contacts with HIV-infected partners are multiple sex partners, receiving money or drugs in exchange for sex, reporting unprotected sex and non-consistent condom use with regular and casual partners [143, 195]. There is growing evidence of unsafe injecting within intimate partner relationships which increases potential for HCV and HIV transmission, especially among women; "having a sexual partner who also injected drugs" is increasingly being reported as a risk factor [152, 196-199].

Underlying determinants of risk: socio-demographic and structural factors

Several underlying factors have been associated with HIV-related risk among PWID; they include demographic and social, as well as factors resulting from the social, legal, policy and cultural environment in which people inject drugs (i.e. structural) [170, 182]. Demographic and social factors associated with unsafe injecting practices, HIV or HCV in the literature were younger age, female gender, lower education, belonging to a minority ethnicity, being socially disadvantaged or homeless [9, 131, 200-204]. Structural factors may be modified by interventions to reduce drug harms and prevent HIV and HCV transmission through the provision of clean needles and syringes, and drug substitution treatment (for opiate dependency) [9, 33, 41, 44]. Conversely, factors in the environment have also been associated with increased HIV-related risks and included injecting in the street, attending shooting galleries, having needles and syringes confiscated or having been incarcerated [171]. In settings where drug use is heavily stigmatised or criminalised, the risk of being caught with needles and syringes by the police may lead to higher levels of unsafe injecting [205-207]. Incarceration may also increase exposure to unsafe injecting practices and to HIV and HCV infection [208, 209].

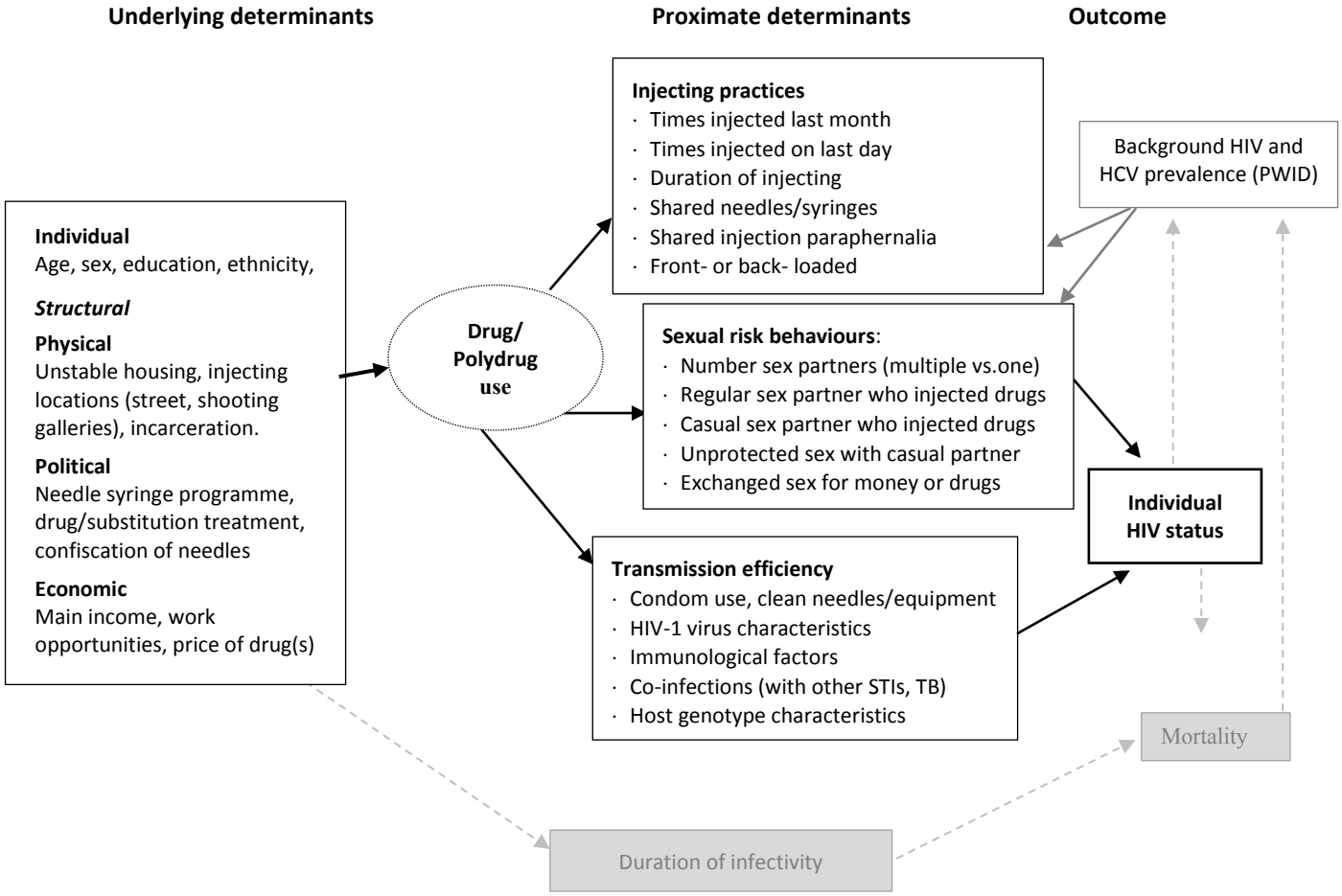


Figure 2.6: Conceptual framework for polydrug use and HIV transmission among people who inject drugs

Note: Shaded areas are included for completeness but not covered in this analysis. PWID=people who inject Drugs. HIV=Human Immunodeficiency Virus. HCV= Hepatitis C virus. STI=Sexually Transmitted Infection. TB=Tuberculosis.

Table 2.4: Variable definitions for determinants of HIV risk among people who inject drugs

Proximate	Variable of interest: definition and timeframe [1]
	Injecting risk behaviours
Age at first injection	Age first time injected
Duration of injecting	Number of months injected since 1st injection
Injecting frequency	Number of days injected in the last month *(last 4 weeks)*
Injecting "intensity"	Number of times injected on the last day injected
Shared needles and syringes	Used needle or syringes previously used by other PWID *(Ever, last 4 weeks). Also referred to as "receptive sharing".*
Lent needles and syringes	Lent needle or syringes previously used by self to other drug user *(last 4 weeks). Also referred to as "distributive sharing".*
Shared drug paraphernalia	Shared drug preparation equipment or implements such as cooker, container, filter, cotton or utensils *(last 4 weeks)*
Filled from working syringe	Filled a syringe from a working syringe (i.e. front-or back-loaded) *(last 4 weeks)*
Primary drug injected	Main drug injected in the preceding 4 weeks, also referred to as "drug of choice"
	Sexual risk behaviours
Any sex	Had any sexual intercourse in last 6 months (vaginal or anal)
Regular sex partner,	Sexual intercourse with regular partner *(last 6 months)*
Regular sex partner who injects	Sexual intercourse with regular partner who injected drugs *(last 6 months)*
Casual sex partner	Sexual intercourse with casual partner *(last 6 months)*
Casual sex partner who injects	Sexual intercourse with casual partner who injected drugs *(last 6 months)*
Being paid for sex	Received money or drugs in exchange for sex *(ever, last 12 months)*
Multiple sex partners	Had two or more sex partners in the last 6 months
Condom use regular sex partner	Used condom with casual sex partner at sexual intercourse *(consistent, last sex)*
Condom use casual sex partner	Used condom with casual sex partner at sexual intercourse *(consistent, last sex)*
Unprotected sex	At least one instance of sexual intercourse without a condom *(last 4 weeks)*
Underlying	**Demographic variables**
Sex [2]	Male or female
Age	Respondent's age at time of interview
Ethnicity	Context-specific: being of a different ethnic or underrepresented group
Education level	Context-specific: usually completed 1) basic or vocational school, 2) secondary School or 3) higher (university-level) education
Main source of income	Context-specific: usually salaried, irregular or dependent, illicit (theft, dealing)
Living arrangements	Usually categorised into "stable" or "unstable" accommodation.
	Contextual factors
Drug/substitution treatment	Received drug/substitution treatment (OST) *(i.e. lifetime, last 6 months)*
Contact with NSP	Had contact with needle/syringe services or NSP outreach worker *(i.e. 4 weeks)*
Incarceration	Reported being incarcerated *(i.e. lifetime, in past 12 months)*
Needles/syringes confiscated	Had needles and/or syringes confiscated by the police *(i.e. last 6 months)*

Notes: Table 2.4. NSP= needle/syringe programme. OST= Opiate substitution treatment. [1] The timeframes provided are recommended but vary from study to study. [2] Surveys among people who inject drugs define sex as a binary variable although a few recent studies have included other gender options (e.g. transgender).

2.4 Discussion: findings on polydrug use and HIV risk, research gaps and next steps

Some research on polydrug use, HIV and HCV risk among PWID has become available but was limited to specialised drug research in the Americas, or related data on the use of multiple drugs in epidemiological reports among PWID. Still, this emerging body of evidence suggested (i) substantial levels of polydrug use with different polydrug patterns among PWID and (ii) specific associations between cocaine, M/ATS stimulants or polydrug use and HIV risk. Though limited in its scope, my narrative review suggested consistent findings and several research gaps, summarised below. The key gaps identified were then used to structure the research needed to answer my questions.

Polydrug use and HIV risk

Considerable levels of polydrug use were reported in epidemiological studies among PWID in community and treatment settings and across regions. Several studies found using multiple drugs associated with HIV risk, including frequent injections and back-loading of syringes, especially in young PWID combining stimulants and opiates rather than opiates alone [2, 9, 17, 101, 112]. Associations between stimulant injection and HIV risk behaviours seemed to differ depending on whether ATS or cocaine were co-injected with other drugs or reported as main drug injected.

Though polydrug use was associated with sharing injecting equipment and/or HIV infection in several studies, the different drugs or classes combined were not detailed and the term covered various possible combinations and patterns of use [210]. Studies of polydrug use also lacked consistent information on the primary drug injected which precluded the ability to differentiate the effects of a primary drug from those resulting from combinations or potential interactions [1, 64]. A few recent studies have examined detailed patterns of polydrug use and found associations with HIV risks but the patterns and associations found could not be generalised [17, 18].

Some pharmacological studies have attempted to elucidate the effects of certain drugs on physiology, cognition and immunity but less is known about drug combinations and their effects [2, 67, 113, 121, 162]. Nevertheless, more consistent assessments of polydrug use in epidemiological studies could generate clearer evaluations of the links between specific drug combinations and HIV and HCV infections and risk behaviours.

Main drug injected and HIV risk

My review suggested differences in risk behaviours according to the type of drug injected and possibly type of drug classes combined, beyond the HIV and HCV risks associated

with specific injecting risk behaviours irrespective of the drug injected. Research linking cocaine and M/ATS stimulants to risky sexual behaviours and HIV infection has increased, as have immunological studies into their effects on HIV risk and immunity [67, 121, 211]. Several epidemiological studies in this review found that cocaine or ATS injection, compared to not injecting a stimulant, was associated with HIV infection. Others consistently reported positive associations between stimulant use and multiple sex partners, unprotected sex and paid sex. However drug group definitions, comparison groups and variables adjusted for in multivariate analysis were not consistent [99, 135, 142].

Cocaine injection tended to be associated with HIV infection when compared to not-injecting the stimulant, in settings where PWID also injected other drugs, were older, had injected longer, and where needle/syringe, and drug treatment programmes for opiate dependency were developed. However, HIV prevalence was lower in studies comparing self-identified primary cocaine or M/ATS injectors to heroin injectors, in settings where PWID were younger, street-recruited, where stimulants were more recent and NSP services less established. Interestingly, PWID injecting both heroin and stimulants (opiate-stimulant combination) consistently reported higher levels of sharing (i.e. needle and syringe sharing and filling syringe from used syringe) and multiple sex partners [101, 131, 212]. Cocaine and M/ATS reduce inhibition, increase social cognitive function and sexual desire and may impair judgment; these stimulants have also been associated with less regular but high intensity injecting during which the use of uncontaminated needles/syringes may be compromised and may account for increased sharing of injecting equipment, and more so in the presence of an addictive opiate [142].

Studies among PWID combining heroin with other opiates or sedatives also found that the co-injection of heroin with sedatives, tranquilisers or prescription opioids (opiate-opiate combination) was associated with greater injecting frequency, in this case possibly resulting from the need to make up for low potency of other substances by injecting more often [91, 149, 213-215].

Determinants of behavioural risk

Analyses of large PWID cohorts in the United States and Canada have demonstrated the importance of sexual as well as injecting risk in the acquisition of HIV infection among PWID, highlighting that HIV infection acquired sexually between PWID, non-injecting drug users and their sexual partners need to be considered in the changing dynamics of HIV epidemics [143, 216]. Studies of stimulant users and injectors in Eastern Europe and

Asia have examined associations between HIV infection and injecting risk behaviours but less consistently those with sexual risk [98, 217-220]. Given the likelihood of sexual as well as parenteral transmission among PWID, a notable omission in early studies was the limited reporting of sexual risk variables to 'being sexually active' which precluded a complete analysis and interpretation of HIV risk among PWID [105, 193, 221]. More systematic reporting of sexual risk behaviours is required in all PWID settings.

High levels of risk among PWID

Even in PWID populations with good access to harm reduction services and where needles and syringe sharing had decreased, the sharing of injection implements and paraphernalia remained relatively high [141, 222]. High levels of behavioural risk may reflect new or young injectors entering the PWID population pool over time and/or vulnerable sub-groups not being reached, or reached consistently, by programmes. The challenge of engaging and treating stimulant-dependent individuals for whom no effective treatment options are available may also explain high levels of risk among stimulant (co-) injectors [74, 75]. Improving methods to reach less visible PWID with on-going prevention and harm reduction is key to slowing both HIV and HCV epidemics [92, 98, 131, 157, 223].

Research gaps identified and next steps

Several research gaps were identified in the review, three of which are addressed in the subsequent chapters.

Research gap 1: Most epidemiological studies among PWID were cross-sectional and reported HIV or HCV prevalence with few studies reporting HIV incidence, thus limiting the interpretation of results. Prevalence is the result of cumulative incidence (itself resulting from cumulative exposure to risk) and deaths; in the case of HIV, prevalence only reacts to changes in risk behaviours with an extended time lag. Cross-sectional surveys also limit interpretation of associations in time and therefore causality. HIV incidence on the other hand may allow more accurate measurement of temporal associations to study the determinants of HIV infection.

I addressed this gap *in chapter 3* by systematically reviewing HIV incidence in PWID sub-groups injecting different drugs to provide a more accurate assessment of infection risk associated with different drugs or drug combinations in different settings.

Research Gap 2: Some studies in the review reported associations between polydrug use, risk behaviours and HIV but several limitations precluded meaningful comparisons, not least the absence of standardised definitions for polydrug use. Few studies of polydrug use and HIV risk accounted for the main drug injected by PWID, while those comparing HIV risk in different primary drug groups did not generally account for polydrug use. Given more recent evidence of associations between polydrug use and HIV, and risk behaviours, future research should account for the main drug and for polydrug use among PWID, within similar timeframes. This would allow comparisons of HIV, HCV and risk behaviours in different drug groups while adjusting for the effect of polydrug use; similarly comparisons of HIV and HCV risk among polydrug injectors would also take into account the main injection drug.

This research gap was addressed in *chapters 4 to 6* by comparing HIV, HCV and risk behaviours among primary ATS and opiate injectors, and then poly- and single drug injectors among each primary group in two settings.

Research Gap 3: Though the presence of polydrug use among PWID was generally recognised in epidemiological studies, there was limited conceptual or analytical examination to explain distinct patterns and combinations of substances in different PWID populations [107, 224]. When highlighting the risks associated with different drugs or polydrug patterns, few studies developed consistent characterisations of polydrug use to compare HIV risks across them [49, 225, 226]. Detailed and consistent reporting of a main drug and polydrug use in studies and surveys could contribute to identifying and addressing the patterns of risk that may contribute to heterogeneity in this key population. More research is also needed on the individual, community and environmental factors that predict polydrug use and on the context-specific factors that determine transitions to polydrug use or drug-switching over the life course of drug use.

This gap was addressed *in chapter 7*: a generic classification of polydrug use patterns was developed using latent class analysis in the same two PWID surveys, and associations between polydrug class and HIV and risk behaviours were modelled using multinomial logistic regression.

This preliminary review has a number of limitations. Although the search focused on PWID studies, comparisons were limited by differences in PWID recruitment criteria and the absence of consistent measure of drug dependence and vulnerability to risk in PWID studies (e.g. injecting frequency, Addiction Severity Index (ASI)). It is generally accepted that risky injecting practices are more likely to occur among drug-dependent injectors,

especially when about to experience withdrawal symptoms. Consistent reporting on proportions of injectors and/or drug-dependency scores could facilitate comparisons between studies.

While it was comprehensive, this review was neither exhaustive, nor systematic and may have missed some studies. However it sought to include essential peer-reviewed research publications on individual drugs and polydrug use among PWID in different epidemic settings and drug use contexts. The search was rigorous and regularly updated with key references from new publications, if they had not already been included.

Chapter 3

Influence of different drugs on HIV incidence in people who inject: systematic review and meta-analysis

Publication

The research in this chapter was published in the journal Addiction. **"Influence of different drugs on HIV risk in people who inject: systematic review and meta-analysis"** Marie-Claude Boily, Peter Vickerman and Francisco Bastos are co-authors. Isabel Tavitian-Exley is the primary author of this material and conducted the review, data extraction and compilation and statistical analyses with MCB. Critical review was provided by MCB and PV and the manuscript was reviewed by MCB, PV and FIB.

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Chapter 3 Influence of different drugs on HIV risk in people who inject: systematic review and meta-analysis

3.1 Introduction

Opiates have historically been the dominant illicit drugs injected by people who inject drugs (PWID) but cocaine, meth/amphetamine type substances (M/ATS) and prescription opioids have gained prominence and contribute to the growing burden of drug use, dependency, and HIV and Hepatitis C (HCV) among PWID in several regions of the world [68, 92, 227-229]. While there is evidence that different drug use patterns such as the type of drug injected and polydrug use may influence HIV and HCV infection risk, these are not fully understood, yet crucial for interventions to be effective [17, 68, 91, 213, 230, 231].

The literature review on polydrug use and HIV risk in chapter 2 found that polydrug use was substantial among PWID and conceivably associated with HIV infection; however, drug combinations were often not reported [2, 9, 93, 232, 233]. In studies citing specific drugs, injecting stimulants such as cocaine or M/ATS was often associated with more risky sexual behaviours, however, associations with injecting risk and HIV infection were not consistent across studies [17, 143, 157, 212, 234]. Cocaine and M/ATS injection were positively associated with having multiple sex partners, unprotected sex and trading sex, compared to opiate injection, but less consistently with frequent injecting, needles and syringe- sharing and HIV transmission [99, 142, 146, 150, 235]. However the settings, substances injected and co-injected, and reference categories used, varied across studies. While many studies used opiate injectors as comparison group, some used all other PWID as comparison, and few studies took into account the co-injection of other drugs. Cocaine injection for example seemed to be associated with higher HIV prevalence compared to opiate injection, among PWID samples who also injected other drugs, were older, had injected for longer, and where needle/syringes, and drug treatment programmes for opiate dependency were developed. In contrast, HIV prevalence was lower among self-identified primary cocaine or M/ATS injectors compared to heroin injectors, in PWID samples who were young, street-recruited, where stimulant use was more recent and needle and syringe services less established. Positive associations were reported between cocaine injecting and HIV incidence in a few incidence studies, where cocaine injectors co-used other drugs and were compared to PWID who did not inject stimulants (but injected other drugs) [140, 142, 235].

Studies of behavioural risk among PWID injecting stimulants and heroin (opiate-stimulant) also found higher levels of needle and syringe sharing, filling syringe from used syringe, and multiple sex partners compared to those only injecting heroin [101, 131, 212] and M/ATS injection was associated with multiple sex partners and unprotected sex among PWID who injected M/ATS stimulants with opiates [92, 101, 152, 236]. Aside from the behavioural risks, recent immunological studies have found that cocaine and M/ATS increased the biological risk of HIV infection by modulating the host's immune response to infection (i.e. cocaine), promoted viral replication (i.e. M/ATS) or both, thus increasing an individual's biological susceptibility to HIV [160, 162, 165].

Most epidemiological studies of HIV among PWID in chapter 2, especially those in resource-limited settings, reported on prevalent rather than incident HIV infection, thus limiting the interpretation of results. Since HIV prevalence is the result of cumulative incidence and deaths, it will only react to changes in risk behaviours with an extended time lag which challenges interpretation. Comparing HIV incidence on the other hand typically allows better inference on temporal associations to study the determinants of new HIV infection. Better evidence on the magnitude of associations between specific drugs or polydrug use and HIV, and their public health implications would usefully inform programmes and policy decisions. Risk differences arising from drugs(s) injected are not completely understood; yet they are critical to understanding HIV epidemics among PWID and to ensuring that interventions respond appropriately to dynamic changes in patterns of drug use [90, 93, 95, 146].

Accordingly, this chapter set out to examine whether major psychoactive substances injected by drug users for non-medical purposes influence differentially the risk of HIV transmission, by conducting the first systematic review of HIV incidence studies in PWID sub-groups injecting different drugs or drug combinations.

The objective was to systematically evaluate the results from published studies on HIV transmission among PWID, to estimate the magnitude of associations and understand sources of heterogeneity, and to provide estimates of risk associated with different drugs or drug combinations.

3.2 Methods

3.2.1 Search strategy

A systematic search of the published literature was conducted to identify studies reporting data on HIV incidence and sexual and injection risk behaviours in PWID injecting

different drugs. The search strategy was developed in Embase and adapted for use in Medline. Database searches were conducted in Ovid, Medline and Embase, included studies published up to 1st January 2012 the search was updated to 1st January 2013. Additional searches were conducted via Google Scholar. Key search terms are shown in Table 3.1 and the full search strategy, in appendix Table S3.1. After detailed evaluation of individual studies, authors were contacted where data for the analyses were missing or incomplete. Authors were not contacted if the time elapsed since the study was published exceeded 10 years or data was missing for several variables.

Table 3.1: Systematic review search terms

("opiate addiction" OR "drug abuse" OR "substance abuse" OR "street drug" OR "poly drug" OR "polydrug" OR "psychoactive" OR "psycho active" OR "intravenous drug abuse") AND ("Human immunodeficiency virus infection" OR "HIV transmission" OR "HIV seroconversion" OR "HIV" OR "Human immunodeficiency virus" OR "HCV" OR "hepatitis C" OR "Hepatitis C virus") AND ("Incidence" OR "Human immunodeficiency virus prevalence" OR "HIV risk" OR "HIV incidence" OR "HIV prevalence" OR "Hepatitis C virus" OR "HCV incidence" OR "infection risk") AND ("risk behaviour$" OR "behaviour" OR "risk factor" OR "behavioral research" OR "behavioral risk factor").

3.2.2 Selection criteria and extraction of data

Observational cohort studies of HIV infection risk among PWID were reviewed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Table S3.2 in appendix 3) [237].

Cohort studies were included if PWID were the primary population of interest (> 70% injectors), study samples were greater than 30 participants and study outcomes were HIV incidence and/or hazard or incidence rate ratio. We included primary research data from epidemiological cohort studies where HIV status was determined by laboratory testing and drugs injected were specified. No a-priori limitations were placed on language or region of publication and relevant papers were translated by native speakers. Given the limited number of PWID cohorts, we considered retrospective cohort study designs from lower and middle-income countries when available.

A first screening by two reviewers assessed titles and abstracts for relevance. Potentially relevant studies were retrieved for further evaluation. The quality of studies retained for possible inclusion into the meta-analysis was graded using the Newcastle-Ottawa Scale (NOS) for cohort studies. The scale goes beyond a simple checklist and has been used in several studies to rate the quality of observational studies [238, 239]. Those studies reporting HIV incidence or rate ratios for different substances injected were included. Among

eligible studies, different reports of the same cohort were identified, ranked for completeness of data and date of publication. When several reports were available for the same cohort, we selected the report with most complete and recent data.

The key characteristics extracted for each study included the main drug(s) injected (referred to as primary drug), country, sample size, study design, number of HIV seroconversions during the study period, follow-up period duration, baseline HIV prevalence in PWID, year of publication, prevalence of needle and syringes sharing, past month frequency of injecting, proportion of cohort injecting each substance and prevalence of PWID with multiple sex partners (defined as two or more sex partners). PWID exposure to HIV prevention including contact with drug treatment and needle and syringes programmes (NSP) were extracted, if available. Study region and cohort duration were also extracted as possible proxy for exposure to HIV prevention and harm reduction if NSP and drug treatment data were not available. Studies were analysed using UNAIDS-defined geographical regions and country-specific drug prices (street), adjusted for purity and inflation, published annually by the United Nations Office on Drugs and Crime [71].

Crude Incidence (cIRR) or Hazard (cHRR) rate ratios, adjusted IRR (aIRR) or HRR (aHRR) when available, and HIV incidence rate with 95% confidence intervals, were extracted by drug injected for all studies comparing risk between PWID injecting a specific drug, and not-injecting, when possible, or otherwise comparing to those reported not to have injected the specific drug of interest. Where confidence intervals were not provided, these were calculated using the Poisson distribution for rates. HIV incidence and rate ratios were extracted using established classifications for psychoactive drugs primarily injected: cocaine, (including crack-cocaine), methamphetamine or amphetamine type-substances (MATS or ATS) and heroin [51, 52]. PWID injecting multiple drugs (i.e. polydrug users) were categorised into *opiate-stimulants* (i.e. injecting heroin with cocaine, ATS or MATS) and *opiate-sedatives* (i.e. injecting heroin with benzodiazepines or other tranquilisers), based on the drug(s) classes injected and their psychoactive properties.

3.2.3 Meta-analysis

A progressive approach was used for the meta-analysis to evaluate whether study estimates could be combined. Some heterogeneity was expected between studies and pooled estimates of risk (IRR or HRR) with 95% confidence intervals, were derived using inverse variance weighting to calculate random-effects summary estimates [240]. Using rate ratios (IRR and HRR, subsequently referred to as IRR) allowed comparisons within and across different drug use and epidemic settings. Forest plots were used to display

study and pooled estimates, and results from the sub-groups analyses by drug or combination of substances. Statistical heterogeneity across study estimates was explored using the I^2 statistic, subgroup analyses and meta-regression techniques [241]. A cut-off point of I^2=40%[7] suggested sufficient homogeneity to pool study estimates to allow measures to be combined in a random effects summary estimate [240, 242]. A sensitivity analysis to assess the influence of individual study estimate on pooled estimates was carried out and sources of bias in the meta-analysis considered.

Univariate (and multivariate) random effects meta-regression analyses were carried out to identify independent variables and study characteristics explaining most of the variation across study estimates (IRR). Factors that may have been directly or indirectly associated with HIV incidence and for which data was available were examined in univariate meta-regression. Given observed differences in comparison groups used across studies, we considered their influence in sub-group and meta-regression analyses. Variables included in the analysis were study design, baseline HIV prevalence among PWID in the cohort, year of publication, drug injected, duration of cohort follow-up, risk behaviours such as frequency of injecting, prevalence of syringe-sharing and multiple sex partners and finally, region. Available data on country and year-specific drug price were also investigated as a possible influence on the IRR.

Between-study variance explained by covariates was assessed for significance using adjusted R^2 and residual heterogeneity (I^{2Res}). Multivariate meta-regression modelling was carried out and models were fitted using random effects models in STATA version 12 (Der Simonian-Laird method).

3.3 Results

Search results

Out of 5779 papers screened, 226 full text studies were identified and reviewed (Figure 3.1). After detailed review of publications, 15 studies reporting incidence by drug were eligible and included in this analysis (Table 3.2). Duplicate reports from the same cohorts and studies for which missing data were not received were excluded (Table S3.3, in appendix 3).

[7] I^2 can be interpreted as the proportion of variance that is due to heterogeneity rather than sampling errors. Values can be categorised as follows: 0% to 40%: might not be important; 30% to 60%: may represent moderate heterogeneity; 50% to 90%: may represent substantial heterogeneity; 75% to 100%: considerable heterogeneity. A high I^2 and p-value < 0.05 indicate a high degree of heterogeneity unlikely to be due to sampling error/chance.

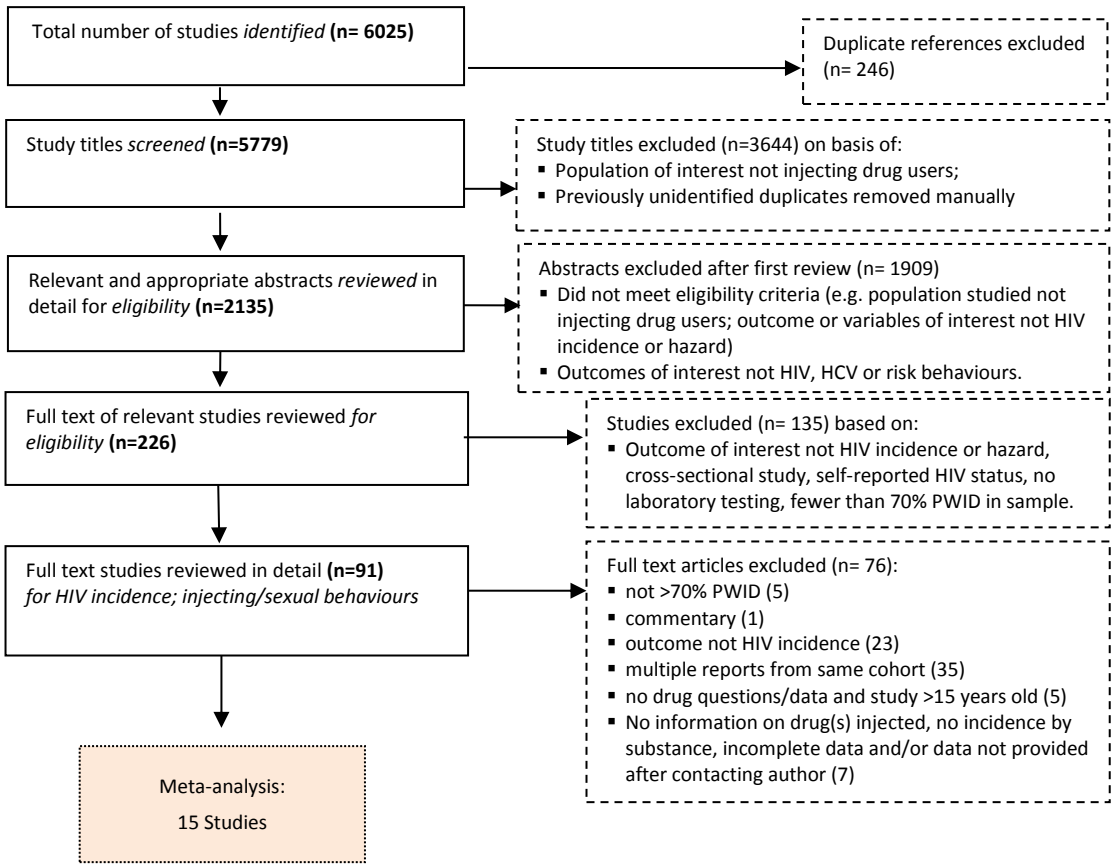


Figure 3.1: Flow of information and stages of the systematic review

Study population and characteristics

Out of these 15 HIV incidence studies among PWID, three were conducted in the United States, two in Canada, two in Europe, one in Russia, three in Thailand, three in China and one in India. Detailed study and PWID population characteristics, and effect estimates are summarised in Table 3.2. Fourteen studies were prospective cohorts recruited in community settings; one was retrospective. Study populations were predominantly male (88% of PWID across studies were male). Most study settings had some form of needle and syringe programme but only five studies reported on PWID contact with needle and syringe services which ranged from 10% to 90%, and opiate substitution treatment (11% to 55%). Thirteen studies reported crude HIV incidence rate ratios (cIRR) and only seven also provided adjusted IRR (aIRR). Five studies reported IRR estimates using those not injecting in the last 6 months as the reference group. Ten studies compared HIV incidence rates among PWID injecting their primary drug to the rate among those not injecting the specific drug, or in some cases injecting other drugs, which were often unspecified.

HIV incidence estimates across studies

A total of 1507 incident HIV infections were reported over 35,700 person-years of follow-up across studies. HIV incidence rates in each cohort varied between study settings and regions and are shown in Figure 3.2. The lowest HIV incidence rate among PWID was 1.7/100 person-years (95% CI: 1.6-1.8) in Amsterdam in 2005 while the highest incidence rates reported were 11.4/100 person-years (95% CI: 9.9-13.0) in Chiang Mai (Thailand) in 1997 and 8.8/100 person-years (95% CI: 6.4-12.0) in Xinjiang (China) in 2004. HIV prevalence among PWID ranged between 2.4% in Amsterdam (Netherlands) in 2005 and 45.4% in Yunnan (China) in 2008 (Figure 3.2).

The prevalence of needle and syringe-sharing was lowest among PWID in Amsterdam (14%) in 2005 and highest among PWID in St Petersburg (79%) in 2002 (Figure 3.3). The prevalence of multiple sex partners was lowest among PWID in Bangkok (11.1%) in 1996 and highest in Montreal (50.2%) in 2008, Vancouver (49.7%) in 2005 and St Petersburg (49.4%) in 2002.

HIV incidence also varied within each cohort. High incidence rates were reported among PWID who injected cocaine in North-America (1.4 to 7.2 per 100 person-years) and ATS in Russia (7.7/100 person-years). In the same cohorts, HIV incidence among heroin injectors was between 0.8/100 and 1.96/100 person years in North-America and 4.3/100 person-years in Russia, respectively. HIV incidence among ATS injectors was 9.5/100 person-years and 7.8/100 person-years in heroin injectors in Thailand in 1996. HIV incidence was consistently high in stimulant injectors in Canada, the United States and Russia.

Table 3.2: HIV Incidence and injecting drug use: summary of studies, outcomes and effects

Author, Year	**Cohort, Country**	**Study period**	**Sample, follow-up** *(p/y)*	**Primary drug injected** † *(exposure)*	**Outcome** *HIV IR, HIV IRR*	**Ser oco nv**	**Rate ratio reported** crude (95% CI) *(per 100 person-years)*	**Comparison group** *(reported)*	**Adjusted Rate ratio** *(95% CI)*	**Factors adjusted for**
Bruneau, 2011	St Luc cohort, Canada	2004 - 2008	N= 2137 4501 p/y	Cocaine, Heroin, Crack-cocaine	IR, HR, IRR, HR	148	HRR (Co) = 5.45 (3.4 -8.75) HRR (Her) = 0.48 (0.3-0.76) HRR (Cr-Co) = 1.3 (0.92-1.84)	Not injecting primary drug	aHRR (Co-mth) =3.77 (2.32-6.12) aHRR (Her-mth) = 0.69 (0.43-1.12)	Daily injecting, sharing, 'booting'‡, recruitment period
DeBeck, 2009	VIDU cohort, Canada	1996-2005	N= 1048 9601 p/y	Cocaine, Heroin, Crack-cocaine	HR	137	HRR (Coc daily) = 3.71 (2.62-5.26) HRR (Her daily) = 1.55 (1.10-2.20)	Not injecting (any drug)	aHRR (Co daily) =2.94 (2.00-4.33) aHRR (Her daily) = 1.05 (0.71-1.54)	Sex, age, ethnicity, duration drug use, crack smoking, unprotected sex
Strathdee, 2001	ALIVE cohort, USA Male Female	1988-1998	N= 1447 6842 p/y N= 427 1978 p/y	Cocaine, Heroin, Speedball	IRR, HR	213 64	HRRm (Co) = 3.02 (1.85-4.93) HRRm (Her) = 0.52 (0.19-1.46) HRRm (Co, Her, Sp) = 2.44 (1.71-3.48) HRRf (Co) = 4.05 (1.78-9.24)) HRRf (Her) = 0.00 (...) HRRf (Co, Her, Sp) = 2.4 (1.28-4.47)	Not injecting (any drug)	aRR (Co) = 1.57 (1.02-2.42) aRR (Inj >daily) = 2.36 (1.61-3.46)	Injection freq, att. shooting gallery, multi sex partners, age
Ouellet, 2000	COIP Chicago, USA	1994-1996	N=793 617 p/y	Cocaine, Heroin Speedball	IRR	7	IRR (Co) = 2.79 (0.44-17.66)	Not injecting primary drug	-	-
Friedman, 1995	5 cities (HIV > 21%), USA 10 cities (HIV < 8%), USA	1988-1991	N=1680 948 p/y N=5202 4226 p/y	Cocaine, Heroin, Speedball	IRR	52 27	RR (Co) = 2.40 (1.39-4.14) RR (> 2sex p) = 1.69 (0.78-3.65) RR (Co) =1.97 (0.86-4.49) RR (> 2sex p) = 0.85 (0.28-2.61)	Not injecting primary drug Not injecting primary drug	RR (NS re-use) = 5.41 (1.94-15.2) RR (Crk-Co) = 2.94 (1.33-6.53)	Sex, ethnicity, age, frequency of injecting, drug injecting sex partner, sharing needles/ syringes, city PWID sero-prevalence
Kall, 1990	Stockholm, Sweden	1987-1988	N= 1152	ATS, Heroin	IR	16	IR (ATS) = 0.9% (0-2.2%) IR (Her) = 3.6% (0-11%)	Not injecting primary drug	No adjusted measures provided	No adjustment for confounding
Van Den Berg, 2007	ACS cohort, Netherlands	1985-2005	N=710 5468 p/y	Cocaine, Heroin, Speedball, ATS, Methadone, Other	IRR	90	IRR (Co) = 4.76 (1.88-12.1) IRR (ATS) = 4.92 (1.54-15.7) IRR (Sp) = 8.97 (4.54-17.7) IRR (Her) = 5.96 (2.61-13.6)	Not injecting (any drug)	-	-
Kozlov, 2006	St Petersburg cohort, Russia	2002-2002	N= 520 443 p/y	Heroin, psycho - stimulants (ATS)	IRR, HR	20	HRR (ATS) = 3.00 (1.2-8.02) HRR (Her) = 0.44 (0.12-2.78) HRR (ATS&Her) = 2.34 (0.96-5.87)	Not injecting primary drug	HRR (ATS >3x/wk)=8.15(2.43-27.3) *Significant (P < 0.001)* HRR (ATS <3x/wk)= 1.98 (0.7-27.3)	Frequency of injecting, Sharing needle & syringe, Sex with casual partner

Author, Year	**Cohort, Country**	**Study period**	**Sample, follow-up** *(p/y)*	**Primary drug injected** † *(exposure)*	**Outcome** *HIV IR, HIV IRR*	**Ser oco nv**	**Rate ratio reported** crude (95% CI) *(per 100 person-years)*	**Comparison group** *(reported)*	**Adjusted Rate ratio** *(95% CI)*	**Factors adjusted for**
Martin, 2010	AIDSXAX B/E HIV, Thailand	1999-2003	N=2546 6796 p/y	Heroin, ATS, Midazolam	IRR, HR	211	HRR (Her)= 4.6 (3.1-6.9) HRR (ATS)= 2.9 (2.1-3.9) HRR (Mid) = 2.1 (1.5-2.9)	Not injecting (any drug)	aHRR (Her)= 3.0 (2.0-4.6) aHRR (ATS)= 1.7 (1.2-2.3) *Significant (P<0.001)* aHRR (Mid) = not significant	Daily inject, sharing needle & syringes, unprot sex, age, sex
Vanichseni, 2001	AIDSXAX B/E HIV, Thailand	1995-1996	N=1209 2310 p/y	Heroin, Stimulants (ATS), Tranquilisers	IRR, HR ('risk ratio' in study)	133	HRR (Her) = 0.8 (0.4-1.9) HRR (ATS) = 1.7 (0.9-3.1) RR (OpSed) = 0.7 (0.2-3.0)	Not injecting primary drug	aHRR (Her day)= 2.4 (1.4-3.9) aHRR (Her day+shar) = 3.2 (1.8-5.8) aHRR (Inj Incar) = 4.5 (2.6-7.8)	Inject freq, sharing needle & syringe, casual sex partner, arrest history
Jittiwutikarn, 2000	Chiang Mai, Thailand	1993-1997	N= 9774 1845 p/y	Heroin, 'Non-heroin'	IR, IRR	211	IRR (Her) = 17.12 (14.58-29.13) IRR (non-Her) = 3.81 (2.57-5.43)	Not injecting primary drug	No adjusted measures provided	No adjustments for confounding
Mehta, 2011	MIDACS, HPTN033, Chennai, India	2005-2009	N=855 76 p/y	Heroin, Heroin & Bupre-norphine	IR, IRR	5	IRR (Bp) = 1.46 (1.14-1.86) IRR (Her-Bp) = 0.72 (0.48- 1.01)	Not injecting primary drug	aHRR (Bp) *not significant* aHRR (non-inj) = 0.76 (0.64-0.90)	Adjusted for age, gender, education & marital status.
Zhang, 2006	HPTN033, Xinjiang, China	2002-2003	N= 508 475 p/y	Heroin, Heroin + tranquilisers	IR, IRR	42	IRR (Her) = 8.8 (6.4-12.0) IRR (Her+Tranq) = 11.2 (3.6-26.2) IRR (OpSed/Heroin) = 1.31 (0.5-3.45)	Not injecting primary drug	No adjusted measures provided	No apparent adjustments for confounding
Ruan, 2007	Xichang cohort, Sichuan, China	2002-2004	N=333 619 p/y	Heroin only	IR, IRR	14	IRR (Her) = 2.3 (1.1-3.5) Recalc HR w/not injecting as comparison group	Not injecting primary drug		Adjusted for sex, ethnicity, frequent injecting, sharing needles & syr., syphilis
Duan, 2009	Dehong cohort, Yunnan, China	2004-2008	N=540 1154 p/y	Heroin only	IR, IRR	47	IRR (Her) = 4.07 (2.4 - 6.2) HRR (Inj/not inject) = 3.14 (1.52- 6.51) HRR (Inj&Sh/not) = 5.64 (2.56 - 12.43)	Not injecting (any drug)	aHRR (Inj/noshar)= 2.27 (0.98-5.25) aHRR (Inj&Sh)= 5.27 (2.25 - 12.34)	Adjusted

Note Table 3.2. †Drug categories injected: (Co) Cocaine, (ATS) Amphetamine-Type-Stimulants, (Her) Heroin, (Sp) Speedball=heroin and cocaine co-injection (EMCDDA, 2009). Drug combinations injected were categorized into (OATS) opiate-stimulants (i.e. heroin with cocaine or heroin with ATS) and (OpSed) opiate-sedatives (i.e. heroin with benzodiazepines, methadone or other sedative). HIV=Human Immune Deficiency Virus. IR(R)=Incidence rate (ratio). HR(R)=Hazard rate (ratio). CI= Confidence Interval. p/y= persons/years. Other specific drug injected: Mid=Midazolam, Her+Tranq=heroin and tranquilisers, Bp=Buprenorphine. ‡Booting' and 'flushing' describe a practice in which the plunger is pulled back and the fluid (mostly blood, sometimes blood only) is re-injected [2, 243, 244].

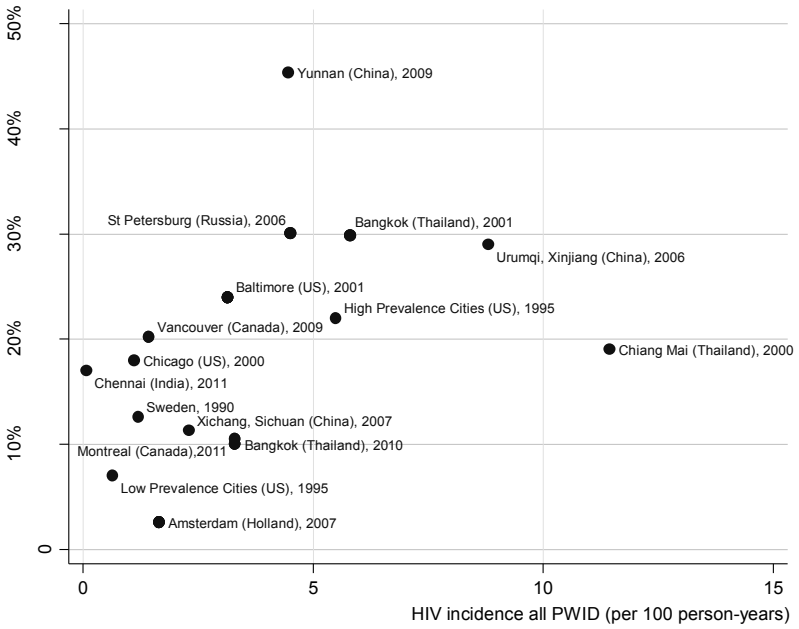


Figure 3.2: HIV prevalence and incidence among PWID by study setting

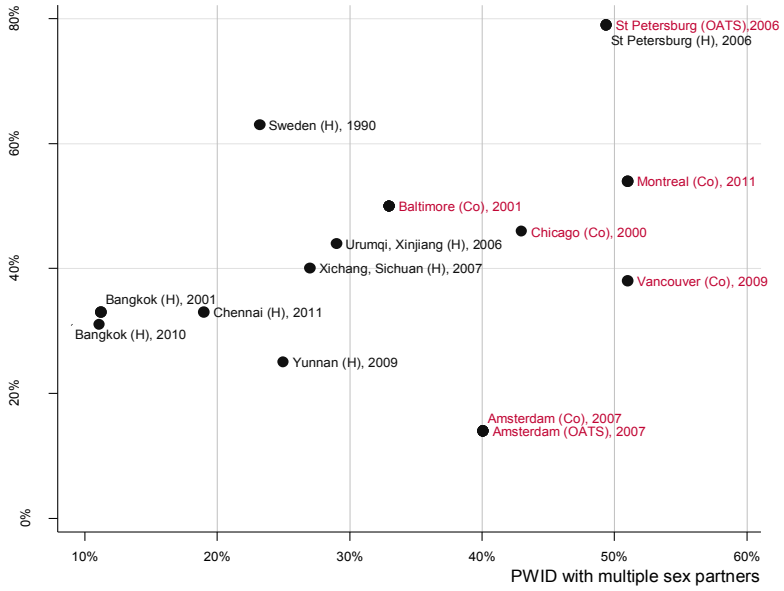


Figure 3.3: Behavioural characteristics among PWID by study setting

Note Fig 3.2. (Co) refers to the primary drug injected using drug categories in Table 1. (Co) = cocaine; (H) = heroin; (OATS) = opiates and stimulants combined.

3.3.1 Measures of increase in HIV acquisition risk between exposure to different drugs: HIV incidence rate ratio

Thirty-two HIV incidence rate estimates were categorised using the standard classification for psychoactive drugs [51, 52] (Figure 3.4). Eight studies reported HIV incidence in people injecting cocaine (North-America and Europe)[140, 222, 245-248], 11 in people injecting heroin (North-America, West Europe and Eastern Europe, and Asia)[140, 147, 193, 222, 227, 245-247, 249-254], 4 in ATS injectors (Europe, Eastern Europe and Asia)[147, 222, 227, 249, 250], 4 in opiates-stimulants injectors (North-America, West and Eastern Europe)[222, 247, 249] and 5 for people injecting opiates-sedatives (Europe and Asia)[193, 222, 227, 250, 254].

3.3.2 Main meta-analysis: HIV incidence rate ratios by drug category

The meta-analysis included estimates from 15 studies reporting crude HIV incidence rate ratios (IRR) for 5 drug injector categories. HIV IRR ranged from 0.44 to 8.97 and showed significant heterogeneity (I^2 = 78%; p≤0.001) (Figure 3.4 and Table 3.3).

Stratifying the estimates by primary drug injected considerably reduced heterogeneity for estimates in the cocaine, ATS and opiate-sedatives drug categories (Figure 3.5; Table 3.3). Pooled estimates by drug injected were 3.5 (95% CI: 2.8-4.4, I^2=14%) for cocaine injecting, and 2.7 for injecting ATS (95% CI: 1.9-3.7, I^2=19%) when studies compared to PWID either "not injecting in the past 6 months" or "not injecting their primary drug". People injecting opiates-sedatives had 2.1 (95% CI: 1.1-3.9, I^2=53%) times the (pooled) risk of HIV infection compared to "not injecting in the past 6 months" or "not injecting opiates-sedatives". For the opiates-stimulant injector category, stratifying by drug yielded a pooled estimate of 3.3 (95% CI: 1.8- 6.1, I^2=75%) compared to PWID either "not injecting in the past 6 months" or "not injecting opiates-stimulants" (Figure 3.5).

Variations across study estimates for heroin remained high after stratifying by main drug, with three estimates in the North-America and Eastern Europe regions reporting IRR<1 (I^2=92%) (Figure 3.4; Table 3.3). Differences in comparison groups used and region were explored in sub-group and univariate meta-regression analyses.

Table 3.3: Sub-group analysis; pooled study estimates stratified by selected covariates

Covariates examined in univariate meta-regression	Study estimates (n)	IRR Pooled estimate*† (95% CI)	Heterogeneity I^{2} **	Heterogeneity P-value	Variance explained† (adjusted R^2)
All study estimates *[140, 147, 193, 222, 227, 245-249, 251-254]*	32	2.61 (2.07-3.29)	78.3%	0.000	
By drug injected					5.37% (p= 0.10)
Amphetamine-Type Stimulants	4	2.67 (1.92- 3.70)	18.9%	0.307	
Cocaine	8	3.51 (2.79-4.40)	13.8%	0.322	
Opiates-Stimulants	4	3.30 (1.80- 6.07)	75.1%	0.007	
Opiates-Sedatives	5	2.09 (1.11-3.94)	52.5%	0.077	
Heroin	11	2.01 (1.17- 3.47)	91.8%	0.000	
By comparison group (n=32)					34.64% (p<0.001)
Not injecting	17	3.19 (2.55- 3.98)	64.5%	0.000	
Not injecting primary drug	11	2.92 (2.15-3.96)	49.6%	0.031	
Injecting other specific drug	4	0.50 (0.34-0.74)	0.0%	0.952	
By sharing syringes & needles (n=31)					13.1% (p= 0.03)
0 - 19%	5	6.66 (4.47-9.93)	0.0%	0.799	
20-39%	10	2.48 (1.87-3.29)	68.2%	0.001	
40-59%	10	1.91 (1.09-3.35)	86.8%	0.000	
60% and above	5	2.97 (1.75 - 5.03)	58.4%	0.047	
By sexual risk (≥ 2 partners) (n=29)					-3.4% (p=0.58)
≤ 10%	1	4.60 (3.08-6.86)	.%	-	
10.1 - 30%	10	2.32 (1.86-2.89)	18.7%	0.271	
30.1 - 45%	11	3.51 (2.35-5.23)	66.9%	0.001	
≥ 45%	7	1.85 (0.91-3.78)	92.5%	0.000	
By HIV Prevalence IDUs (n=32)					13.36% (p= 0.01)
0 - 9.99%	9	3.98 (2.78-5.69)	68.7%	0.000	
10-19.99%	7	2.46 (1.05- 5.79)	91.8%	0.000	
20-29.9%	8	2.35 (1.70- 3.24)	69.8%	0.000	
Above 30%	8	1.89 (1.32-2.70)	23.8%	0.001	
By drug prices‡ *(USD/ gr)* (n=32)					36.9% (p=0.004)
Drug price (< 0.90)	19	3.36 (2.67- 4.24)	62.5%	0.000	
Drug price (0.91-1.40)	4	2.45 (1.32-4.54)	52.7%	0.096	
Drug price (1.41-2.5)	4	2.65 (2.01-3.50)	0.0%	0.636	
Drug price (> 2.5)	5	1.16 (0.60-2.24)	85.3%	0.000	
By region (n=32)					-5.36% (p= 0.99)
North America	12	2.13 (1.40-3.23)	89.2%	0.000	
Europe (W)	6	5.85 (4.14-8.25)	0.0%	0.661	
Eastern Europe	3	1.76 (0.69-4.50)	54.4%	0.112	
Southeast Asia	11	2.57 (1.93-3.43)	63.1%	0.002	
Percent injecting > daily (n=28)					-3.6% (p=0.66)
0-39%	11	2.56 (1.98-3.32)	70.3%	0.000	
40-59%	1	2.79 (0.44-17.67)	.%	0.256	
60-79%	16	2.79 (1.73-4.49)	85.7%	0.000	
By duration PWID cohort (n=32)					4.34% (p= 0.06)
0- 5 years	18	2.55 (2.04-3.19)	51.3%	0.006	
5-19 years	9	2.08 (1.26 -3.44)	90.0%	0.000	
over 19 years	5	6.66 (4.47-9.93)	0.0%	0.799	

Table 3.3 (*) Pooled estimate corresponds to the risk of HIV infection, stratified by covariate. IRR= Incidence Rate Ratio. (†) Random-effects model. Fraction of variability across study estimates explained by each covariate, calculated on the ln scale (adjusted R2). (**) I-squared is the amount of heterogeneity remaining in each strata when stratifying by covariate. ‡ Source: UNODC World Drug Report

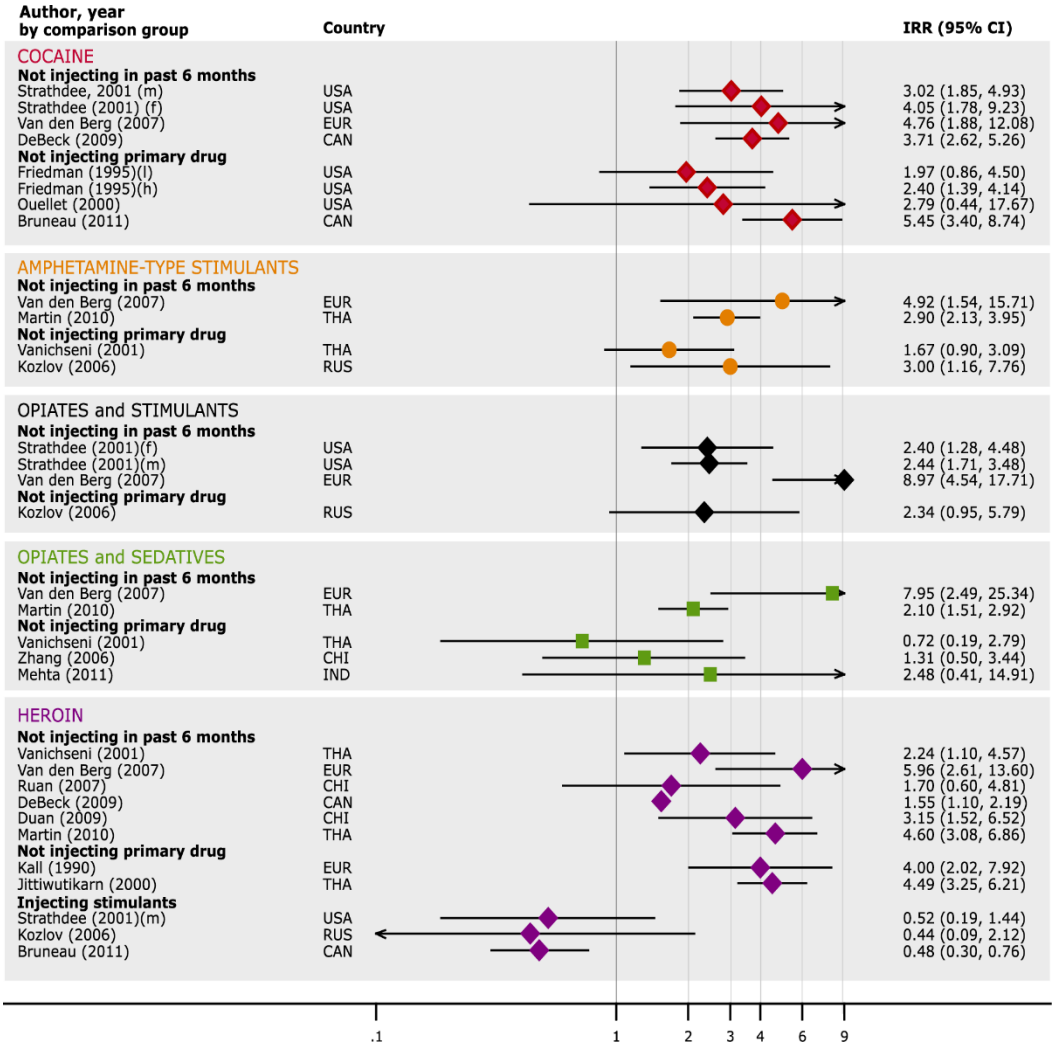


Figure 3.4: Crude study estimates of HIV risk by drug injected and comparison group.
The reference line at x= 1 corresponds to crude incidence rate ratios (IRR) where the risk of HIV acquisition is equal for both groups. USA: United States of America; CAN: Canada; EUR: Europe; RUS: Russian Federation; THA: Thailand; CHI: China; IND: India.

3.3.3 Variations in sub-group analysis

The primary drug injected and comparison group explained substantial heterogeneity for several drug categories (Figure 3.5). In sub-group analysis, the IRR of each specific type of drug injected was greater when the comparison group was "not injecting in the past 6 months" than it was when the reference group was "not injecting primary drug".

The pooled risk of HIV acquisition among PWID injecting cocaine was 3.6 (95% CI: 2.8-4.7, I^2=0%) times higher than for those not injecting in the past 6 months and 3.1 (95% CI: 1.7-5.5, I^2=58%) times higher than for those who did not inject cocaine (Figure 3.5). Similarly, HIV risk in ATS injectors was 3.0 (95% CI: 2.3-4.1, I^2=0%) times higher than for those not injecting in the past 6 months and 2.0 (95% CI: 1.2-3.4, I^2=3%) times compared to those not injecting ATS.

Compared to not injecting, opiate-stimulant injectors had 3.6 (95% CI: 1.7- 7.8, I^2=83%) times the risk of HIV acquisition; for opiate-sedatives injectors the risk was 3.6 (95% CI: 1.0- 13.1, I^2=79%) times higher but with wider confidence intervals. HIV seroconversion risk for drug users injecting opiates-sedatives compared to not injecting opiates-sedatives was lower (1.5, 95% CI: 0.65-3.54, I^2=0%) and may have been influenced by one study estimate IRR <1 which used a comparison group that effectively included heroin injectors (*Vanichseni, 2000* in Figure 3.4). Three study estimates for opiate-stimulants included injectors whose primary drug(s) were combinations of cocaine with heroin (speedball) and one ATS with heroin [222, 247, 249]. The considerable variance remaining in this category and small number of studies precluded further stratification and analysis (I^2=83%, p=0.003).

After stratifying estimates for heroin by comparison group, heroin injectors had 2.8 (95% CI: 1.7-4.7, I^2=77%) times the risk of HIV seroconversion compared to those not injecting in the past 6 months and 4.4 (95% CI: 3.3-5.9, I^2=0%) times the risk compared to those not injecting heroin (Figure 3.5). The higher pooled estimate of 4.4 resulted from two early retrospective cohorts where comparison groups were not clearly defined. Three studies reported primary heroin injecting compared to a reference "not injecting heroin" in settings where most injectors injected stimulants (i.e. cocaine, speedball or ATS) [140, 247, 249]. In this sub-group, the pooled estimate of increased risk of HIV for heroin injectors was 0.5 (95% CI: 0.3-0.7, I^2=0%); an apparent "protective" effect in relation to the risk associated with stimulant-injection in these settings.

Given the heterogeneity across estimates for heroin, the influence of several other factors was explored in sub-group analysis (Figure 3.6). Stratifying estimates for heroin injection by comparison group (p=0.02), region (p=0.06) and sharing (p=0.06) further reduced between-study heterogeneity. The pooled risk of HIV seroconversion from injecting heroin was high in Asia and Western Europe where heroin injectors had 3.5 (95% CI: 2.3-5.2; I^2=40%) times the risk of HIV acquisition, compared to those not recently injecting. In cohorts in North America and Eastern Europe where stimulants such as cocaine or ATS were widely injected, the pooled HIV risk from injecting heroin showed an inverse association compared to stimulant injectors (0.5; 95%CI: 0.3-0.7; I^2=0%). This suggested a higher risk of HIV infection among cocaine and ATS injectors, at least compared to heroin injectors in this region (Figure 3.6).

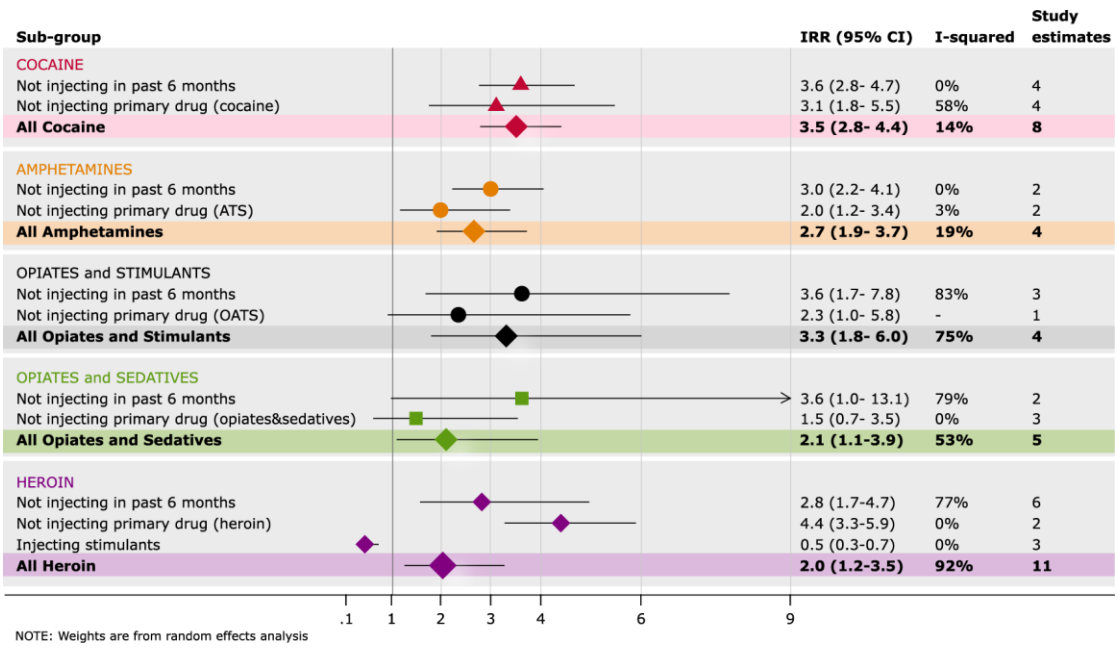


Figure 3.5: Sub-group analysis: pooled estimates of risk by drug injected and comparison group
The pooled estimate corresponds to the risk of HIV infection, stratified by drug and comparison group. The reference line at x = 1 corresponds to crude incidence rate ratios where the risk of HIV is equal for both groups. Random effects meta-analysis methods were used to calculate pooled estimates. Heterogeneity statistic used was I2, calculated on the ln scale.

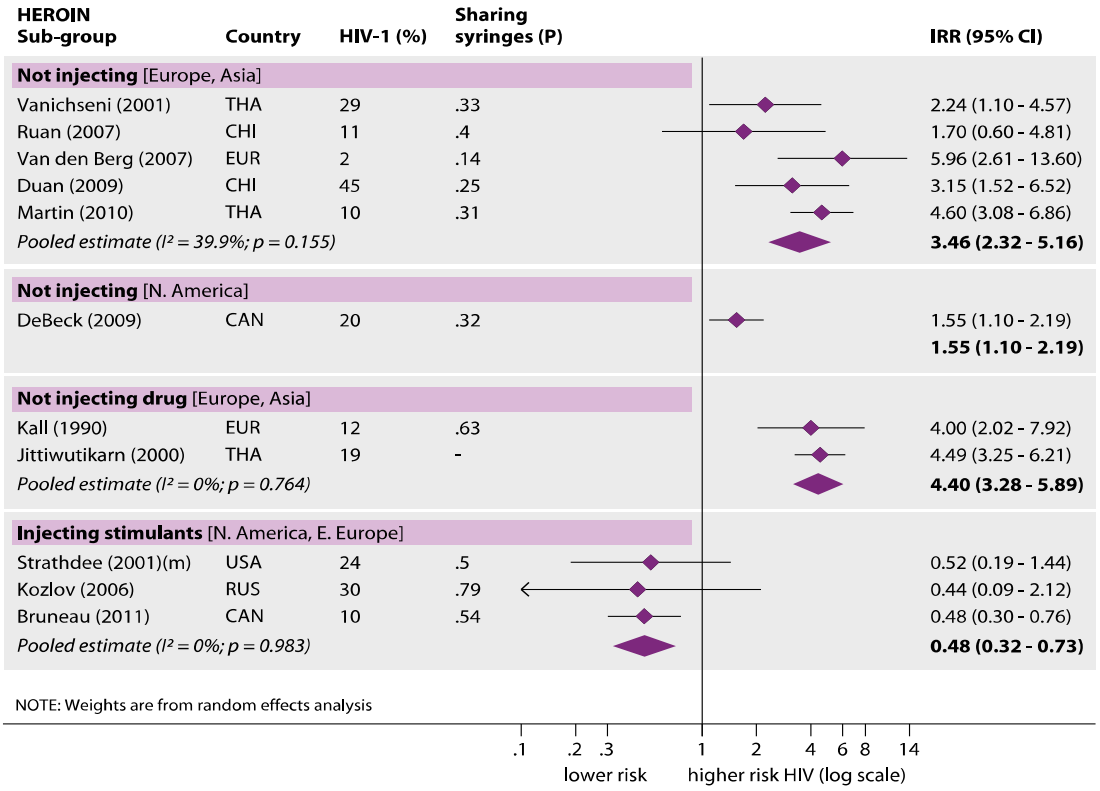


Figure 3.6: Pooled estimates of risk for heroin, stratified by comparison group and region.
The pooled estimate corresponds to the risk of HIV infection for heroin, stratified by comparison group and region. The I2 statistic was used to assess heterogeneity.

3.3.4 Results from univariate meta-regression analysis

In univariate meta-regression, a sizable proportion of variance between study estimates was explained by drug comparison group ($p \leq 0.001$), needle and syringe sharing ($p=0.03$), background HIV prevalence in PWID ($p=0.01$) and street price of the drug injected ($p=0.004$) and significance of "cohort duration" was marginal ($p=0.06$) (Table 3.3). Although geographical region did not account for substantial heterogeneity in univariate meta-regression across all study estimates, it accounted for heterogeneity among PWID injecting heroin ($p=0.05$). A higher risk of HIV seroconversion was associated with injecting cocaine or opiate-stimulants, with the comparison group 'not-injecting in the past 6 months' and with lower drug prices.

3.4 Discussion

This systematic review and meta-analysis aimed to assess HIV infection risk for different drugs across longitudinal HIV incidence studies among people injecting heroin, cocaine, ATS, opiates-stimulants or opiate-sedatives in different settings. Studies have suggested that the drug injected was associated with different risk practices, behaviours and interactions with social networks and settings, which mediate infection risk and lead to different levels of HIV-1 acquisition [90, 145, 146, 150, 152, 212]. This is the first systematic review to provide pooled estimates of the increase in HIV risk by drug use and to explore the sources of variability in detail across studies.

These findings suggest that the risk of HIV acquisition from injecting stimulants (cocaine and ATS) was consistently high across comparison groups, yielding a pooled risk of HIV infection 3.6 times that of PWID not recently injecting. Similarly high levels of injecting and sexual risk were also observed among cocaine injectors in North-America and amphetamines injectors in Eastern Europe, who were also in cohorts reporting the highest prevalence of multiple sex partners in Figure 3.3. PWID injecting opiates and stimulants (i.e. speedball) also had 3.6 times the risk of HIV acquisition compared to PWID not recently injecting.

However the magnitude of HIV infection risk associated with heroin injection differed markedly by context and comparison group. The risk of HIV acquisition among PWID injecting heroin was 2.8 times that of not recently injecting, 4.4 times that of not injecting heroin (and injecting other unspecified drugs) and 0.5 times that of injecting stimulants. Estimates of HIV risk among heroin injectors came from different regions and settings,

with different other drugs used and varied access to harm reduction and prevention services, which may have contributed to heterogeneity.

Heroin injectors in Asia and Europe had 3.5 times the risk of acquiring HIV compared to those who did not inject in the past 6 months but in cohorts where stimulants such as cocaine or ATS were widely injected, the risk of HIV acquisition among PWID injecting heroin showed an inverse association compared to stimulant injectors which suggests a higher risk of HIV infection in cocaine injectors.

My literature review in chapter 2 found some evidence that associations between cocaine or M/ATS stimulants and HIV risk were positive when i) stimulants were co-injected with an opiate such as heroin and when ii) they were compared to opiate injection alone. Similar differences in the drugs co-injected and comparison groups used may explain differences in these results among heroin injectors.

Several studies have also suggested that psychoactive substances influence PWID behaviours, physiology (especially neuroendocrine physiology) and immunity in different ways. Certain drugs have been associated with higher levels of unsafe injecting and sexual risk resulting in a greater chance of HIV acquisition and transmission [150, 212, 255]. Cocaine and ATS stimulate the central nervous system and result in increased energy and stamina, euphoria and decreased appetite [51, 75, 76]. Stimulants can also affect the immune function and increase susceptibility to infection [160]. Studies have found stimulant injectors to engage in more sexual risk and have higher HIV prevalence than those injecting opiates [75, 90, 92, 147, 150, 249]. Out of treatment stimulant injectors in particular have been found to have more sex partners and more frequent intercourse with casual partners and regular partners [90, 255].

Increased sexual risk, measured by proportions of PWID with multiple sex partners in our analysis, was found in cohorts reporting cocaine or M/ATS injection [140, 222, 245, 248, 249]. For example, in North-American and East-European cohorts, where the risk of HIV seroconversion from cocaine and ATS injection was greatest, a greater prevalence of sexual risk was reported [140, 222, 245, 248, 249]. In Asia where heroin is still mostly injected, PWID cohorts reported a lower prevalence of sexual risk [227, 250-254](Figure 3.3).

The choice of comparison group explained significant variance across estimates. IRR for cocaine, ATS, opiate-stimulants and opiate-sedatives were higher when compared to “not injecting in the past 6 months”. Lower ratios tended to be obtained when using “not

injecting primary drug" as reference and suggested that PWID in the comparison group were injecting other drugs.

Geographical region explained some heterogeneity among heroin injectors, suggesting differences in HIV risk between settings. Although needle and syringe- and opiate substitution programmes have been associated with lower injecting risk and HIV transmission, these programmes are more recent in Asia, where the prevalence of needle and syringe sharing among PWID remained high [41, 256]. While background HIV prevalence among PWID, mixing within PWID or other risk populations may also influence HIV risk, factors such as the price and availability of heroin and other drugs may also explain high behavioural risks observed in Asia [71, 193, 227, 257]. When heroin becomes more costly, lacks purity or is less available, PWID may switch drugs or mix heroin with other drugs which require more frequent injecting for a similar effect [12, 123]. Studies in North-America and Australia have found heroin injectors engaging in higher levels of injecting risks compared to injectors of other substances and reported greater frequency of syringe-sharing and risk of blood-borne infections [95, 149, 150].

Finally, some studies in the review reported combinations of drugs injected although none explicitly cited polydrug use. There was evidence that study reports of PWID cohorts where heroin and cocaine were injected engaged in more sexual risk and syringe-sharing [149, 152, 251, 254]. Cohorts where opiate-stimulants were injected reported higher proportions of injectors engaging in sexual risk behaviours (30-40%), consistent with findings from studies of PWID primarily injecting cocaine. All but one study reported IRR for stimulant and opiates-stimulants, suggesting a gradient with higher IRR for cocaine or ATS alone and lower IRR when the drug was combined with opiates.

This study has a number of limitations. All available study reports which reported HIV incidence and/or IRR data by drug injected were included, with no limitations on language but the number of PWID cohorts was limited. It is possible that research findings from well-resourced, established cohorts were more likely to be disseminated or published in full. The final set of studies was compared with other published reviews for completeness and satisfied me that available published data had been captured.

Consistency across samples was ensured by including only injectors but several factors may also have influenced HIV transmission. Levels of drug dependence lead to different risk behaviours and exposure to HIV but could not be factored in our analysis as most studies did not report scores from validated addiction severity scales (ASI). Access to harm reduction, especially clean needles and syringes and substitution treatment, could

also explain variations in incidence between cohorts resulting from reduced risk behaviours; however this could not be adjusted for as programme data was non-specific or unavailable for several cohorts [41, 42]. Crude HIV incidence rate ratios were used as several studies did not report adjusted estimates and while using rate ratios allowed within-cohort comparisons, confounding may have occurred. Additionally, the absence of effective treatment for cocaine and amphetamine injectors may also have contributed to higher HIV incidence in these populations.

Sero-converters were categorised into primary drug groups based on the previous 6-months follow-up. Research suggests that group characterisation of primary drug use over time offers reliable information about the use of heroin, cocaine or methamphetamines but switching between drug groups could have occurred during the 6 month follow-up [112]. The comparison group "not-injecting' included PWID reporting not to have injected in the previous 6 months but they may have smoked or snorted drugs. Similarly, recall bias among PWID omitting to report occasional injecting could have led to mis-classification, contributing to underestimating HIV risk.

Follow-up measures were fairly consistent across cohorts but sexual risk variables were limited and we used those consistent across samples. The limited data available and small number of studies precluded an analysis by gender.

3.5 Conclusions

HIV risk was consistently high among cocaine injectors and PWID injecting stimulants and opiates, for all comparison groups. Among heroin injectors, HIV infection risk was higher in Asia and Europe, and lower in America and Eastern Europe where stimulants were also widely injected. Several HIV epidemics among PWID have started with heroin, followed by other drugs and their associated risks, and rapid transmission has been attributed to low awareness of HIV and opportunities for efficient mixing [93, 102, 258].

The risk of HIV acquisition among people who inject appeared to vary by drug type but differences were not statistically significant and precluded a conclusive grading of risk. Compared to non-injectors, the risk of acquiring HIV was 3.6 (95%CI: 2.8-4.7, I^2=0%) times higher for cocaine injectors; it was 3.0 (95%CI: 2.2- 4.1, I^2=0%) and 3.5 (95%CI: 2.3- 5.2, I^2=40%) respectively, for ATS, and heroin injectors in Asia and Europe.

Though few studies accounted for polydrug use, cocaine and ATS injectors in these cohorts may have co-injected opiates with stimulants, drug combinations associated with both greater injecting and sexual risk behaviours than only injecting opiates in several

studies in chapter 2. Greater injecting and sexual risks in these poly-injectors, combined with the absence of treatment modalities for stimulants dependence may explain the consistently high risk of HIV acquisition and would warrant further study to unravel the role of polydrug use from that of individual drugs. Chapters 4 to 7 aim to address this gap in an analysis of two PWID samples where opiates and stimulants are injected.

Finally, more consistent definitions of drug and comparison groups, standardised reporting of sexual and injecting risk, and of exposure to interventions, would increase the comparability of epidemiological research in PWID and help elucidate differences in HIV risk between drugs. This has important implications on surveillance, prevention and treatment which, if confirmed, would need to tailor to behavioural risks, drug treatment and differential engagement in drug and HIV treatment associated with specific substances [75, 76, 143, 148, 234].

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Chapter 4

People who inject drugs in Kohtla-Järve in Estonia and St Petersburg in the Russian Federation: Study design and population characteristics

Chapter 4 People who inject drugs in Kohtla-Järve in Estonia and St Petersburg in the Russian Federation: study design and population characteristics

4.1 Background

The preceding chapters demonstrated that, while the risk of HIV infection from injecting drugs is well-established, the impact of drug use patterns including the type of drug injected and polydrug use on HIV and Hepatitis C (HCV) infection risk are not fully understood; this despite polydrug use practices being frequent among PWID [17, 68, 91, 213, 230, 231].

My literature review highlighted a real data gap on the potential amplified risks associated with polydrug use among people who inject drugs (PWID). The routes by which polydrug use practices may influence patterns of infection are (i) biological - through greater susceptibility to infection, where stimulants for example are known to modulate the immune response [160-162] and (ii) behavioural, through increased sexual risk taking, frequency of injecting and sharing of injection equipment [195, 210, 259]. Combining stimulants with highly addictive opiates for example could result in increasing biological and behavioural risks leading to HIV and HCV infection. The mix of addictive opiates, which require frequent and regular injecting with M/ATS, known to reduce inhibition, impair judgement and increase sexual drive and compulsivity may increase opportunities for sharing needles/syringes and unsafe sex, especially in group/social settings. M/ATS use has been associated with multiple sex partners and unprotected sex among PWID and other populations [5, 150, 155, 236, 260]. There is also evidence that M/ATS affect the immune response and promote viral replication, thus increasing the biological risk of HIV infection [160, 162]; although the effects of drug combinations and their interactions on the immune system are not fully understood. Thus a more thorough understanding of polydrug use and its influence on HIV and HCV risk could better guide prevention and treatment strategies.

In chapters 5 and 6, I will address some of these gaps by conducting a two-part analysis in two PWID populations where different drugs are injected and HIV prevalence is high: in Estonia (Kohtla-Järve) and in the Russian Federation (St Petersburg).

Chapter 5 examines whether primarily injecting amphetamine-type stimulants (ATS) is associated with specific injecting and sexual risk behaviours, by comparison of these behaviours among PWID injecting stimulants (ATS) and opioids (heroin, synthetic heroin or methadone) as their primary drug.

Chapter 6 builds on chapter 5 to examine whether polydrug use is associated with specific injecting and sexual risk behaviours compared to single drug use, by comparing (i) opiate poly-injectors vs. opiate only injectors, and (ii) stimulant poly-injectors vs. stimulants-only injectors. Investigating the effect of polydrug use stratified by primary drug may help to more clearly differentiate between the risks associated with a specific drug from those associated with using multiple drugs and to examine whether polydrug use varies by main drug injected.

Finally, the current chapter 4 lays the grounds for chapters 5 and 6. It presents (i) background information on each study setting and PWID sample, including data on drug and polydrug use to ensure their relevance to my research, (ii) a description of the survey design and details of the methods common to chapters 5 and 6, while relegating specific methodological details to the respective chapters, and (iii) it compares socio-demographic and drug use characteristics among PWID in St Petersburg and Kohtla-Järve.

4.1.1 Background information on the study settings

Kohtla-Järve and St Petersburg have epidemiologically comparable epidemics of drug use and HIV, are geographically close and have reported some of the highest HIV prevalence in any key population outside of sub-Saharan Africa [9, 22, 261, 262]. Drug use epidemics in Eastern Europe and Central Asia emerged at the end of 1990s as a result of several related factors. The disintegration of the former soviet union in the early 1990s opened up countries that were previously closed, to political, economic and social change, exposing weakening social welfare and education systems to multiple challenges, including unemployment, drugs and HIV [73, 263]. As Afghanistan became a key source of the global supply of heroin in the 1980s, several of these countries in economic and social transition found themselves on drug routes with many experiencing substantial HIV epidemics largely driven by drug use [40, 98, 264, 265]. Kohtla-Järve and St Petersburg are two cities situated on the northern part of two major heroin trafficking corridors linking Afghanistan to the heroin markets of the Russian Federation and Western Europe [9, 71].

The most recent estimate of numbers of people having ever injected drugs in St Petersburg was 83,118 in 2010 (95% CI: 77,320 - 88,920), equivalent to 5.5% of people aged 20-45 years old or 1.8% of the total population of the city [266]. The latest available estimates of PWID in Estonia was 13,801 in 2008 (min-max: 8,178-34,732) [22, 267, 268]. HIV sero-positivity among PWID was 53% in Tallinn, the capital of Estonia, and 54% in Kohtla-Järve, the fifth largest city in the country in 2009 [93, 269]. HIV

prevalence estimates among PWID in the Russian Federation ranged from 18.4% to 30.7% in 2013 and St Petersburg had among the highest prevalence in the Russian Federation with 59% of PWID sampled in 2012 testing positive for HIV [40, 264]. HIV transmission among PWID in the region is concerning; the few incidence studies available reported rates of 4.5 HIV infections/100 person-years among PWID in St Petersburg and 9/100 person-years among injectors who had been injecting for less than 3 years in Tallinn, Estonia in 2009 [249, 269, 270].

Opioids are still the main drug injected both in Russia and Estonia. Commercial heroin has gradually replaced traditional poppy straw mixture among injectors in urban areas and the majority of PWID now inject heroin or synthetic opioids (e.g. fentanyl, methadone) [178, 233, 264]. At the same time, Estonia reported one of the highest prevalence of ATS use in Europe, together with Denmark and the UK, and data suggest that ATS have become a major secondary drug among PWID in St Petersburg and Kohtla-Järve [9, 58, 233]. ATS is reported to be the most produced, trafficked and used synthetic stimulant in Europe whereas methamphetamine are more widespread in South East Asia [40, 271]. Nonetheless, despite increasing reports of its use and injecting, ATS risk has garnered less research attention until recently, compared to other drugs like heroin, cocaine or even cannabis.

4.1.2 Context of HIV interventions in Kohtla-Järve and St Petersburg

Despite similarities in drug use and HIV epidemics, structural differences in the social, legal, policy and cultural environments exist between St Petersburg and Kohtla-Järve. Estonia has been providing accessible low-threshold[8] HIV prevention and care for PWID for over 10 years, including harm reduction and opioid substitution treatment (OST). Between 2002 and 2013, the provision of clean needles and syringes through needle and syringe programmes (NSP) has expanded from 13 to 26 sites and reached an estimated 30% of PWID (range: 12%-51%) [33, 267]. Over-the-counter sterile syringes are also available in Estonian pharmacies without prescription [272]. Of an estimated 9,000 PWID in Estonia, 1,166 were reported to be on OST in 2013 [267].

By contrast, although HIV testing and treatment are provided by government health services in the Russian federation, needle and syringe programmes are not endorsed by the authorities and oral substitution therapy remains illegal despite being effective in reducing HIV, HCV, improving adherence to HIV treatment, and being on WHO's list of essential medicines [32, 41, 273]. Most drug treatment is therefore abstinence-based with

[8] services that place limited requirements on drug users to facilitate access and entry into care.

some psychological support and medication to manage withdrawal symptoms [33, 266]. NSP coverage is low in Russia and only 7% (min-max: 5%-9%) of PWID obtained needle and syringe from NSPs run by non-governmental organisations (NGO) with limited funding or political support [32]. Although sterile needles and syringes can be bought in pharmacies, PWID risk being arrested for carrying needles. Possessing syringes is not illegal in Russia (or Estonia) but PWID often face extrajudicial police arrests and a punitive legal environment. In Estonia, the possession or use of drugs for personal purposes is punishable by a fine or detention up to 30 days in a police arrest house, a provision applied rigorously by some police authorities [9, 274, 275]. Difficulties in access to clean needles and syringes and risk of arrest have shown to increase unsafe injecting and HIV risk, constituting major impediments to harm reduction [171, 207].

4.2 Methods used in chapters 5 and 6

4.2.1 Study population and data sources

The analyses in chapter 5 and 6 are based on integrated biological and behavioural surveys (IBBS) of HIV prevalence, conducted among PWID in Kohtla-Järve and St Petersburg, two cities situated close to the border between Estonia and the Russian Federation (Figure 4.1). PWID were recruited between May and July 2012 in Kohtla-Järve and from November 2012 to June 2013 in St Petersburg, using comparable recruitment criteria, sampling, survey methodology and questionnaire for which details of the methods have already been published [100, 276-278].

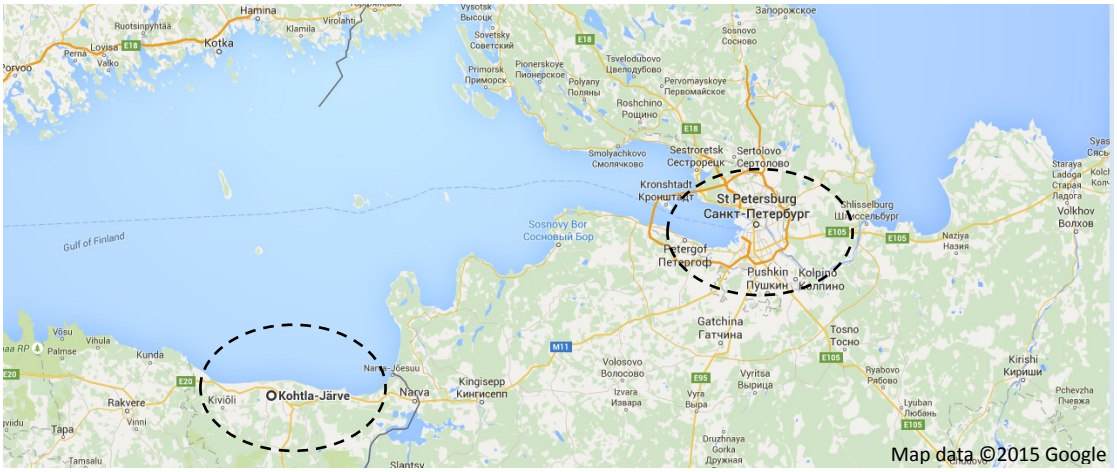


Figure 4.1: Study sites: Kohtla-Järve in Estonia and St Petersburg in the Russian Federation

In short, the surveys used respondent driven sampling (RDS), a variant of chain-referral sampling, to recruit a sample of 588 participants in Kohtla-Järve and 811 in St Petersburg [279]. Six seeds representing different PWID sub-groups in terms of gender, main drug

injected and HIV status, were selected through outreach programmes in Kohtla-Järve, and 16 seeds in St Petersburg. Each seed was tasked with recruiting 3 PWID from their personal networks, who on completing the survey then recruited a maximum of 3 new participants [278, 280, 281]. Recruitment was tapered once the HIV outcome converged to a sample equilibrium and the target sample size was reached [282]. The sample population included men and women aged 18 or over, "who had injected drugs in the past 30 days", lived in St Petersburg or Kohtla-Järve and had provided informed consent for the study. Participants' eligibility was checked through the presence of injection marks and if this was not possible, interviewers familiar with the process of injecting and able to discern appropriate responses, asked questions on injection practices before the start of the interview. PWID intoxicated at the time of the survey were asked to return for participation the following day or when sober. Information on social and demographics, injection and sexual risk behaviours, testing and access to harm reduction services was elicited in a structured confidential face-to-face interview using a questionnaire administered by trained fieldworkers. The study questionnaire for both sites included standardised items from established tools including the WHO Drug Injecting study Phase II survey (v2b) for risk behaviours [125, 278].

4.2.2 Relevant variables used in both analyses

In chapter 5, the dependant variable of interest (primary drug injected) was dichotomised into two mutually exclusive groups of primary amphetamine- (ATS) or primary opiate-injectors (heroin, fentanyl, non-prescription methadone) based on the survey item *main drug injected in the past 4 weeks* and established classification of psychoactive substance [51-53, 55] (Figure 4.2, Part I).

These primary drug categories were used consistently throughout my study of polydrug use. Non-injection substances such as marijuana, tobacco or alcohol were not eligible primary drugs in this classification. In chapter 6 (risk behaviour by polydrug use), the dependant variable polydrug use was defined as the "injection or use of another drug *in addition* to the main/primary drug injected regularly in the past 4 weeks" (Figure 4.2, Part II). Polydrug use was a binary variable which was defined for:

(i) Opiate injectors, and
(ii) amphetamine (ATS) injectors, respectively

The independent variables examined in this study were drawn from my conceptual framework described in chapter 2 and included key injecting and sexual risk behaviours

among PWID, HIV and HCV status as well as socio-demographic and contextual variables. The variables used are described briefly below and detailed in Table 4.1.

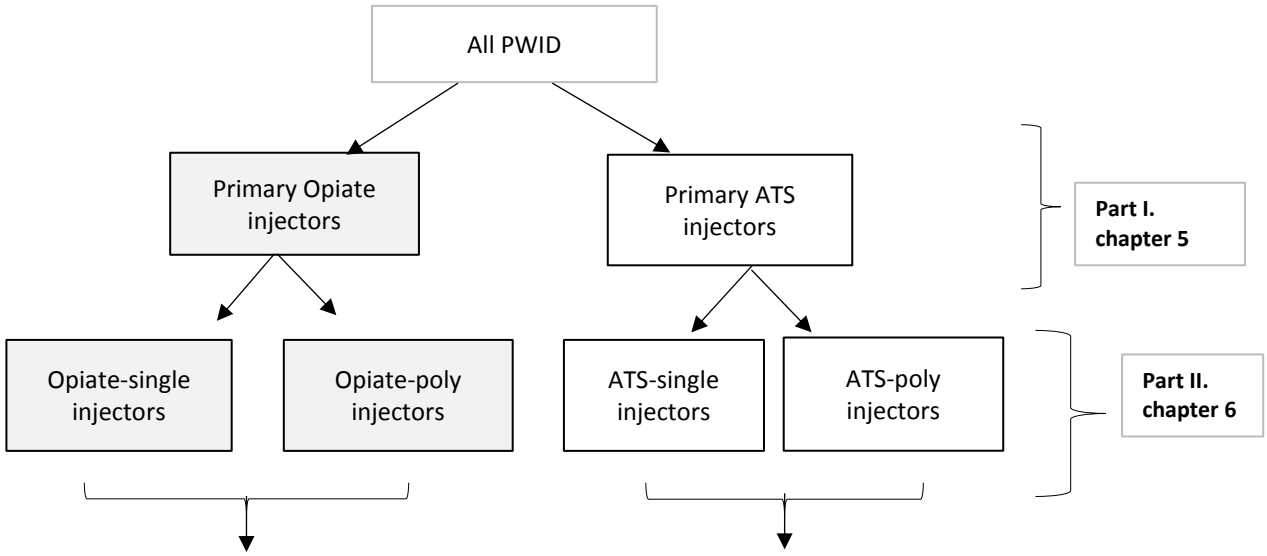


Figure 4.2: Outline of the two analyses conducted by primary drug, then by poly-injection in chapter 5 and 6, respectively.

The **social and demographic variables** examined were age, sex, ethnicity, education level, living arrangements and main source of income. Contextual and structural factors that have been associated with *reductions* in risky injecting behaviours and HIV infection in the literature were included in the analysis, including contact with needle and syringe services and drug substitution treatment [42, 44, 179]. Factors associated with increased levels of unsafe injecting among PWID also included having needles and syringes confiscated by the police and incarceration [170, 171, 208, 209, 283].

Injecting risk variables included past month injecting-related practices for which there is evidence of increased risk of HIV and HCV infection: frequency of injecting, times injected on the last day (a measure of intensity of injecting) and duration of injecting; receptive and distributive sharing of needles and syringes, sharing of drug paraphernalia and filling a syringe from a working syringe (front- or back-loading) [284].

Sexual risk variables for which there is evidence of elevated risk of HIV transmission, included past 6 month reports of: multiple sex partners; sex with regular partner; sex with regular partner who injected drugs; sex with casual partner; sex with casual partner who injected drugs; receiving money or drugs in exchange for sex; frequency of unprotected sex and frequency of condom use with casual partners. Categorical variables were generated for “multiple sex partners” and “unprotected sex”.

Table 4.1 Demographic, contextual and HIV risk variables from conceptual framework

Variables	Description based on survey questionnaire item	Chapter used in		
Social and demographic variables		**4**	**5**	**6**
Sex[1]	Respondent's sex at birth (1.male/2.female)	✓	✓	✓
Age group	Age at time of interview (1. <30 years or 2. ≥ 30 years)	✓	✓	✓
Ethnicity	Ethnicity (1.Russian, 2.Estonian, 3.other ethnicity)	✓	✓	✓
Education level	Completed 1. Basic or vocational, 2.secondary school (11th grade) or 3.higher/university education.	✓	✓	✓
Living arrangements	Stable vs unstable accommodation: 1.stable (living in own/partner's flat, house or communal apartment); 2.unstable (staying in dormitory, hostel room, shelter, no fixed address, with relatives).	✓	✓	✓
Main income source	Main source of funds: 1. regular/salaried; 2. irregular/dependant on others or 3. illicit (selling drugs, sex or theft).	✓	✓	✓
Service coverage and context variables				
Ever drug treatment	Ever received drug treatment to help modify drug use (Yes(Y)/No(N))	✓	✓	✓
Drug/substitution treatment	Received drug/substitution treatment in last 12 months (Y/N)	✓	✓	✓
Contact with NSP	Contact with needles and syringes services in last 4 weeks (Y/N)	✓	✓	✓
Needles/syringes source	Main source of needles/syringes (1.NSP; 2. pharmacy/chemist; 3.Other sources: friend, family, other PWID, drug dealer, street)	✓	✓	✓
Injection with clean needles/ syringes	Proportion of injections for which new needles/syringe were used (1. < 50%; 2. 51-99% or 3. 100%)	✓	✓	✓
Incarceration	Ever been in jail or prison (Y/N)	✓	✓	✓
Needles/syringes confiscated	Needles/injecting equipment confiscated by police in 6 months(Y/N)	✓	✓	✓
Injecting risk variables *(last 4 weeks unless specified)*				
Primary drug	Main drug injected in last 4 weeks (1.opiate, 2. ATS or 3. other drug)	✓	✓	✓
Duration of injecting	Time respondent has injected drugs (1.< 5 years or 2.≥ 5 years)	✓	✓	✓
Age at first injection	Mean age of respondent the first time they injected drugs (in years)	✓	✓	✓
Frequency of injecting	Times injected in last 4 weeks (1. ≥ daily or 2. < daily).	✓	✓	✓
Intensity of injecting	Times respondent injected on last day injected (1. once; 2. ≥ twice)	✓	✓	✓
Ever shared needles/syringes	Ever injected with needle/ syringe used by someone else (Y/N)	✓	✓	✓
Shared needles/syringes	Injected with needle/or syringe used by someone else (Y/N)	✓	✓	✓
Lent needles/syringes	Lent used needle/syringe to someone else (Y/N)	✓	✓	✓
Shared drug paraphernalia	Shared ≥ 1 of either cooker, container, filter, cotton or utensils (Y/N)	✓	✓	✓
Filled from working syringe	Filled syringe from a working syringe="back- or front-loaded" (Y/N)	✓	✓	✓
Any polydrug use	Injected or used ≥ 2 drugs including main injection drug (Y/N)	✓	✓	✓
Non-injection polydrug use	Used ≥ 1 other drug(s) in addition to main injection drug (Y/N)	-	-	✓
Poly-injection	Injected ≥ 1 other drug(s) in addition to main injection drug (Y/N)	-	-	✓
Other non-injected drug used	Number of other drugs used in addition to the main injection drug	-	-	✓
Other drugs injected	Number of other drugs injected in addition to main injection drug	-	-	✓
Sexual risk variables *(last 6 months unless specified)*				
Any sex in last 6 months	Had sexual intercourse in the 6 months preceding interview (Y/N)	✓	✓	✓
Regular sex partner	Had sex with regular sex partner (dichotomised into 1 or ≥ 2)	✓	✓	✓
Regular sex partner injects	Had regular sex partner who injected drugs (Y/N)	✓	✓	✓
Casual sex partners	Had sex with casual sex partner(s) (none/≥1)	✓	✓	✓
Casual sex partner injects	Had casual sex partners who injected drugs (none/≥1)	✓	✓	✓
Ever paid for sex	Ever received money, goods or drugs in exchange for sex (Y/N)	✓	✓	✓
Multiple sex partners [2]	Number of sex partners in past 6 months (1 or ≥2 sex partners)	✓	✓	✓
Condom regular sex partner	Used a condom with regular sex partner consistently (Y/N)	✓	✓	✓
Condom casual sex partner	Used a condom with casual sex partners consistently (Y/N)	✓	✓	✓
Unprotected sex *(4 weeks)*	Any sexual intercourse without condom in the last 4 weeks	✓	✓	✓
Serological markers				
HIV status	Test for HIV (positive or negative)	✓	✓	✓
HCV status	Test for HCV (reactive or non-reactive) (Kohtla-Järve only)	✓	✓	✓
HSV status	Test for HSV (positive or negative) (Kohtla-Järve only)	✓	✓	✓
Dependent variables	**Variable description**	**4**	**5**	**6**
Primary drug	Main drug injected in the last 4 weeks (Opiates or ATS)	-	✓	-
Polydrug use	Injected or used ≥ 2 drugs including main injection drug (Y/N)	-	-	✓

Table 4.1: NSP=Needle and Syringe Programme. ATS= Amphetamine-Type Stimulants; PWID= People Who Inject Drugs; HIV= Human Immune deficiency Virus; HCV= Hepatitis C; HSV= Herpes Virus Simplex. [1] The survey question was binary (male or female). [2]Composite variable for the total number of sexual partners generated from separate variables by type of sex partner.

The biological markers of interest were HIV, Hepatitis C (HCV) and Herpes Virus Simplex (HSV), which were binary variables describing PWID serological status; HCV and HSV were only available for Kohtla-Järve.

4.2.3 Statistical analysis

The statistical analyses were conducted in three main steps [285, 286]:

(i) chapter 4: descriptive analysis comparing demographic characteristics, access to services, injecting and sexual risk behaviours and HIV and HCV sero-prevalence among PWID in each city;

(ii) chapters 5 and 6: univariate data analysis, comparing demographic characteristics, access to services, injecting and sexual risk behaviours between relevant groups of PWID: (i) primary drug: primary ATS vs. primary opiate in chapter 5, (ii) polydrug use: opiate only vs. opiate poly-injectors, and ATS only vs. ATS poly-injectors in chapter 6 (Figure 4.2);

(iii) chapters 5 and 6: multivariate analysis, variables associated with the dependent variable in univariate analysis were included in multivariable models and confounding by demographic or contextual factors was adjusted for, separately for each city.

In univariate analysis, demographic and service coverage characteristics, drug use behaviours and HIV status were examined for each city to identify any relevant and important differences between samples (chapter 4). Demographic variables, drug use patterns (drug type and use of multiple drugs), risk behaviours and HCV and HIV status in the sample population were then explored by primary drug (in chapter 5) and by polydrug use (in chapter 6), and characteristics at least moderately associated with injecting a main drug or polydrug use were identified to investigate the influence of the main drug, and polydrug use, respectively [287, 288].

For categorical covariates, two-way contingency tables were used and categories combined in an appropriate way when required, giving consideration to cells with low numbers. Odds ratios with 95% confidence intervals and p-values were calculated using Pearson's chi-square test [286]. Throughout the analysis by primary drug in chapter 5, primary opiate injectors were used as the reference group. For the analysis of polydrug use in chapter 6, single drug injectors were used as the reference category, namely, i) primary single opiate injectors and ii) primary single ATS injectors.

For continuous variables, means and 95% CI were calculated and compared using t-tests. For non-normally distributed variables, medians and interquartile range were calculated and tested using the non-parametric Mann-Whitney U test (=Wilcoxon rank-sum)[286]. A complete case analysis was used and variables with non-response rates above 20% were excluded from the analysis, if this was the case for both cities.

The potential effects of clustering by recruitment seed was considered as it could lead to underestimating standard errors and overly narrow confidence intervals resulting in erroneous inferences [286]. Clusters were defined by a recruitment chain started by a given seed to account for the possibility that a participant may be more likely to recruit other PWID with similar characteristics. Robust variance estimation, using the Huber/White sandwich estimator (svy command in Stata 13.1) was used to take into account the survey design with standard errors clustered at the seed level [286, 289, 290].

The statistical analysis of the sample was conducted after examining key measures of recruitment effectiveness, recommended in the STROBE-RDS statement and summarised in Table 4.2 [279, 291-293]. Detailed results of these measures are provided in appendix 4. Recruitment homophily was defined as the ratio of the number of recruits with similar characteristic as their recruiter, to the number expected if there was no homophily on the characteristic [281, 282, 294]. A measure of homophily for HIV status close to +1 for example indicated little or no preferential recruitment on this characteristic and suggested that the recruitment was similar to what would have been expected by chance [281, 295].

Table 4.2: Key measures to report epidemiological studies using Respondent Driven Sampling

✓ Rationale for the use of RDS	✓ Formative research conducted
✓ Number of RDS seeds used	✓ Methods for seed selection
✓ Number of coupons per participant	✓ Coupon tracking method
✓ Recruitment homophily	✓ Recruitment trees
✓ Number of waves	✓ Convergence plots
✓ Personal network size question	✓ Population estimates (RDSI, RDS-II, Giles-SS)
✓ Estimator(s) used	✓ Data analysis software used

Note Table 4.2: Different RDS estimators have been developed to compensate for the non-random collection of data and in theory, produce unbiased population-based estimates for RDS data. RDS-I (Salganik-Heckathorn) uses network and recruitment characteristics which will differ for each variable (i.e. individual network size, referral patterns, number of cross-relation ties between subgroups of interest (homophily). RDS-II (Volz-Heckathorn) relies on sampling probabilities and incorporates network size (individual degree) to create sampling weights, but does not rely on cross-group relations (homophily). Giles SS (Giles' Successive Sampling) also addressed issues related to sampling without replacement in studies where the RDS sample constitutes a significant fraction of the estimated PWID population.

Unweighted sample proportions and means observed for key variables of interest were compared with three estimates: RDS-I (Salganick-Heckathorn), RDS-II (Volz-Heckathorn) and Giles Successive Sampling (GSS) weighted estimates (Table S4.3 and Table S4.4 in appendix 4)[296]. Observed proportions falling within the 95% CI of RDS-adjusted population estimates suggested that survey weighting was not required for the

sample to be representative of the population and unweighted estimates are presented (a comparison of weighted and unweighted estimates is included in appendix Table S4.3). RDS diagnostic measures and weighted estimates were generated using RDS package for R version 0.7-3 and RDS Analyst version 0.42 [295, 297].

Multivariate logistic regression analysis were run for different risk behaviours where the binary dependent variable was the primary drug injected in chapter 5, and polydrug use in chapter 6.

Models were adjusted for socio-demographic variables and available risk factor variables from the conceptual framework with p-value <0.15 in univariate analysis, including confounders recognised in the literature; they included age, sex, education, contact with a needle and syringe programme, drug or substitution treatment, injecting frequency, having needles or syringes confiscated by the police [42, 44, 170, 171, 179, 208, 209, 283]. Data were examined for outliers and points that may have a large influence or unexpectedly affect regression analyses and for collinearity between variables; collinear variables that were correlated and measuring similar things were omitted [285, 287, 288].

Finally, adjusted odds ratios (aOR) with 95% confidence intervals and p-values were calculated with an adjustment for possible clustering by seed, using the svy command as in univariate analysis [285, 289, 290]. RDS weights were not used in regression modelling as they were unlikely to affect effect size estimates (odds ratios) [298]. The adjusted odds ratios obtained were examined and the direction and significance of the association for variables of interest compared.

All univariate and multivariate logistic regression were conducted separately for each city after preliminary analyses for both cities combined were tested for interactions and revealed possible effect modification for several variables [285, 288, 299]. Separate analyses were therefore conducted to explore differences in the direction and scale of associations for each city separately.

In the next section, I describe key demographic characteristics of each PWID population, their access to services and contextual variables in Kohtla-Järve and St Petersburg.

4.3 Results: demographic and programme characteristics, risk behaviours and HIV status among PWID in Kohtla-Järve and St Petersburg

RDS sampling results among PWID in Kohtla-Järve and St Petersburg

Five hundred and eighty eight PWID were recruited in Kohtla-Järve from 6 diverse seeds over 11 waves with a median PWID network size of 15 (IQR: 9-20). In St Petersburg, a sample of 811 recruits was produced by 16 seeds in 12 waves with a median network size of 10 (IQR: 6-12). RDS measures and recruitment trees suggested differential recruitment in St Petersburg and some recruitment homophily in Kohtla-Järve. In St Petersburg, recruitment homophily for "polydrug use" and "HIV status" among participants were 1.10 and 0.99, respectively, close to what would be found by chance. The same measures in Kohtla-Järve, were 1.01 and 1.25 respectively, signifying a differential recruitment on polydrug use and slight oversampling of HIV positive respondents. The unweighted sample proportions for the main variables fell within 95% CI of RDS-adjusted population estimates, suggesting minimal bias, except for HIV status in Kohtla-Järve (key variables shown in Table 4.3; detailed results in appendix 4. Table S4.3 and S4.4). Unweighted statistics were therefore used in the risk factor analyses. Detailed RDS diagnostic results are presented by city in appendix 4. (Tables S4.1, S4.2 and Fig. S4.1 to S4.7). Twenty seven individuals not reporting a main drug in Kohtla-Järve were excluded from the analysis after comparison with the rest of the sample showed that socio-demographic and contextual characteristics did not differ (Table S5.1).

Table 4.3 Sensitivity analysis: unweighted and RDS-weighted estimates for key variables in each city

Variables	Unweighted (%, 95% CI)	RDS I estimator (%, 95% CI)	RDS II estimator (%, 95% CI)	Giles SS estimator (%, 95% CI)	n
Kohtla-Järve (n=591)					
Any polydrug use					
Yes	46.9% (44.2%-49.5%)	43.5% (38.8%-48.3%)	43.3% (36.7%-50.0%)	44.1% (39.4%-49.0%)	277
No	53.1% (50.5%-55.8%)	56.5% (51.7%-61.2%)	56.7% (50.0%-63.4%)	55.9% (51.0%-61.0%)	314
HIV status					
Positive	61.9% (56.4%-67.2%)	51.0% (45.7%-56.4%)	52.3% (45.5%-59.1%)	53.1% (47.2%-59.0%)	366
Negative	38.1% (32.8%-43.6%)	49.0% (43.6%-54.3%)	47.7% (40.9%-54.5%)	46.9% (41.2%-53.0%)	225
St Petersburg (n=811)					
Any polydrug use					
Yes	41.3% (35.0%-48.0%)	43.4% (39.1%-47.6%)	43.8% (39.3%-48.4%)	43.8% (40.6%-47.1%)	335
No	58.7% (52.1%-65.0%)	56.6% (52.4%-60.8%)	56.2% (51.6%-60.7%)	56.2% (52.9%-59.4%)	476
HIV status					
positive	55.7% (51.3%-60.1%)	54.6% (50.6%-58.6%)	54.6% (50.4%- 58.9%)	54.6% (51.6%-57.7%)	452
negative	44.3% (39.9%-48.7%)	45.4% (41.4%-49.4%	45.4% (41.1% -49.6%)	45.4% (42.3%-48.4%)	359

Table 4.3: Estimates were run on complete PWID sample in RDS Analyst using the recruiter id for Kohtla-Järve and the coupon method for St Petersburg. PWID population size estimates use were n=9,000 for Kohtla-Järve and n=83,118 for St Petersburg (only for Giles SS). RDS=Respondent-driven sampling. CI= Confidence Intervals. NSP=Needle/Syringe Programme. HIV= Human Immune deficiency Virus. RDS estimators were described in Methods, Table 4.2. The complete list of variables is included in appendix 4, table S4.3 for Kohtla-Järve and table S4.4 for St Petersburg.

Socio-demographic characteristics

A summary of socio-demographic and drug use characteristics is presented in Table 4.4a. for Kohtla-Järve and St Petersburg. The majority of participants were men (73.7% in Kohtla-Järve and 77.8% in St Petersburg), Russian-speaking (81.8% and 95.6%) and two thirds reported stable living conditions (59.7% and 64.0%) with no statistically significant difference between cities for any of these variables.

However, PWID in Kohtla-Järve were younger than in St Petersburg with nearly 50% of the sample in Kohtla-Järve under the age of 30 compared to nearly 30% in St Petersburg ($p<0.001$). A greater proportion of PWID in Kohtla-Järve had completed basic education or vocational training (80.2%) than in St Petersburg (58.6%, $p<0.001$) while the reverse was observed for higher education (0.5% in Kohtla-Järve and 11.5% in St Petersburg). More PWID reported being salaried or having a regular job in Kohtla-Järve (63.5%) than in St Petersburg (44.8%, $p<0.001$).

HIV prevention programmes and contextual factors

Over half of PWID reported ever receiving some form of drug treatment to modify their drug use (55.1% in Kohtla-Järve; 71.8% in St Petersburg, $p<0.001$); while 13.1% and 10.6% respectively had received substitution therapy in Kohtla-Järve and drug treatment in St Petersburg in the past 12 months ($p=0.158$)(Table 4.4b).

Significantly more PWID reported having been in contact with a needle and syringe programme in the past 6 months in Kohtla-Järve (81.7%) than in St Petersburg (15.6%, $p<0.001$), reflecting the expansion of harm reduction and needle and syringe services in Estonia. More PWID in Kohtla-Järve had ever been incarcerated (54.6%) or had needles and syringes confiscated by the police in the last 6 months (32.0%) than in St Petersburg (33.7%, $p=0.001$) and (26.1%, $p=0.020$), respectively.

Injecting risk behaviours

Over three quarters of PWID in both cities had injected for over 5 years. The mean age at first injection was just under 19 years in both cities ($p=0.188$)(Table 4.4c). Reported injection risk behaviour were lower in Kohtla-Järve than St Petersburg however polydrug use (use of multiple drugs) was equally widespread in both cities. Fewer PWID had injected daily or more in the last 4 weeks in Kohtla-Järve (23.7%) than in St Petersburg (35.5%, $p<0.001$). Similarly, unsafe sharing practices were almost 9 times less prevalent in Kohtla-Järve than in St Petersburg. Significantly fewer PWID reported sharing needles

and syringes (6.2% and 58.1%, p<0.001) or lending needles and syringes (14.6% and 54.4%, p<0.001) in the last 4 weeks in Kohtla-Järve than in St Petersburg. Likewise, fewer PWID reported back-loading (5.6% and 52.9%, p<0.001) or sharing drug paraphernalia (6.8% and 68.3%, p<0.001) in Kohtla-Järve than in St Petersburg.

Type of drugs injected and polydrug use

PWID in both cities reported injecting and using a range of psychoactive drugs. The main drugs injected in both cities were opiates (heroin and synthetic opioids, namely *fentanyl*[9] and *methadone*[10]) and amphetamine-type stimulants (ATS)[11] (Table 4.4c). Opiates were primarily injected by 65.0% PWID in Kohtla-Järve and 96.7% in St Petersburg; ATS were the main drug for 35.0% of PWID in Kohtla-Järve and 3.3% in St Petersburg (p=0.001).

Polydrug use (i.e. the use of other non-injected or injected psychoactive substances in addition to their primary injection drug) was reported by 44.5% PWID in Kohtla-Järve and 41.4% in St Petersburg (Table 4.4c). Several other drugs were injected and used by PWID in addition to their primary drug, the detailed description and characteristics of which are described in chapter 6.

Sexual risk behaviours

Over 75% of PWID in both cities reported having sexual intercourse in the last 6 months, more than half reported a regular sex partner who also injected drugs and close to 5% had ever been paid for sex (Table 4.4d). On the other hand, fewer PWID in Kohtla-Järve reported casual sex partner(s) who also injected drugs (46.3%) than in St Petersburg (64.4%, p<0.001) or multiple sex partners (34.1% and 48.8%, p<0.001). More PWID reported having a regular sex partner in Kohtla-Järve (99.7%) than in St Petersburg (61.2%, p<0.001). Similar proportions of PWID reported ever being paid for sex in both cities (6.4% in Kohtla-Järve and 4.4% in St Petersburg), the majority of whom were women. Almost half PWID in St Petersburg reported having unprotected sex in the past 4 weeks (46.3%) and at least 35.7% in Kohtla-Järve (p<0.001). However since the non-response rate for questions on unprotected sex (54.7%) and condom use with casual sex partner (69.1%) was high for Kohtla-Järve, the results for this city should be interpreted with caution (results were shown for completeness).

[9] Fentanyl is a synthetic opioid used to manage pain in surgery and cancer care (Table 1.2 in chapter 1).
[10] Methadone hydrochloride is a synthetic opioid used in the treatment of opiate dependency.
[11] The dominant stimulant drug injected was amphetamines, referred to subsequently as ATS.

Table 4.4: Demographic and contextual characteristics, risk behaviours and serological status among PWID in Kohtla-Järve and St Petersburg

a. Demographic characteristics	**Kohtla-Järve** (%)[(1)]	n=557	**St Petersburg**(%)[(1)]	n=811	**P-value**[(2)]
Sex [missing: n=2,n=0]					
Female	26.3%	146	22.2%	180	0.080
Male	73.7%	409	77.8%	631	
Age group [missing: n=0,n=0]					
< 30 years	50.3%	279	29.7%	241	<0.001
>= 30 years	49.8%	278	70.3%	570	
Ethnicity [missing: n=1,n=0]					
Estonian	10.8%	60	0.0%	0	
Other	7.4%	41	4.4%	36	<0.001
Russian	81.8%	455	95.6%	775	
Education [missing: n=0,n=0]					
Basic/vocational	80.2%	447	58.6%	475	<0.001
Secondary	19.4%	108	30.0%	243	
Higher	0.4%	2	11.5%	93	
Living arrangements [missing: n=1,n=0]					
Unstable	40.3%	224	36.0%	292	0.109
Stable	59.7%	332	64.0%	519	
Main income source [missing: [n=7,n=3]					
Non-regular/dependant	33.6%	186	38.6%	312	<0.001
Regular/salaried	63.5%	349	44.8%	362	
Irregular/illicit	2.7%	15	16.6%	134	
b. Service coverage and context variables					
Lifetime drug treatment [missing: n=0,n=0]					
Ever drug treatment	55.1%	307	71.8%	582	<0.001
Never in treatment	44.9%	250	28.2%	229	
Drug/Substitution treatment [missing: n=0,n=1]					
Yes *(12 months)*	13.1%	73	10.6%	86	0.158
No	86.9%	484	89.4%	724	
NSP programme *(4 weeks)* [missing: n=36,n=47]					
Contact with NSP	81.7%	426	15.6%	119	<0.001
no contact with NSP	18.2%	95	84.4%	645	
Needles/syringes source [missing: n=36,n=47]					
Other	5.0%	26	3.9%	30	<0.001
Pharmacist/chemist	13.2%	69	80.5%	615	
Needle Syringe programme	81.8%	426	15.6%	119	
Incarceration [missing: n=0,n=0]					
Ever in prison	54.6%	304	33.7%	274	<0.001
Never in prison	45.4%	253	66.2%	537	
Needles/syringes confiscated [missing: n=3,n=0]					
Yes	32.0%	177	26.1%	212	0.020
No	68.0%	377	73.9%	599	
c. Injecting risk behaviours *last 4 weeks unless specified*					
Primary drug injected [missing: n=0,n=2]					
Opiates (heroin/synthetic heroin)	65.0%	362	96.7%	784	<0.001
Amphetamine-type simulants (ATS)	35.0%	195	3.3%	27	
Duration of injecting [missing: n=0,n=0]					
≤ 5 years	12.8%	71	2.6%	21	<0.001
> 5 years	87.3%	486	97.4%	790	
Age at first injection *(mean, SD)* [missing: n=2,n=0]					
All	18.6 (3.7)	555	18.8 (3.3)	811	0.188
Male	18.4 (3.6)	409	18.7 (3.2)	631	0.187
Female	18.9 (4.1)	146	19.1 (3.8)	180	0.581
Frequency of injecting [missing: n=0,n=0]					
Daily or more	23.7%	132	35.5%	288	<0.001
Less than daily	76.3%	425	64.5%	523	
Injections per day [missing: n=0,n=2]					
Twice or more	45.1%	251	46.0%	372	0.737
Once a day	54.9%	306	54.0%	437	

c. Injecting risk behaviours *(continued)*	**Kohtla-Järve** (%)[1]	n=557	**St Petersburg**(%)[1]	n=811	**P-value**[2]
Ever shared needles/syringes [missing: n=2,n=0]					
Yes	64.7%	359	90.3%	732	<0.001
No	34.3%	196	9.7%	79	
Shared needles/syringes [missing: n=5,n=7]					
Yes	6.2%	34	58.1%	467	<0.001
No	93.8%	518	41.9%	337	
Lent used syringe to someone[missing: n=0,n=4]					
Yes	14.6%	82	54.4%	439	<0.001
No	85.4%	475	45.6%	368	
Filled from working syringe [missing: n=2, n=0]					
Yes	5.8%	32	52.9%	429	<0.001
No	94.2%	523	47.1%	382	
Shared drug paraphernalia [missing: n=0,n=0]					
Yes	6.3%	35	68.3%	554	<0.001
No	93.7%	522	31.7%	257	
Polydrug use [missing: n=0,n=0]					
Any polydrug use	44.5%	248	41.4%	335	0.237
Primary drug only	55.5%	309	58.6%	476	
d. Sexual risk behaviours					
Any sex in 6 months [missing: n=4,n=0]					
Yes	80.7%	446	76.8%	623	0.091
No	19.4%	107	23.2%	188	
Among PWID reporting sex in last 6 months					
Regular sex partner [missing: n=62,n=2]					
One or more	99.7%	383	61.2%	380	<0.001
None	0.3%	1	38.8%	241	
Casual sex partners [missing: n=308,n=0]					
One or more	100%	138	41.1%	256	<0.001
None	0%	0	58.9%	367	
Regular sex partner injects [missing: n=1,n=5]					
Yes	55.1%	210	57.6%	217	0.488
No	44.9%	172	42.4%	158	
Casual sex partner injects [missing: n=2,n=26]					
Yes	46.3%	63	64.4%	148	0.001
No	53.7%	73	35.6%	82	
Was ever paid for sex [missing: n=11,n=54]					
Yes	6.4%	28	4.4%	24	0.145
No	93.6%	407	95.7%	528	
Multiple sex partners [missing: n=38,n=6]					
One sex partner	65.9%	269	51.2%	316	<0.001
Multiple (>= 2)	34.1%	139	48.8%	301	
Condom with regular partner [missing: n=0, n=2]					
Yes *(consistent)*	23.4%	92	16.8%	64	0.021
Not consistent	76.6%	293	83.3%	318	
Condom with casual partner [missing: n=0, n=2]					
Yes *(consistent)*	58.1%	80	48.0%	122	0.051
No	41.9%	58	52.0%	132	
Unprotected sex (4 weeks) [missing: n=45,n=5]					
Yes *(had unprotected sex)*	35.7%	43	46.3%	331	<0.001
No *(always used condom)*	9.6%	114	53.5%	285	
Had sex but did not respond	54.7%	244	0.2%	2	
e. Serological markers					
HIV positive [missing: n=0,n=0]	62.7%	349	55.7%	452	0.011
HCV reactive [missing: n=0,n=0]	74.7%	416	not collected	-	-
HSV status [missing: n=0,n=0]	31.9%	173	not collected	-	-

Notes Table 4.4: (1) Column percentage. (2) Unadjusted p-value using Pearson's Chi-squared test for proportions, t-test for difference between means and non-parametric Mann-Whitney U test (=Wilcoxon rank-sum). SD= standard deviation. The annotation [missing: n=x, n=y] indicates the number of missing values for each variable, in Kohtla-Järve (x) and St Petersburg (y). Injecting risk measured in the last 4 weeks and sexual risk in last 6 months, unless specified. NSP=Needle and Syringe Programme. HIV= Human Immune deficiency Virus; HCV= Hepatitis C Virus. HSV=Herpes Simplex Virus.

Prevalence of HIV, HCV and HSV

Over half the PWID sample were positive for HIV in both cities and HIV prevalence was higher in Kohtla-Järve, at 62.7% (95%CI: 55.0%-69.7%) than in St Petersburg where prevalence was 55.7% (95%CI: 51.1%-60.2%; p=0.011)(Table 4.4e). Serological results for HCV and HSV were only available for Kohtla-Järve where 74.7% (95%CI: 67.3%-80.9%) of PWID were reactive for HCV and 31.9% (95%CI: 23.4%-41.7%) for HSV.

4.4 Discussion

This chapter described the study setting and context of drug use and HIV in Estonia and the Russian Federation, provided important background information and explored methodological issues to guide and validate the statistical analyses in chapters 4 to 6. My analysis summarised differences in the socio-demographic, contextual and drug use characteristics, HIV risk behaviours and status among PWID samples between cities (see summary in Box 1), the epidemiological findings of which will be discussed in chapters 5 and 6. These initial results allowed me to establish that the two surveys conducted among PWID in Kohtla-Järve (Estonia) and St Petersburg (Russian Federation), were particularly relevant to explore my research questions because of their large sample sizes, because both surveys were conducted recently, using similar sampling and data collection methods which facilitated comparisons across sites, and importantly, because of the high prevalence of polydrug use. In addition, the two main drug classes injected and polydrug use prevalence were similar but the range of additional drugs used seemed to vary across the two settings. This preliminary analysis also allowed to determine that the pre-requisites for RDS sampling were respected and to make informed decisions on the methods and use of unweighted results which did not differ sufficiently from RDS-weighted measures.

Having examined differences between the two PWID study samples and settings allowed me to investigate the effect of the primary drug and of polydrug use and to interpret their results with a better appreciation for each context.

Box 1: Summary of socio-demographic, contextual, drugs use characteristics and HIV risk behaviours among PWID samples

Socio-demographic and drug use characteristics of PWID were presented for Kohtla-Järve (n=557) and St Petersburg (n=811), two cities in which PWID primarily injected either ATS or opioids.

PWID were comparable in terms of gender and living arrangements but were younger in Kohtla-Järve and more frequently reported having a stable income compared to St Petersburg. There were important contextual differences in the proportion of PWID reporting recent contact with needle and syringe services and drug/substitution treatment, with wider access to harm reduction in Kohtla-Järve compared to St Petersburg, where opiate substitution remained illegal.

In Kohtla-Järve, where the majority of PWID had been in recent contact with needle and syringe services, unsafe injecting and sharing practices were up to 9 times less prevalent than in St Petersburg; a difference likely to have resulted from increased availability of needles and syringe services and drug treatment in the Estonian city. PWID in Kohtla-Järve injected less frequently, reported less sharing of needles and syringes, less sharing of drug paraphernalia and less injecting from prefilled syringes. The prevalence of polydrug use was similarly high in both cities, as was the frequency of sexual risk behaviours.

More than half the PWID in both cities tested positive for HIV. In Kohtla-Järve where PWID were also tested for HCV and HSV, three quarters were HCV reactive and a third were HSV positive.

Chapter 5

Comparison of HIV risk among primary amphetamine and primary opiate injectors in Kohtla-Järve and St Petersburg

Chapter 5 Comparison of HIV risk among primary amphetamine and primary opiate injectors in Estonia and Russia

5.1 Background

Chapter 2 found that associations between stimulant injection and injecting risk behaviours (i.e. frequent injecting and sharing of injection equipment) or HIV prevalence seemed to differ depending on whether PWID identified stimulants as a main (or primary) drug and whether they co-used other drugs [17, 143, 157, 212, 234]. The meta-analysis in chapter 3 also found that the risk of HIV acquisition among PWID injecting cocaine or meth/amphetamine stimulants (M/ATS) was consistently higher compared to those who had not recently injected cocaine, but not significantly different from that among PWID injecting opiates compared to not injecting opiates in samples where stimulants were less common [140, 142, 235]. Stimulant injection was found to be associated with more sexual risk behaviours compared to not injecting stimulants and cohorts where stimulants were injected also reported higher levels of sexual risk in chapter 3. However, both reviews identified important data gaps that may explain some of the divergent results in different studies, including insufficient clarity in drug definitions (i.e. whether the drug under study was considered primary drug or not) and in the reference groups used in drug comparisons, and incomplete reporting of other drugs co-used or co-injected (polydrug use).

HIV prevalence was often higher among cocaine and M/ATS injectors when they were compared to PWID not injecting stimulants and possibly injecting other drugs [127, 140, 300]. Similarly, studies of PWID injecting stimulants with heroin (opiate-stimulant) found that co-injectors had higher levels of injecting and sexual risk (needle and syringe sharing, filling syringe from used syringe, and multiple sex partners) compared to PWID who did not inject stimulants [101, 131, 212]. Most studies found that M/ATS injection (compared to not injecting M/ATS) was associated with multiple sex partners and unprotected sex [92, 101, 152, 236]. By contrast, HIV prevalence was often lower in young, self-identified primary cocaine- or M/ATS-injectors compared to heroin injectors, in settings where stimulants were more recent and NSP services less established [130, 131].

There was also evidence that cocaine and M/ATS may increase the biological risk of HIV infection by modulating the host's immune response to infection (i.e. cocaine), promoting viral replication (i.e. M/ATS) or both, thus increasing the biological susceptibility to HIV [160, 162, 165]. Using multiple drugs has also been linked with greater risk of injury,

overdose and drug-induced deaths and may be associated with HIV infection [2, 9, 93, 232, 233]. Thus the risks associated with injecting M/ATS remain unclear [1, 58, 68, 72].

Finally, most of the available evidence on stimulant injection and HIV risk came from American and west European studies and may not apply to more recent drug use and HIV epidemics such as those in Eastern Europe and Asia. This chapter therefore examined whether injecting amphetamines (ATS) was associated with HIV-related injecting or sexual risk behaviours, compared to injecting opiates. To answer this question, injecting and sexual risk behaviours were compared in two PWID populations injecting opioids or amphetamine-type stimulants (ATS) as their primary drug, in Estonia and in the Russian Federation.

The specific objectives of this chapter were to 1) identify differences in demographic characteristics, risk behaviours and HIV status by drug injected and 2) to determine if these patterns differed between the two cities, which both share and differ in certain contextual and epidemiological characteristics.

5.2 Methods

Details of the surveys and methods of analysis were presented in chapter 5. Briefly, this section examines whether HIV-related injecting and sexual risk behaviours are greater among PWID injecting ATS stimulants compared to those injecting opiate/opioids drugs (heroin, synthetic heroin or methadone) as their primary drug. Here, the dependant variable used was the primary drug injected, dichotomised into mutually exclusive groups of primary ATS or primary opiate injectors based on the survey item *main drug injected in the past 4 weeks* in Table 4.1. These primary drug categories were used consistently throughout the chapter, always using opiate injectors as the reference group. Results are presented independently for Kohtla-Järve and then St Petersburg following the plan of analysis described in section 4.2.

5.3 Results

5.3.1 Kohtla-Järve: comparison of primary amphetamine and opiate injectors

Socio-demographic characteristics by primary drug

Results of univariate and multivariate comparisons between primary opiate and ATS injectors are presented for each city separately in Table 5.1a to Table 5.1e. In Kohtla-Järve, ATS injectors were statistically significantly younger (< 30 years old) than opiate injectors and this association remained significant after adjusting for other factors

(aOR=2.1; 95%CI: 1.4-3.2). More women primarily injected ATS (29.7%) than opiates (24.4%) but the difference was not statistically significant (p=0.126). PWID did not differ in terms of ethnicity, education, main source of income or living arrangements by primary drug injected.

HIV programmes and contextual factors

Primary ATS injectors had lower odds of being in contact with harm reduction services including, ever receiving treatment to modify their drug use (aOR=0.3; 95%CI: 0.2-0.5) and receiving drug treatment in the last 12 months (aOR=0.5; 95%CI: 0.3-0.9) compared to opiate injectors; these differences remained significant after adjusting for demographic factors (Table 5.1b). Similarly, ATS injectors also had lower odds of having been in contact with a needle and syringe programme (NSP) in the preceding 4 weeks compared to opiate-injectors (aOR=0.3; 95%CI: 0.2-0.6). Consistent with this finding, primary ATS injectors had greater odds of obtaining clean needles and syringes from a pharmacy or chemist, than from a NSP (aOR=4.9; 95%CI: 3.5-6.9). There were no significant differences in the proportion of ATS and opiate injectors having access to clean needles and syringes for all injections. In terms of contact with law enforcement, ATS-injectors reported lower odds of having needles and syringes confiscated by the police in the last 6 months (aOR=0.3; 95%CI: 0.1-0.8) or ever being incarcerated (aOR=0.3; 95%CI: 0.1-0.8) compared to opiate injectors (Table 5.1b).

Injecting risk behaviours

In univariate analysis, primary ATS-injection was associated with several injecting behaviours; associations which remained significant in multivariate regression. Primary ATS injectors started injecting at a mean age of 19.7 years (SD:3.2), significantly later than opiate injectors (mean: 17.9 years, SD: 4.4) and were more likely to have injected for less than 5 years (aOR=3.3; 95% CI: 1.8-6.1) (Table 5.1d). ATS injectors had lower odds of injecting daily or more (aOR=0.3; 95%CI: 0.1-0.6) and of reporting ever sharing needles and syringes (aOR= 0.4; 95%CI: 0.2-0.6) after adjusting for age, sex, needle and syringe programme, drug treatment, having needles and syringes confiscated and injecting frequency. Any past month polydrug use was also more frequent in primary ATS (57.4%) than opiate injectors (37.6%, p=0.012). Both *non-injected polydrug use* (using other drug(s) in addition to the main drug injected) (aOR=1.9; 95%CI: 1.5-2.4) and *poly-injecting* (injecting other drug(s) than the main drug injected) were positively associated with primary ATS injection in Kohtla-Järve (aOR=1.8; 95%CI: 1.1-3.2).

Risky injecting practices such as past month sharing of needles and syringes, lending needles and syringes, filling from a working syringe (back-loading) and sharing of drug paraphernalia were generally low in Kohtla-Järve and did not differ between the two primary drug groups.

Sexual risk behaviours

The prevalence of multiple sex partners in the previous 6 months was high but did not differ significantly between primary ATS (31.4%) and -opiate (35.6%) injectors. In multivariate analysis however, ATS injectors had greater odds of reporting ever being paid for sex (aOR=2.4; 95%CI: 1.1- 5.2) than opiate injectors. The two drug groups did not differ on other sexual risk variables (Table 5.1e).

HIV prevalence, Hepatitis C and HSV

Consistent with the younger age, shorter duration of injecting and fewer injecting risk behaviours in this group, primary ATS injectors in Kohtla-Järve had lower odds of testing positive for HIV (aOR=0.6; 95%CI: 0.4-0.9) and being reactive to Hepatitis C (aOR=0.5; 95%CI: 0.4-0.6) compared to primary opiate injectors in multivariate analysis. No significant difference was found in HSV prevalence between the two drug groups (Table 5.1c).

Table 5.1a Univariate and multivariate association between socio-demographic characteristics and primary drug injected in Kohtla-Järve (n=557) and St Petersburg (n=811)

a. Demographics	**Kohtla-Järve - Primary ATS** compared to opiate injectors								**St Petersburg - Primary ATS** compared to opiate injectors							
by primary drug injected	**ATS** (%)	**n** 195	**Opiates** *(1) (ref)*	**n** 362	**Odds ratio** *(95% CI)*	**P-value** *(2)*	**aOR**[3] *(95%CI)*	**P-value**	**ATS**	**n** 27	**Opiates** *(1) (ref)*	**n** 784	**Odds ratio** *(95%CI)*	**P-value** *(2)*	**aOR** [3] *(95%CI)*	**P-value**
Sex																
Female	29.7%	58	24.4%	88	1.3 (0.9-1.9)	0.126	1.3 (0.9-1.6)	0.136	48.2%	13	21.3%	167	3.4 (1.0-11.5)	0.046*	1.8 (0.7- 4.9)	0.227
Male	70.3%	137	75.6%	272	*ref*		*ref*		51.9%	14	78.7%	617	*ref*		*ref*	
Age group																
< 30 years	61.5%	120	43.9%	159	2.0 (1.3-3.3)	0.013*	2.1 (1.4-3.2)	0.001*	74.1%	20	28.2%	221	7.3 (2.6-20.3)	0.001*	5.3 (2.5-11.3)	<0.001*
>= 30 years	38.5%	75	56.1%	203	*ref*		*ref*		25.9%	7	71.9%	563	*ref*			
Ethnicity																
Estonian	12.3%	24	10.0%	36	1.2 (0.8-1.9)	0.300	-	-	-	-	-	-	-	-	-	-
Other	5.1%	10	8.6%	31	0.6 (0.2-1.8)	0.276	-	-	3.7%	1	4.5%	35	0.8 (0.1-9.2)	0.867	-	-
Russian	82.6%	161	81.4%	294	*ref*				96.3%	26	95.5%	749	*ref.*			
Education level																
Basic/vocational	81.0%	158	79.8%	289	1.1 (0.6-1.8)	0.736	**-**	**-**	29.6%	8	59.7%	467	0.3 (0.05-1.7)	0.154	2.8 (1.2-6.7)	0.023*
Secondary	19.0%	37	20.2%	73	*ref*				51.9%	14	29.3%	229	1.1 (0.4-3.2)	0.924	2.5 (0.7-9.6)	0.160
Higher *(StP only)*	-	-	-	-	-	-	-	-	18.5%	5	11.0%	86	*ref*			
Living arrangements																
Unstable	39.5%	77	40.7%	147	0.9 (0.6-1.4)	0.757	-	-	51.9%	14	35.5%	278	2.0 (0.9-4.1)	0.069	1.9 (0.9-4.0)	0.074
Stable	60.5%	118	59.3%	214	*ref*				48.2%	13	64.5%	506	*ref*		*ref*	
Main income source																
irregular/illicit*(StP only)*	-	-	-	-	-	-	-	-	3.7%	1	17.1%	133	0.2 (0.02-1.6)	0.111	-	-
non-regular/dependant	38.5%	74	35.5%	127	1.1 (0.8 -1.6)	0.476	**-**	**-**	37.0%	10	38.7%	301	0.7 (0.4-1.5)	0.338	-	-
regular/salaried	61.5%	118	64.5%	231	*ref.*				59.3%	16	44.2%	344	*ref*			

Table 5.1a. (1) Column percentage (2) Unadjusted p-value using Pearson's Chi-squared test for proportions (or Fisher's exact when cells<4), t-test to test difference between means and non-parametric Mann-Whitney U test (=Wilcoxon rank-sum); (3) Reference group was "primary opiate injectors". (4) Odds ratio adjusted for age, sex, education (and unstable living arrangements in St Petersburg). CI: Confidence Intervals. ATS= Amphetamine-Type Stimulants. StP= St Petersburg. * P-value ≤0.05.

Table 5.1b. Univariate and multivariate association between contextual variables, serological markers and primary drug in Kohtla-Järve (n=557) and St Petersburg (n=811)

b. Service coverage	**Kohtla-Järve - Primary stimulant-** compared to opiate injectors								**St Petersburg - Primary stimulant-** compared to opiate injectors							
by primary drug injected	**ATS** (%) [(1)]	**n** 195	**Opiates** [(1)]	**n** 362	**Odds ratio** *(95%CI)*	[(2)] **P-value**	**aOR**[(3)] *(95%CI)*	**P-value**	**ATS** (%)[(1)]	**n** 27	**Opiates** *(ref)* [(1)]	**n** 784	**Odds ratio** *(95%CI)*	[(2)] **P-value**	**aOR** *(95%CI)*	[(3)] **P-value**
Lifetime drug treatment																
Ever drug treatment	32.8%	64	67.1%	243	0.2 (0.2-0.3)	<0.001*	0.3 (0.2-0.5)	<0.001*	25.9%	7	73.3%	575	0.2 (0.1-0.6)	0.005*	0.2 (0.1-0.5)	0.002*
Never in treatment	67.2%	131	32.9%	119	*ref*		*ref*		74.1%	20	26.7%	209	*ref*		*ref*	
Drug/substitution treatment																
Yes *(12 months)*	6.7%	13	16.6%	60	0.4 (0.2-0.7)	0.003*	0.5 (0.3-0.9)	0.035*	14.8%	4	10.6%	83	1.5 (0.4-5.8)	0.568	-	-
No	93.3%	182	83.4%	302	*ref.*		*ref*		85.2%	23	89.4%	701	*ref*		-	-
NSP programme *(4 weeks)*																
Contact with NSP	66.7%	124	90.2%	302	0.2 (0.1-0.3)	<0.001*	0.2 (0.2-0.6)	<0.001*	3.7%	1	16.0%	118	0.2 (0.05-1.0)	0.052	0.4 (0.1-2.2)	0.260
No contact with NSP	33.3%	62	9.9%	33	*ref*		*ref*		96.3%	26	84.0%	619	*ref*		*ref*	
Injections w/clean needles																
<50%	6.1%	8	4.8%	12	1.2 (0.7-2.3)	0.522	1.1 (0.8-1.5)	0.498	6.3%	1	9.5%	67	0.3 (0.03-2.9)	0.291	-	-
50-99%	9.9%	13	10.3%	26	0.8 (0.6-1.3)	0.419	1.5 (0.8-2.9)	0.169	6.3%	1	18.0%	127	0.2 (0.02-2.0)	0.095	-	-
100%	84.0%	110	84.9%	214	*ref*		*ref*		87.5%	14	72.5%	511	*ref*			
Clean needles/syringes																
Other	66.7%	124	90.2%	302	2.4 (0.7-9.9)	0.169	2.0 (0.5-7.9)	0.291	40.7%	11	2.6%	19	67 (8.1-544)	0.001*	35 (2.7-472)	0.009*
Pharmacist/chemist	26.3%	49	6.0%	20	6.0 (4.1-8.6)	<0.001*	4.9 (3.5-6.9)	<0.001*	55.6%	15	81.4%	601	2.9 (0.6-14.2)	0.174	1.8 (0.3-9.3)	0.478
Needle/syringe programme	7.0%	13	3.9%	13	*ref*		*ref*		3.7%	1	16.0%	118	*ref*			
Incarceration																
Ever in prison	30.3%	59	67.7%	245	0.2 (0.1-0.3)	<0.001*	0.3 (0.2-0.5)	<0.001*	7.4%	2	34.7%	272	0.2 (0.1-0.3)	<0.001*	0.2 (0.1-0.8)	0.025*
Never in prison	69.7%	136	32.3%	117	*ref*		*ref*		92.6%	25	65.3%	512	*ref*		*ref*	
Needles/syringes (N/S) confiscated																
Had N/S confiscated	15.9%	31	40.7%	146	0.3 (0.1-0.9)	0.040	0.3 (0.1-0.8)	0.006*	0.0%	0	27.0%	212	-		-	-
No N/S confiscated	84.1%	164	59.3%	213	*ref*		*ref*		100.0%	27	73.0%	572				
c. Serological markers																
HIV status																
Positive	49.2%	96	69.9%	253	0.4 (0.3-0.6)	<0.001*	0.7 (0.5-0.9)	0.032*	22.2%	6	56.9%	446	0.2 (0.1-0.4)	<0.001*	0.4 (0.2-0.7)	0.008*
Negative	50.8%	99	30.1%	109	*ref*		*ref*		77.8%	21	43.1%	338	*ref*		*ref*	
Hepatitis C																
HCV reactive	60.0%	117	82.2%	299	0.3 (0.2-0.4)	<0.001*	0.5 (0.4-0.6)	<0.001*	not collected		-	-	-	-	-	-
Non-reactive	40.0%	78	17.4%	63	*ref.*		*ref*		-	-	-	-	-	-	-	-
HSV status																
Positive	31.2%	59	32.2%	114	1.0 (0.6-1.5)	0.846	**1.0** (0.6-1.6)	0.855	not collected		-	-	-	-	-	-
Negative	68.8%	130	67.8%	240	*ref.*		*ref*		-	-	-	-	-	-	-	-

Table 5.1b and c: (1) Column percentage. (2) Unadjusted Pearson's Chi-squared test for proportions p-value; t-test for difference between means; non-parametric Mann-Whitney U test (=Wilcoxon rank-sum). (3) Odds Ratio adjusted for age, sex, NSP, drug treatment and in St Petersburg, unstable living arrangements. aOR (HIV, HCV) adjusted age, sex, needle/syringe programme, drug treatment, needles/syringes confiscated, injecting frequency (and living arrangements in St Petersburg). CI: Confidence Intervals. ATS= Amphetamine-Type Stimulants; NSP= Needle and Syringe Programme; HIV= Human Immune deficiency Virus; HCV= Hepatitis C; HSV= Herpes Virus Simplex. StP= St Petersburg. * P-value ≤0.05.

Table 5.1d. Univariate and multivariate association between injecting risk and primary drug injected in Kohtla-Järve (n=557) and St Petersburg (n=811)

d. Injecting risk	**Kohtla-Järve - Primary stimulant-** compared to opiate injectors								**St Petersburg - Primary stimulant-** compared to opiate injectors							
by primary drug injected [4]	**ATS** (%)	**n** 195	**Opiates** *(ref)*	**n** 362	**OR**[3] *(95%CI)*	[2]P-value	**aOR** [3] *(95%CI)*	P-value	**ATS** (%)	**n** 27	**Opiates** *(ref)*	**n** 784	**OR** [3] *(95%CI)*	[2] P-value	**aOR** [3] *(95%CI)*	[3]P-value
Duration of injecting																
≤ 5 years	26.2%	51	5.5%	20	6.1 (3.8-9.6)	<0.001*	3.3 (1.8-6.1)	<0.001*	22.2%	6	1.9%	15	14.7 (4.2-51)	<0.001*	4.0 (1.5-10.5)	0.007*
> 5 years	73.9%	144	94.5%	342	*ref.*		*ref*		77.8%	21	98.1%	769	*ref.*		*ref*	
Age at first injection																
(mean, SD)	19.7 (3.2)	195	17.9 (4.4)	362	1.1 (1.1-1.2)	<0.001*	1.1 (1.1-1.2)	0.001*	20.7 (4.1)	27	18.8 (3.3)	784	1.1 (1.0-1.3)	0.031*	1.1 (1.1-1.4)	0.036*
Frequency of injecting																
Daily or more	9.7%	19	31.2%	113	0.2 (0.1-0.5)	<0.001*	0.3 (0.1-0.6)	0.002*	11.1%	3	36.4%	285	0.2 (0.1-1.0)	0.044*	0.2 (0.1-0.7)	0.020*
Less than daily	90.3%	176	68.8%	249	*ref.*		*ref.*		88.9%	24	63.7%	499	*ref.*		*ref.*	
Injections last day injected																
Twice or more	42.1%	82	46.69	169	0.8 (0.6-1.1)	0.244	1.3 (0.9-1.7)	0.195	14.8%	4	47.1%	368	0.2 (0.1-0.6)	0.006*	0.4 (0.2-1.0)	0.055
Once	58.0%	113	53.3%	193	*ref.*		*ref.*		85.2%	23	52.9%	414	*ref.*		*ref.*	
Ever shared needles/syringes																
Yes	40.0%	78	78.1%	281	0.2 (0.1-0.3)	<0.001*	0.4 (0.2-0.6)	<0.001*	37.0%	10	92.1%	722	0.05 (0.03-0.1)	<0.001*	0.1 (0.1-0.3)	<0.001*
No	60.0%	117	21.9%	79	*ref.*		*ref.*		63.0%	17	7.9%	62	*ref.*		*ref.*	
Injected w/used needles/syringes																
Yes	3.6%	7	7.5%	27	0.5 (0.1-1.6)	0.169	0.6 (0.1-2.7)	0.404	14.8%	4	59.6%	463	0.1 (0.05-0.3)	<0.001*	0.3 (0.1-0.8)	0.028*
No	96.4%	186	92.5%	332	*ref.*		*ref.*		85.2%	23	40.4%	314	*ref.*		*ref.*	
Gave used syringe to someone else																
Yes	10.3%	20	16.7%	60	0.6 (0.2-1.5)	0.230	0.8 (0.3-2.0)	0.610	7.4%	2	56.0%	437	0.1 (0.03-0.2)	<0.001*	0.2 (0.1-0.4)	0.001*
No	89.7%	175	83.3%	300	*ref.*		*ref.*		92.6%	25	43.9%	343	*ref.*		*ref.*	
Filled from working syringe																
Yes	3.6%	7	6.9%	25	0.5 (0.2-1.2)	0.104	0.6 (0.2-1.5)	0.226	11.1%	3	54.3%	426	0.1 (0.1-0.3)	<0.001*	0.3 (0.1-0.8)	0.027*
No	96.4%	188	93.1%	335	*ref.*		*ref.*		88.9%	24	45.7%	358	*ref.*		*ref.*	
Shared drug paraphernalia																
Yes	4.1%	8	7.5%	27	0.5 (0.2-1.3)	0.151	0.7 (0.3-1.4)	0.257	29.6%	8	69.6%	546	0.2 (0.1-0.3)	<0.001*	0.4 (0.2-0.8)	0.017*
No	95.9%	187	92.5%	335	*ref.*		*ref.*		70.4%	19	30.5%	238	*ref.*		*ref.*	
Any polydrug use																
Yes *(≥ 2 drugs)*	57.4%	112	37.6%	136	2.2 (1.4-3.4)	0.001*	1.9 (1.2-3.0)	0.012*	33.3%	9	41.7%	326	0.7 (0.4-1.2)	0.392	0.9 (0.4-1.9)	0.783
No *(main drug only)*	42.6%	83	62.4%	226	*ref.*		*ref.*		66.7%	18	58.3%	458	*ref.*		*ref.*	
Polydrug use *(≥ 2 drugs used)*																
Yes	51.8%	101	32.3%	117	2.2 (1.7-3.0)	<0.001*	1.9 (1.5-2.4)	<0.001*	11.1%	3	6.7%	53	1.7 (0.3-9.8)	0.522	4.6 (1.1-21.3)	0.049*
No	48.2%	94	67.7%	245	*ref.*		*ref.*		88.9%	24	93.3%	731	*ref.*		*ref.*	
Poly-injection *(≥ 2 drugs injected)*																
Yes	21.5%	42	13.0%	47	1.8 (1.0-3.3)	0.043*	1.8 (1.1-3.2)	0.030*	25.9%	7	40.0%	314	0.5 (0.3-0.8)	0.004*	0.6 (0.4-1.1)	0.090
No	78.5%	153	87.0%	315	*ref.*		*ref.*		74.1%	20	60.0%	470	*ref.*		*ref.*	

Notes table 5.1d: (1) Column percentage (2) Unadjusted p-value using Pearson's Chi-squared test for proportions (Fisher's exact when cells<4), t-test to test difference between means and non-parametric Mann-Whitney U test (=Wilcoxon rank-sum). (3) Odds ratios (OR) adjusted for age, sex, needle/syringe programme, drug treatment, needles/syringes confiscated, injecting frequency (and living arrangements in St Petersburg). (4) Injecting risk in the last 4 weeks, unless specified. CI: Confidence Intervals. SD= Standard Deviation. ATS= Amphetamine-Type Stimulants. * P-value ≤0.05.

Table 5.1e Univariate and multivariate association between sexual risk and primary drug injected in Kohtla-Järve (n=557) and St Petersburg (n=811)

e. Sexual risk	**Kohtla-Järve -Primary stimulant-** compared to opiate injectors								**St Petersburg -Primary stimulant-** compared to opiate injectors							
by primary drug injected [4]	**ATS** (%)	**n**	**Opiates**	**n**	**Odds ratio**	[2] P-value	**aOR** [3]	P-value	**ATS** (%)	**n**	**Opiates**	**n**	**Odds ratio**	[2] **p-value**	**aOR** [3]	P-value
		195	*(ref)*	362	*(95%CI)*		*(95%CI)*			27	*(ref)*	784	*(95%CI)*		*(95%CI)*	
Any sex in 6 months																
Yes	86.2%	168	77.7%	278	1.8 (1.0-3.3)	0.059	1.5 (0.6-3.4)	0.376	85.2%	23	76.5%	600	1.8 (0.8-3.9)	0.152	1.7 (0.7- 4.3)	0.208
No	13.9%	27	22.4%	80	*ref.*		*ref*		14.8%	4	23.6%	184	*ref.*		*ref*	
Regular sex partners																
one or more	100%	138	100%	246	-	0.454	-	-	65.2%	15	61.0%	365	1.2 (0.6-2.4)	0.593	1.1 (0.5-2.3)	0.834
None	0%	0	0%	1	-		-	-	34.8%	8	39.0%	233	*ref.*		*ref*	
Casual sex partners																
one or more	100%	51	100%	87	-	-	-	-	43.5%	10	41.0%	246	1.1 (0.5-2.4)	0.783	1.2 (0.7-1.9)	0.560
None	0%	0	0%	0	-	-	-	-	56.5%	13	59.0%	354	*ref.*		*ref*	
Regular sex partner injects																
Yes	49.3%	68	58.3%	144	0.7 (0.4-1.1)	0.130	0.9 (0.5-1.7)	0.750	53.3%	8	57.7%	209	0.8 (0.2-3.3)	0.789	0.9 (0.2- 3.1)	0.802
No	50.7%	70	41.7%	103	*ref.*		*ref*		46.7%	7	42.3%	153	*ref.*		*ref*	
Casual sex partner injects																
Yes	48%	24	45%	39	1.1 (0.8-1.5)	0.430	1.9 (0.6-5.7)	0.260	50.0%	5	65.0%	143	0.5 (0. 1-2.6)	0.420	0.8 (0.2-4.0)	0.760
No	52%	26	55%	47	*ref.*		*ref*		50.0%	5	35.0%	77	*ref.*		*ref*	
Was ever paid for sex																
Yes	7.3%	12	5.9%	16	1.3 (0.9-1.8)	0.225	2.4 (1.1-5.2)	0.025*	30.0%	6	3.4%	18	12.2 (3.7-40)	<0.001*	2.3 (0.4-27)	0.366
No	92.7%	152	94.1%	255	*ref.*		*ref*		70.0%	14	96.6%	514	*ref.*		*ref*	
Condom with regular partner																
Yes (consistent)	23.2%	32	24.2%	60	0.9 (0.7-1.4)	0.760	1.0 (0.7-1.4)	0.930	26.7%	4	16.4%	60	1.9 (0.4-4.6)	0.231	1.3 (0.4-3.7)	0.659
No	76.8%	106	75.8%	188	*ref.*		*ref*		73.3%	11	83.7%	307	*ref*		*ref*	
Condom with casual partner																
Yes (consistent)	62.8%	32	55.2%	48	1.4 (0.6-3.0)	0.409	1.4 (0.7-2.7)	0.358	90.0%	9	46.3%	113	10.4 (1.9-57)	0.009*	3.4 (0.4-31)	0.257
No	37.3%	19	44.8%	39	*ref.*		*ref*		10.0%	1	53.7%	131	*ref*		*ref*	
Multiple sex partners																
>= 2 sex partners	31.4%	48	35.6%	91	0.8 (0.4-1.6)	0.567	0.8 (0.4-1.5)	0.463	47.8%	11	48.8%	290	0.9 (0.5-1.8)	0.898	0.7 (0.4-1.4)	0.329
one sex partner	68.6%	105	64.5%	165	*ref*		*ref*		52.2%	12	51.2%	304	*ref*		*ref*	
Unprotected vaginal sex *(4 wks)*																
Yes	8.9%	15	10.1%	28	0.7 (0.4-1.5)	0.371	0.8 (0.4-1.6)	0.541	45.4%	10	54.0%	320	0.8 (0.4-1.7)	0.494	0.8 (0.3-2.3)	0.694
No	28.6%	48	23.7%	66	*ref*		*ref*		54.6%	12	46.0%	273	*ref*		*ref*	
Had sex, no answer [5]	*62.5%*	*105*	*66.2%*	*184*	-	-	-	-	-	-	-	-	-	-	-	-

Notes Table 5.1e: (1) Column percentage (2) Unadjusted p-value using Pearson's Chi-squared test for proportions (or Fisher's exact when cells<4), t-test to test difference between means and Mann-Whitney U test (=Wilcoxon rank-sum) for non-parametric data (medians). (3) Odds ratios (OR) adjusted for age, sex, contact with needle/syringe programme, drug treatment (and living arrangements in St Petersburg). (4) Last 6 months sexual risk behaviours, unless specified. (5) Figures shown for completeness despite high non-response rate in Kohtla-Järve. CI: Confidence Intervals. ATS= Amphetamine-Type Stimulants. * P-value ≤0.05.

5.3.2 St Petersburg: comparison of primary amphetamine and opiate injectors

Socio-demographic characteristics

In St Petersburg, more primary ATS injectors than opiate injectors were younger than 30 years old compared to opiate injectors, an association that remained significant in multivariate analysis (aOR=5.3; 95%CI: 2.5-11.3). More ATS injectors were female (48.2%) than opiate injectors (21.3%) although this difference was not statistically significant after adjustment (aOR=1.8; 95%CI: 0.7-4.9). Fewer ATS injectors had completed basic education or vocational school (29.6%) than opiate injectors (59.7%) but differences were not statistically significant (p=0.154). Similarly, ATS injectors were more likely to report unstable living conditions (51.9%) than opiate injectors (35.5%) but the difference was not significant in multivariate analysis (p=0.069). ATS and opiate injectors did not differ on gender, ethnicity and main source of income. Univariate and multivariate comparison results between opiate and ATS injectors are presented in Table 5.1a to Table 5.1e.

HIV programmes and contextual factors

ATS injectors had lower odds of ever receiving drug treatment, compared to opiate-injectors, an association that remained significant after adjusting for socio-demographic factors (aOR=0.2; 95%CI: 0.1-0.5). ATS-injectors also had greater odds of obtaining needles and syringes from "other" sources such as a friend, family member, other PWID, drug dealer or from the street, rather than from an NSP (aOR=35.0; 95%CI: 2.7-472). Past 12 months drug treatment and past 4 weeks contact with needle and syringe services in St Petersburg were equally low in both groups, with no significant difference between ATS and opiate injectors. None of the ATS-injectors had needles or syringes confiscated by the police in the last 6 months compared to 27.0% of opiate injectors. ATS injectors had lower odds of ever being incarcerated compared to opiate injectors, and this association remained significant after adjusting for other factors (aOR=0.2: 95%CI: 0.1-0.8) (Table 5.1b).

Injecting risk behaviours

ATS-injection was associated with several injecting risk behaviours in univariate comparison, most of which remained significant in multivariate regression adjusting for potential confounders (Table 5.1d). Primary ATS injectors started injecting when they were older (mean: 20.7 years, SD: 4.1) than opiate injectors (mean: 18.7 years, SD: 3.3) and were more likely to report less than 5 years of injecting (aOR=4.0; 95%CI: 1.5-10.5).

Primary ATS injection in St Petersburg was negatively associated with reporting ever sharing needles and syringes (aOR=0.1; 95%CI: 0.1-0.3), sharing needles and syringes in the last 4 weeks (aOR=0.3; 95%CI: 0.1-0.8), lending a used syringe to someone (aOR=0.2; 95%CI: 0.1-0.4), filling a syringe from another used syringe (aOR=0.3; 95%CI: 0.1-0.8) and sharing drug paraphernalia in the previous four weeks (aOR=0.4; 95%CI: 0.2-0.8).

ATS injectors reported less frequent injecting (daily or more) than opiate injectors (aOR=0.2; 95%CI: 0.1-0.7) but differences in the number of times they injected on the last day injected were not statistically significant in multivariate analysis.

Polydrug use in the past month was a frequent practice among both ATS (33.3%) and opiate injectors in St Petersburg (41.7%, p=0.392) and did not vary significantly across drug groups. *Non-injected polydrug use* was positively associated with ATS-injection, after adjusting for other variables (aOR=4.6; 95%CI: 1.1-21.3). By contrast, *poly-injecting* was negatively associated with ATS injection in St Petersburg in univariate analysis and no longer significant in multivariate regression (aOR=0.6; 95%CI: 0.4-1.1).

Sexual risk behaviours

Primary ATS injection was positively associated with ever receiving money or drugs for sex and using condoms consistently with casual sex partners in univariate analysis; only being paid for sex remained significant after adjustment for demographic and contextual factors (Table 5.1e). The proportions of primary ATS injectors reporting multiple sex partners (47.8%) and past month unprotected sex (45.4%) was high but did not differ from opiate injectors (48.8% had multiple sex partners, p=0.898 and 54.0% had unprotected sex in the past month, p=0.494, respectively).

HIV status

Consistent with the lower injecting risks reported in St Petersburg, PWID primarily injecting ATS had lower odds of testing positive for HIV infection than those injecting opiates and this association remained significant in multivariate analysis (aOR=0.4; 95%CI: 0.2-0.7). No biological data on Hepatitis C or HSV was available for PWID in St Petersburg.

5.4 Discussion

The comparison of behavioural and HIV risk among self-identified primary ATS and primary opiates injectors in two cities with similar HIV epidemics, on either side of the border between Russia and Estonia, found that ATS injectors were younger, more likely to report less than 5 years' injecting and generally at earlier stages in their drug injecting careers, compared to opiate injectors. In both cities ATS injectors consistently reported later initiation to injecting, injected less frequently and were less likely to report lifetime sharing of needles and syringes, compared to opiate injectors. The younger age and later onset of injecting among ATS injectors suggested they may be at an early stage of injecting and possibly drug dependency, which may also account for the lower injecting frequency reported.

Interestingly, primary ATS injectors reported lower injecting risk behaviours than opiate injectors when harm reduction services were lacking (St Petersburg) and similar levels in the presence of these services (Kohtla-Järve). In St Petersburg where needle and syringe services were not widespread and over half of PWID reported sharing (or lending) needles and syringes, drug paraphernalia and filling syringes from prefilled syringes, ATS injectors (half of whom were female with unstable living arrangements) were less likely to report these sharing practices. By contrast, in Kohtla-Järve, where fewer than one in ten injectors shared needles and syringes, drug paraphernalia or filled a syringe from a prefilled syringe, both ATS and opiate injectors reported a similar frequency in these sharing practices, despite ATS injectors having less contact with a NSP or OST services than did opiate injectors. It is possible that initial differences in modifiable injecting behaviours observed between the two drug groups in the absence of harm reduction (e.g. St Petersburg) may have been "evened out" with the introduction of services proven to be effective in reducing injecting risk and HIV among opiate injectors in Kohtla-Järve. The expansion of NSPs and drug treatment geared to opiate users may have contributed to reducing unsafe injecting behaviours among opiate injectors in Kohtla-Järve, whereas they remained unchanged among primary ATS injectors, who had significantly less contact with harm reduction services.

Both polydrug use and sexual risk behaviours were similarly high in both groups and ATS injection was associated with paid sex in Kohtla-Järve. ATS-injection in both cities was also associated with non-injected polydrug use which may suggest experimentation among younger ATS injectors. Poly-injecting was associated with primary ATS injection in Kohtla-Järve but not in St Petersburg (where the ATS sample was very small).

The finding that primary ATS injectors reported lower or equal injecting frequency and sharing of injection equipment compared to opiate injectors in these PWID samples was consistent with other research where a primary M/ATS stimulant drug was injected, but differed from PWID studies where other drugs may have been co-used with M/ATS (or cocaine) stimulants [5]. Younger age and fewer years of injecting were also associated with M/ATS injection among PWID in Australia, the USA, Ukraine and Estonia [92, 93, 127, 145, 146] and primary M/ATS injectors were less or equally likely to inject more than daily compared to opiate injectors [92, 93, 101, 102, 127, 146]. A Russian study found ATS injectors injected more frequently than opiate injectors in a sample consisting exclusively of drug-dependent PWID in a treatment setting unlikely to cater for stimulant dependency which may have biased results [99]. Comparisons of M/ATS and opiate injectors in California, Australia and Estonia have consistently found no difference in needle and syringe-sharing between the two groups [93, 101, 146]. In contrast, studies of PWID who co-injected M/ATS with heroin or cocaine in the US and Canada, and with heroin or Midazolam in Thailand, reported positive associations between M/ATS and sharing or lending needles/syringes, making it unclear whether the association was with M/ATS or the polydrug combinations involved [68, 93, 127, 145, 260, 301]. The findings above suggest how risk behaviours and HIV infection risk may differ depending on whether the drug under study is a primary drug or a drug co-injected or used, and in the case of the primary drug, whether it was used with other substances. This consistent data gap motivated my analysis in chapter 6, which investigates polydrug use within a specific primary drug group.

HIV prevalence in both cities, and HCV prevalence in Kohtla-Järve, were lower among ATS injectors than opiate injectors and is consistent with lower injecting risk behaviours, younger age and later onset of injecting in this group, which together resulted in a lower cumulative exposure to HIV and HCV risk. M/ATS injection has also been associated with decreased risk of HCV infection compared to PWID injecting opiates in Australia [102]. Nevertheless the frequency of sexual risk in both cities and possible intersection with sex work suggested potential for HIV transmission and an urgent need to engage different PWID sub-groups (i.e. ATS injectors) with prevention and risk reduction messages emphasising sexual risk reduction as well as injecting risks [131, 255, 302].

Although ATS and opiate injectors in this study reported similarly high prevalence of sexual risk behaviours, including multiple sex partners, primary ATS injectors were more likely to have ever been paid for sex. M/ATS increase energy, stamina and libido and are

also used to reduce social and sexual inhibition, with suggestions by authors that M/ATS injection may be more "social" than is heroin [90, 303]. M/ATS injection more likely occurs in environments where peers or sexual partners are present, generating more needle-sharing opportunities, especially among women injectors [199]. Several studies of PWID out-of-treatment also found positive associations between M/ATS injection and multiple sex partners, unprotected sex and trading sex for money or drugs [236, 302].

Nevertheless, primary ATS injectors are vulnerable to HIV as a result of their age (and gender in St Petersburg) and generally low contact with NSP and substitution treatment, even when they were available as in Kohtla-Järve. The tendency of ATS injectors in Kohtla-Järve to source clean needles and syringes from pharmacies rather than NSPs when the majority of PWID in the sample were in contact with these services, suggests a reluctance to attend NSPs. Harm reduction has traditionally focused on reducing harms from opiate dependency and injection, with NSP and opiate substitution largely catering for opiate dependent users and not tailored for the different population demographics or needs of stimulant, or polydrug, injectors [304, 305]. Although opioid substitution therapy was shown to reduce HIV and HCV infection and support adherence to highly active anti-retroviral therapy (HAART), few, if any drug treatment options, exist for stimulants, especially M/ATS [31, 41, 44]. Effective options for the treatment of M/ATS dependency are needed and must be integrated in harm reduction programmes, especially in Eastern Europe and South East Asia, where M/ATS use has increased and which current services do not provide for [304-306]. The growing problem of ATS in these cities and globally also requires effective and appropriate prevention and drug treatment modalities to engage injectors who may be young, female and may not fit a drug use profile associated with heroin nor seek or desire contact with prevention services [302, 307, 308].

It is also possible that in more recent epidemics of drug use and HIV such as in Eastern Europe and Asia, ATS use and associated polydrug use, provide entry to drug use and injecting. Stimulant injectors who experiment with other drugs may also move on to inject other, more addictive substances [309]. As a result, HIV infections from ATS sero-converters who progressed to other drugs (e.g. heroin), leave the ATS pool of injectors and are subsequently reflected in HIV prevalence in another drug category such as heroin. Few longitudinal studies have looked at the life course of drug use among amphetamine injectors, specifically in resource-limited settings [112]. Such research would help to understand how stimulant- and opiate-injecting evolve in different contexts. Dynamically

monitoring drug(s) used and injected could also help researchers, programmes and policy makers to better adjust for differences in risk factors and behaviours associated with certain drugs or their combination, including their changes over time. Information on vulnerability and risk would assist in targeting services, particularly in resource-constrained settings.

Several strengths and limitations are acknowledged. The surveys were conducted among PWID in two Eastern European cities reporting a high prevalence of HIV and injection of different drug categories using consistent study methods and tested tools in both sites, allowing comparisons between them. However these findings may not be generalizable to other PWID populations, especially in the case of St Petersburg where the results were based on a small sample of primary ATS injectors.

Obtaining standard probability samples of populations such as PWID is challenging due to the hidden nature of this population, stigmatised behaviours and absence of a sampling frame. Respondent-driven sampling methods were developed to try and address sampling challenges and methodological issues and RDS surveys have demonstrated the ability to reach hidden sub-groups within networks [279, 281]. RDS measures reported in this study according to the STROBE statement showed that recruitment had penetrated into the PWID population and reached sub-groups not reached by programmes. Although similar results were obtained in comparisons between unweighted and weighted estimates, the representativeness of the sample cannot be determined due to the non-probabilistic sampling methodology [291, 293]. While the nature of associations could be established, causality could not be determined due to the cross sectional nature of these surveys.

Sources of bias in the study included the potential for PWID respondents not to report accurately on behaviours which are highly stigmatised and therefore social desirability bias may affect the results. Self-reports in (face-to-face) interviewer-administered questionnaires have shown reliability in several studies among PWID and an optimum period of 30 days was used to maximise recall on drug use and injecting behaviours [310, 311]. Computer assisted technologies have been found to reduce bias among PWID in resource-rich environments but would require testing in populations where education and/or computer literacy may be lower and in settings where resources are limited [312]. Potential reporting biases in the study were reduced by ensuring that participants remained anonymous and that interviews with PWID were confidential and conducted with well-trained interviewers in a setting familiar to respondents.

Finally, being female and/or transgender has been associated with greater vulnerability to HIV, and may be more so in environments where stigma is high [313]. My study considered age, sex and ethnicity as potential vulnerability factors but the role of gender other than male or female was not examined due to available survey data (i.e. binary sex variable). More inclusive gender variables may be considered in future studies although statistical power for quantitative analyses may be limited by the numbers of transgender women (and men) in PWID samples (e.g. 0.3%-1%) [16, 313, 314].

This chapter compared all primary ATS and all opiate injectors and given the high prevalence of polydrug use in this sample, it is conceivable that misclassification may have occurred due to the way study categories were defined (opiate vs. ATS injectors) thus leading to possible bias. Nonetheless, non-differential misclassification of the outcome generally biases the inferences to the null and as such, these results could be considered conservative [315]. Since several behavioural differences between categories studied remained statistically significant in spite of this, my findings support the argument that these two groups were significantly different and may have been more so in the absence of any polydrug use [112]. Additionally, several associations were marginally significant, despite the small number of ATS injectors in St Petersburg and may have been more so in a larger sample of ATS injectors.

To sum up, the comparisons by primary drug injected in this chapter pointed to several associations with socio-demographic characteristics, injecting and sexual risk behaviours, and HIV status, consistent across cities and with studies in the literature review. This analysis contributed to the evidence on HIV risk and risk factors among primary ATS and opiate injectors in Russia and Estonia, and provided the basis for the analysis of polydrug use by primary drug in chapter 6.

Box 1: Summary of comparison of HIV risk among primary amphetamine and primary opiate injectors in Estonia and Russia

In both cities, self-identified primary ATS injectors were younger, more likely to report less than 5 years' injecting and generally at earlier stages in their drug injecting careers, compared to primary opiate injectors. Primary ATS injectors also reported later initiation to injecting, injected less frequently and were less likely to report lifetime sharing of needles and syringes, compared to opiate injectors.

Generally, ATS injectors reported lower injection-related sharing risk than opiate injectors where harm reduction services were lacking but similar levels of risk where these services were present. In St Petersburg where needle and syringe services were not widespread, ATS injectors (of whom half were female) were less likely to report sharing or lending needles and syringes, drug paraphernalia and filling syringes from prefilled syringes. In Kohtla-Järve however, both ATS and opiate injectors reported similar frequencies in unsafe sharing practices, although ATS injectors had less contact with a NSP or OST services than did opiate injectors.

Polydrug use and sexual risk behaviours were similarly high in both primary drug groups and ATS injection was associated with paid sex in Kohtla-Järve. ATS-injection was also associated with non-injected polydrug use compared to opiate injection and may suggest experimentation with different drugs by the younger ATS injectors.

HIV prevalence in both cities, and HCV prevalence in Kohtla-Järve, were lower among ATS injectors than opiate injectors, consistent with the lower (or equal) injecting risks, younger age and later onset of injecting reported, which together resulted in a lower cumulative exposure to HIV and HCV risk.

Chapter 6

Comparison of HIV risk behaviour among polydrug and single drug injectors in Kohtla-Järve and St Petersburg

Chapter 6 Comparison of HIV risk behaviour among polydrug and single drug injectors in Estonia and Russia

6.1 Background

Polydrug use is frequently reported by PWID (chapter 2, chapter 4 and chapter 5) and has been associated with greater risk of overdose and increased vulnerability to HIV and HCV infection [2, 278, 316, 317]. However, most evidence linking polydrug use to HIV and HCV infection risk was from study reports specific to the North American drug use context or in the form of incidental data in epidemiological studies among PWID elsewhere. Thus, evidence on the behavioural and HIV risks associated with specific forms of polydrug use was insufficient to adequately inform interventions, research and policy in different settings [2, 9, 40, 73].

Patterns of polydrug use can be very varied and may consist of a range of possible drug combinations, taken simultaneously, sequentially or as alternative/replacement, each associated with various practices and administration routes. Polydrug use patterns among PWID may also be determined by the primary drug injected, itself associated with specific risks [65, 112, 224]. As risk behaviours vary by drug injected, they may also influence behaviours and harms associated with polydrug use (chapter 5) [1, 64].

For example *primary* ATS injection was associated with equal or lower frequency of injecting and similar daily injections compared to *primary* opiate injectors (chapters 2 and 5). These results also suggested lower or equal needle-sharing among *primary* ATS injectors, who were also consistently younger than *primary* opiate injectors [127, 131, 260]. In the literature M/ATS injection seemed to be associated with sharing, and lending, needles and syringe, *when co-injected with an opiate* (and in some cases with cocaine) and compared to those only injecting opiates and/or cocaine. ATS injection was also associated with sexual risk taking in several studies and particularly with being paid for sex, both in chapter 5 and in the literature [5, 150, 236, 260].

Nonetheless, the few epidemiological studies to have examined polydrug use and HIV risk either used dichotomous polydrug use definitions, characterised by the use of any two or more drugs within a range, or provided detailed characterisations in a specific drug use context or PWID sample, which limited their applicability [2, 9, 40, 73].

Failing to precisely define and measure polydrug use among PWID by accounting for the main drug and drug combinations may therefore hamper our understanding of the

practice, under- or over- estimate the risks and behaviours associated with different forms of polydrug, use and preclude comparisons between studies.

In order to improve our understanding of the risks of polydrug use among PWID, the current chapter investigates associations between polydrug use and injecting and sexual risk behaviours among PWID in Kohtla-Järve and St Petersburg, separately for each primary drug.

My objectives in this chapter were first, to examine the frequency of polydrug use in both cities and to identify the most frequent drug combinations (section 6.3.1) and secondly, to investigate associations between polydrug use and HIV-related injection and sexual risk behaviours in each city, factoring in socio-demographic characteristics and access to services (section 6.3.3 and 6.3.4). To examine whether polydrug use was associated with injecting and sexual risk behaviours, (i) opiate poly-injectors were compared to opiate-single injectors and (ii) ATS poly-injectors to ATS-single injectors, in each city. This approach helped to develop an understanding of drug combinations in each city, to then inform the interpretation of logistic regression modelling results in this chapter.

6.2 Methods

The analysis was based on the IBBS surveys conducted among PWID in the cities of Kohtla-Järve (Estonia) and St Petersburg (Russian Federation) for which details of methods and statistical analyses were presented in chapter 4 (section 4.2).

6.2.1 Dependent and independent variables

The binary dependant variable of interest in this chapter, was *any polydrug use* among primary opiate or stimulant injectors, defined as the "injection or (non-injection) use of at least one other drug *in addition* to the main drug injected regularly (i.e. primary drug) in the previous 4 weeks" (Table 4.1). PWID who exclusively injected a primary drug and reported no polydrug use were used as reference group in the analysis (opiate-poly- vs. opiate-single injector or ATS-poly- vs. ATS-single injector; Table 6.1). Dependent and independent variables of interest in the conceptual framework were shown in Table 4.1.

Table 6.1: Summary of dependent variables used in sub-group analyses

Polydrug use variables	**Variable description** (past month drug use)
Opiate polydrug injection	Main opiate injected and ≥ 1 other drug(s) injected/used
vs. opiate single injection	Exclusively injected main opiate drug
Opiate-stimulant poly-injection	*Main opiate injected and ≥ 1 stimulant drug(s) (eg. heroin + ATS)*
Opiate-opioid poly-injection	*Main opiate injected and ≥ 1 opioid drug(s) (eg.heroin + methadone)*
ATS poly-injection	Main ATS injected and ≥ 1 or more other drug(s)
vs. ATS-single injection	Exclusively injected main ATS drug

Note Table 6.1: "vs." indicates comparison group. ATS= Amphetamine-Type Stimulants. Past month drug use reported.

6.2.2 Statistical methods and analysis

In the first part of the chapter, i) logistic regression was used to compare patterns of polydrug use (i.e. *any polydrug use, non-injection polydrug use and poly-injection*) between the two cities, and ii) descriptive methods were used to identify common drug combinations and routes of administration for other drug(s) among primary ATS injectors and opiate injectors in each city. In the descriptive analysis, PWID were dichotomised into "any polydrug use" vs. "single drug injection". "Any polydrug use" was further differentiated into "polydrug injection" if PWID had *injected* at least one other drug in addition to their primary drug, and into "non-injection polydrug use" if they had *used* at least one other drug, in addition to their primary injection drug. The drugs injected and used by ATS and opiate injectors was displayed in separate bar graphs for each city. The most common drug combinations were identified using the most frequent additional class of drug *injected* and the most frequent other class of drug *used* in each primary drug group as a reasonable indication of consistent exposure to a second drug class [17, 112][12].

In the second and main part of the chapter, iii) associations between any polydrug use (dependent variable) and risk behaviours (independent variables) were examined separately among primary opiate injectors and primary ATS injectors, using univariate and multivariate regression methods described in chapter 4 (variables in Table 4.1). This approach was used to distinguish the effects associated with a primary drug from those associated with polydrug use.

6.3 Results

6.3.1 Drug and polydrug use patterns by city

Table 6.2 shows univariate and multivariate results of comparisons of polydrug use practices by city. Polydrug use was very frequent among PWID in both samples. PWID in Kohtla-Järve had greater odds of *non-injection polydrug use* (aOR=9.4; 95%CI: 5.9-14.8) and were less likely to report *poly-injection* than in St Petersburg (aOR=0.4; 95%CI: 0.3-0.6). More PWID in Kohtla-Järve *used* two or more additional drugs (26.0%) than in St Petersburg (2.4%, p<0.001). Conversely, fewer PWID *poly-injected* one or two additional drug(s) in Kohtla-Järve (18.8%) than in St Petersburg (38.4%, p<0.001).

[12] The same drug could not be reported as both primary drug and additional drug.

Table 6.2 Polydrug use patterns by city (Kohtla-Järve and St Petersburg)

Polydrug use †	Kohtla-Järve % (1)	n 591	St Petersburg % (1)	n 811	Odds ratio *ref. St Petersburg*	p-value (2)	aOR (3) *(95%CI)*	p-value
Any polydrug use								
No *(one drug)*	53.1%	314	58.6%	476	ref		-	
Yes *(≥ 2 drugs)*	46.9%	277	41.4%	336	1.2 (1.0-1.7)	0.153		
Non-injection polydrug use								
No	59.1%	349	93.1%	755	ref		ref	
Yes *(of which)*	41.0%	242	6.9%	56	9.0 (6.0-13.4)	<0.001	9.4 (5.9-14.8)	<0.001
Main drug + use 1 other	*14.9%*	*88*	*4.6%*	*37*		*<0.001*		
Main drug + use 2 other	*13.0%*	*77*	*2.0%*	*16*				
Used 4 drugs or more	*13.0%*	*77*	*0.4%*	*3*				
Poly-injection								
No	80.2%	474	60.4%	490	ref		ref	
Yes *(of which)*	19.8%	117	39.6%	321	0.4 (0.3-0.5)	<0.001	0.4 (0.3-0.6)	<0.001
Main drug + inject 1 other	*15.1%*	*89*	*30.4%*	*247*		<0.001		
Main drug + inject 2 other	*3.7%*	*22*	*8.0%*	*65*				
Injected 4 drugs or more	*1.0%*	*6*	*1.2%*	*10*				

Note Table 6.2: †All PWID injected in the last 4 weeks. (1) Column percentage. (2) Unadjusted p-value using Pearson's Chi-squared test for proportions. (3) aOR adjusted for age, sex, contact with needle and syringe service, and drug treatment. Reference group = St Petersburg. CI: Confidence Intervals. People who injected drugs (PWID) but did not report a primary drug included (n=27).

6.3.2 Polydrug use combinations by primary drug and by city

Polydrug combinations examined by city are shown by primary drug category in a branch and tree analysis for Kohtla-Järve in Figure 6.1, and for St Petersburg in Figure 6.2.

In Kohtla-Järve, the other drug(s) most frequently injected and used by both primary ATS and opiate injectors were other stimulants (details in Figure 6.1). By contrast, the other drug(s) most frequently injected and used in St Petersburg by primary opiate injectors were opioids or opiates (Figure 6.2). The few primary ATS injectors in St Petersburg injected additional opiates and used other non-injected ATS.

In Kohtla-Järve, where stimulants were the dominant other drug class *injected* and *used,* opiate poly-injectors were referred to as *opiate-stimulant poly-injectors.* In St Petersburg, where opioids/opiates were the main other drug class injected and used by opiate poly-injectors, this group was referred to as *opiate-opioid poly-injectors* [17, 112].

ATS poly-injectors were referred to as ATS-stimulant poly-injectors in Kohtla-Järve based on the most common combination with other stimulants. The sample of ATS injectors using other drugs in St Petersburg was so small it did not permit further analysis and was only shown for completeness.

Based on the drug combinations reported in each city, the second part of this chapter compared HIV-related injection and sexual risk behaviours between (i) opiate-stimulant poly-injectors and opiate-single injectors in Kohtla-Järve, and opiate-opioid poly-injectors and opiate-single injectors in St Petersburg. ATS-stimulant poly-injectors were compared to ATS-single injectors in Kohtla-Järve.

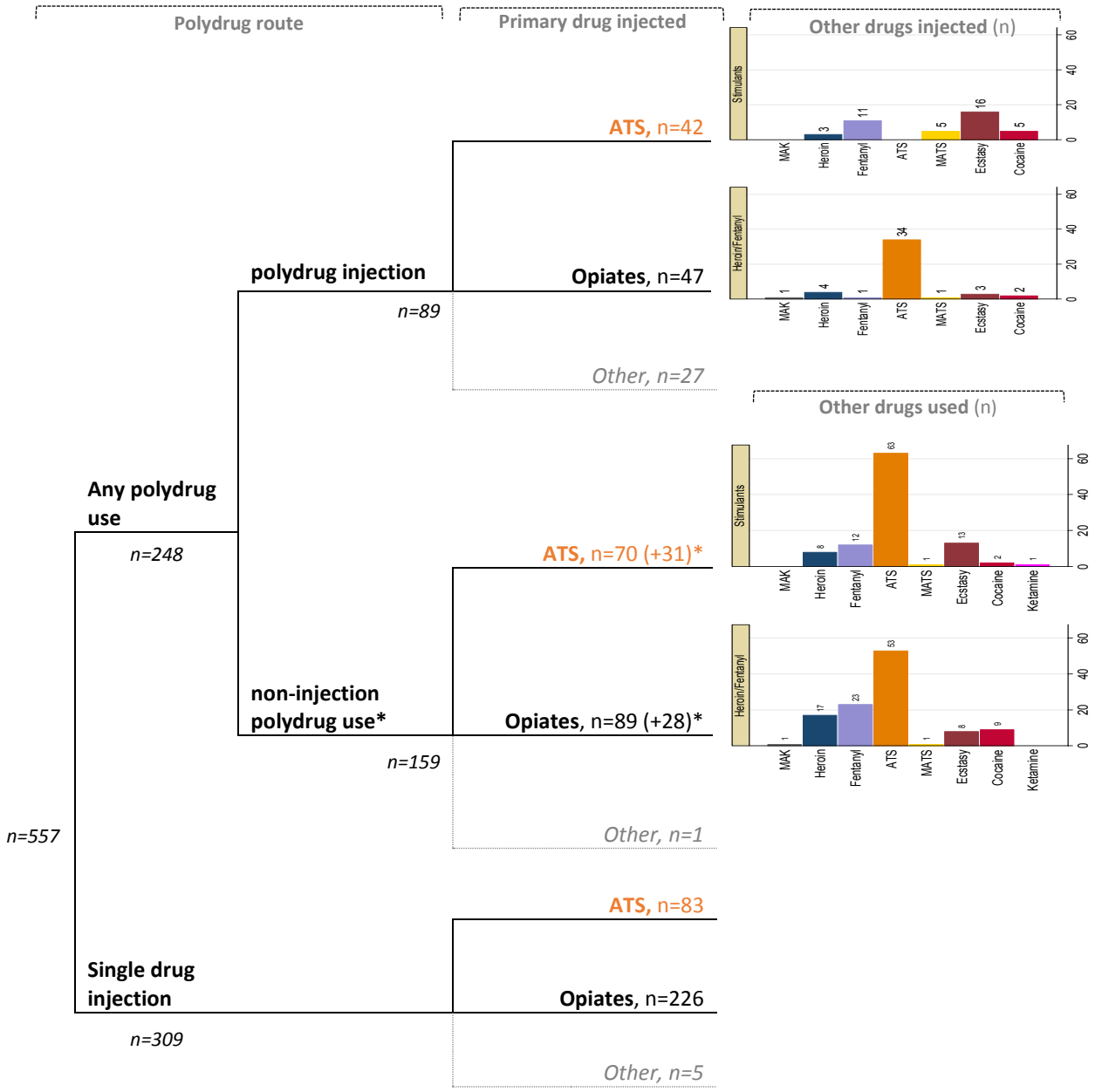


Figure 6.1: Polydrug and single drug use by primary drug in Kohtla-Järve

ATS injectors (n=42) **principally also injected stimulants,** namely ecstasy (39%, n=16), followed by fentanyl (26%, n=11), cocaine (12%, n=5), MATS (12%, n=5) and heroin (6%, n=3).

Opiate injectors (n=47) **predominantly also injected stimulants**, including ATS (72%, n=34), ecstasy (7%, n=3), cocaine (5%, n=2) and MATS (2%, n=1). Few opiate injectors also injected other opiates such as heroin (8%, n=4), fentanyl (2%, n=1) or poppy mixture/mak (2%, n=1). None injected methadone.

ATS injectors (n=70) **mainly also used non-injection stimulants**, namely ATS (90%, n=63), ecstasy (19%, n=13) and ketamine (1.4%, n=1). fentanyl (17%, n=12) and heroin (11%, n=8)[13].

Opiate injectors (n=89) **also used non-injection stimulants** ATS (60%, n=53), followed by fentanyl (33%, n=23), cocaine (13%, n=9), ecstasy (11%, n=8) and heroin (11%, n=17).

Note **Figure 6.1**: The other drugs injected and used are shown by primary drug in each bar graph, from central nervous system (CNS) depressants to CNS stimulants. *PWID who both injected and used other drugs were counted once in the polydrug injection group among ATS (n=31) and opiate (n=28) injectors. PWID who reported no primary drug (n=33, greyed out in figure 6.1) were not included in the analyses, 27 of whom injected other drugs, 1 used other drugs and 5 did not inject or use other drugs). M/ATS=meth/amphetamine-type stimulant. PWID=people who inject drugs.

[13] The sum of other drugs used was greater than 70 as some polydrug users used more than one other drug. Different types of ATS are available and may account for injected and oral ATS being reported by PWID.

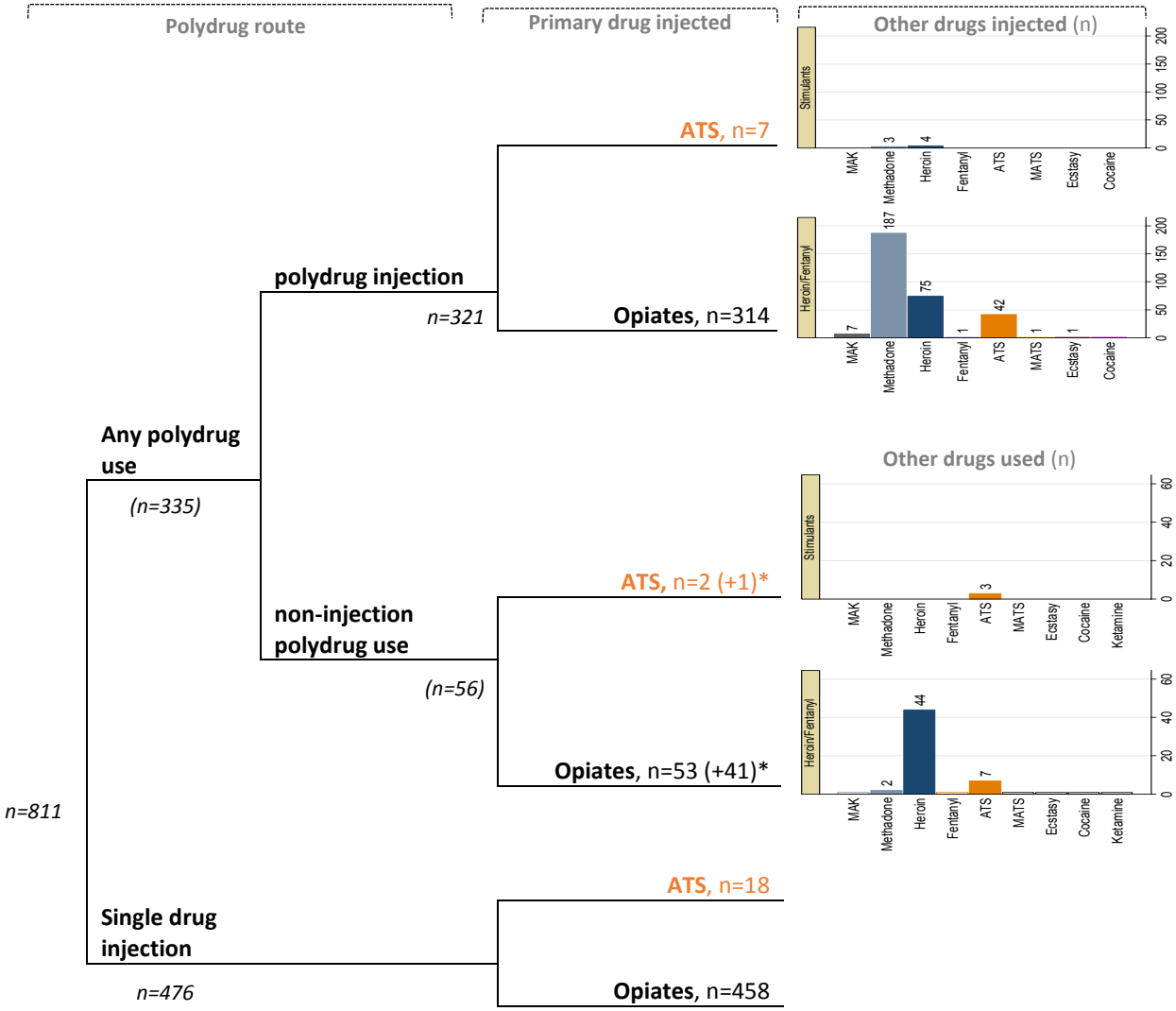


Figure 6.2: Polydrug and single drug use by primary drug in St Petersburg

ATS injectors (n=7) **mainly also injected other opiates** in St Petersburg, namely methadone (43%, n=3) and heroin (57%, n=4).

Opiate injectors (n=314) **predominantly also injected other opiates**, including non-prescribed methadone (83%, n=187), heroin (24%, n=75) or poppy mixture/mak (3%, n=7). Few opiate injectors also injected ATS as additional drug (12%, n=42); ecstasy (0.3%, n=1), MATS (0.3%, n=1) and cocaine (0%, n=0) were almost non-existent.

ATS injectors (n=3) **also used non-injection ATS** (100%, n=3)**.**

Opiate injectors (n=53) **mostly used other non-injection opiates**, especially heroin (83%, n=44), methadone (4%, n=2) and non-injection ATS (13%, n=7).

Note Figure 6.2: The other drugs injected and used are shown by primary drug in each bar graph, ordered from central nervous system (CNS) depressants to CNS stimulants. *PWID who both injected and used other drugs were counted once in the polydrug injection group among ATS (n=1) and opiate (n=41) injectors. M/ATS: meth/amphetamine-type stimulant. PWID=people who inject drugs.

Box 6.1: Polydrug use patterns in Kohtla-Järve and St Petersburg

Polydrug use was frequent among PWID in both cities. The majority of polydrug users in Kohtla-Järve were *non-injection polydrug users.* In St Petersburg most were *poly-injectors*.

Opiate poly-injectors

Primary opiate poly-injectors *in Kohtla-Järve* mostly injected and used other stimulants, a polydrug pattern referred to as **opiate-stimulant poly-injection**. *In St Petersburg* primary opiate poly-injectors mostly injected and used other opioids, a practice referred to as **opiate-opioid poly-injection**.

ATS poly-injectors

ATS injectors in Kohtla-Järve mostly injected and used other stimulants with their main drug and were referred to as **ATS-stimulants poly-i**njectors.

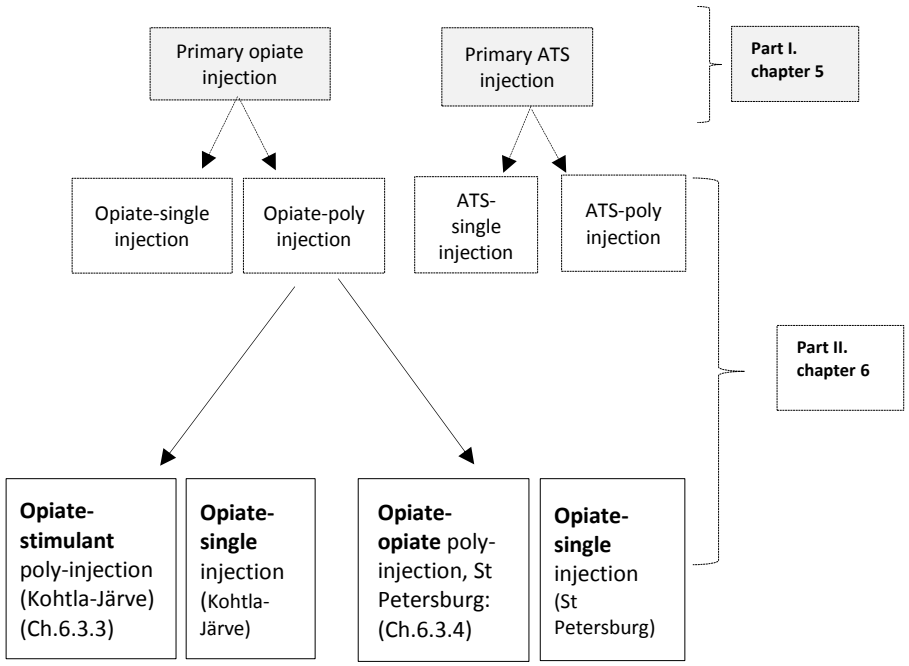


Figure 6.3: Outline of analyses showing opiate poly-injector sub-groups used in Kohtla-Järve and St Petersburg

6.3.3 Comparison of opiate poly- and opiate-single injectors

i) Kohtla-Järve

Socio-demographic characteristics

In univariate analysis, opiate-stimulant poly-injectors in Kohtla-Järve had greater odds of being female (OR=2.4; 95%CI: 1.3-4.3), of having completed secondary education (OR=1.5; 95%CI: 1.2-1.9) and of being of an ethnicity other than Estonian or Russian[14] (OR=1.8; 96=5%CI: 1.2-2.7) than exclusive opiate injectors. They had lower odds of having a non-regular income or depending on someone else (OR=0.7; 95%CI: 0.5-0.9). Age, living arrangements and reliance on an illicit source of income were no longer significant after adjusting for other demographics characteristics (Table 6.3a).

HIV programme and contextual factors

Opiate-stimulant poly-injectors and opiate-single injectors reported similarly high levels of contact with a needle and syringe programme (NSP) (92.1% vs. 89.0%, p=0236), low levels of drug substitution treatment in the preceding 12 months (17.3% vs. 15.4%, p=0428) and a comparable history of ever receiving drug treatment (62.5% vs. 69.9%, p=0.138) (Table 6.3b). Opiate-stimulant poly-injectors however, were less likely than opiate-single injectors to have had needles and syringes confiscated by the police (OR=0.2; 95%CI: 0.1-0.3) and to have ever been incarcerated (OR: 0.5; 95%CI: 0.3-0.7).

Injecting risk behaviours associated with opiate-stimulant poly-injection

Several injecting risk behaviours differed between opiate-stimulant poly-injectors and exclusive opiate injectors in univariate analysis, most of which remained statistically significant in multivariate analysis (Table 6.3d). After adjusting for demographic and contextual factors, opiate-stimulant poly-injectors had lower odds of injecting daily or more in the last month (aOR=0.5; 95%CI: 0.4-0.7) compared to opiate-single injectors. Opiate-stimulant poly-injectors were *more* likely to have filled their syringe from a working syringe (aOR=29.9; 95%CI: 9.3-95.0) and to have shared injecting paraphernalia (aOR=13.7; 95%CI: 1.9-98.0) than exclusive opiate injectors.

No significant differences were found between the two groups in the duration of injecting, number of times injected on last day, or in the frequency of lending needles and syringes after adjusting for demographic and contextual variables (Table 6.3d).

[14] "Other" ethnic groups reported included Byelorussian, Ukrainian, Gypsy, Polish, Lithuanian, Finn, Latvian Tatar, Armenian, Kazakh and "refugee" (technically not an ethnic group).

Sexual risk behaviours associated with opiate-stimulant poly-injection

In univariate analysis, more opiate-stimulant poly-injectors tended to be sexually active (sex in the last 6 months) than opiate-single injectors (OR=1.6; 95%CI: 1.3-2.1) although both opiate-poly and opiate-single injectors reported similarly high prevalence of multiple sex partners (37.6% and 34.2%, p=0.397) and unprotected sex (11.6% and 11.0%, p=0.895) respectively, in the preceding 6 months (Table 6.3e).

Several differences in sexual risk behaviours between opiate-stimulant poly-injectors and exclusive opiate injectors in Kohtla-Järve, remained significant after adjusting for socio-demographic and contextual variables (Table 6.3e). In multivariate analysis[15], opiate-stimulant poly-injectors remained more likely than opiate-single injectors to have had sex in the last six months (aOR=1.5; 95%CI: 1.1-2.0) and to have had multiple sex partners (aOR= 1.5; 95%CI: 1.3-1.9). However opiate-stimulant poly-injectors were less likely to report casual sex with partners who also injected drugs (aOR=0.2; 95%CI: 0.1-0.5) and unprotected sex in the last 4 weeks (aOR=0.8; 95%CI: 0.6-0.9) than exclusive opiate injectors. They were also more likely to report consistent condom use with a regular partner (aOR=1.7; 95%CI: 1.1-2.9). No significant differences in HIV, HCV and HSV status were found between the two groups in Kohtla-Järve in multivariate analysis (Table 6.3b).

Box 6.2: Summary results for opiate-stimulant poly-injectors in Kohtla-Järve

Opiate-stimulant poly-injectors, tended to be female, non-ethnic Russian or Estonian with secondary education and a regular income compared to exclusive opiate injectors.

Opiate-stimulant poly-injection was associated with less frequent injection than exclusive opiate injection, but similar intensity on the days injected. Although opiate-stimulant poly-injectors had similarly high levels of contact with needle and syringe programmes (NSP) and drug substitution treatment compared to exclusive opiate injectors, they were more likely to share injection paraphernalia, to share needles and syringes and to back-or front-load syringes. Opiate-stimulant poly-injectors were less likely to have had needles and syringes confiscated by the police and to have been incarcerated than exclusive opiate injectors. Opiate-stimulant poly-injection was positively associated with having multiple sex partners. The two groups did not differ in HIV, HCV and HSV status.

[15] Variables adjusted for in Kohtla-Järve were age, sex, education, ethnicity, main income, needle and syringe programme, drug treatment and injecting frequency.

Table 6.3a Univariate and multivariate associations between demographic characteristics and polydrug use among opiate injectors: Kohtla-Järve (n=362), St Petersburg (n=784)

a. Demographic variables	**Kohtla-Järve - Opiate-stimulant poly-injectors** vs. opiate-single injectors								**St Petersburg – Opiate-opioid poly-injectors** vs. opiate-single injectors							
by polydrug use [3]	**Opiate single**	**n** 226	**Polydrug** [1]	**n** 136	**Odds ratio** *(95%CI)*	**P-value** [2]	**aOR** [4] *(95%CI)*	**P-value**	**Opiate single**	**n** 458	**Polydrug** [1]	**n** 326	**Odds ratio** *(95%CI)*	**P-value** [2]	**aOR** [4] *(95%CI)*	**P-value**
Sex																
Female	18.2%	41	34.8%	47	2.4 (1.3-4.3)	0.006*	2.4 (1.2-4.7)	0.015*	22.3%	102	19.9%	65	0.9 (0.6-1.3)	0.455	0.7 (0.4-1.1)	0.115
Male	81.8%	184	65.2%	88	*ref*		*ref*		77.7%	356	80.1%	262	*ref*		*ref*	
Age group																
< 30 years	41.6%	94	47.8%	65	1.3 (0.8-2.0)	0.223	1.4 (0.8-2.3)	0.197	23.4%	107	35.0%	114	1.8 (1.2-2.5)	0.004*	1.9 (1.3-2.9)	0.003*
>= 30 years	58.4%	132	52.2%	71	*ref*		*ref*		76.6%	351	65.0%	212	*ref*		*ref*	
Ethnicity																
Estonian	10.7%	24	8.8%	12	0.9 (0.5-1.5)	0.568	1.0 (0.5-1.8)	0.923	-	-	-	-	-	-	-	-
Other	6.7%	15	11.8%	16	1.8 (1.2-2.7)	0.005*	2.1 (1.3-3.4)	0.005*	4.6%	21	4.3%	14	0.8 (0.5-1.4)	0.780	-	-
Russian	82.7%	186	79.4%	108	*ref*		*ref*		95.4%	437	95.7%	312	*ref*		-	-
Education level																
Higher	-	-	-	-	-	-	-	-	12.3%	56	9.2%	30	0.6 (0.4-1.1)	0.097	0.6 (0.4-0.9)	0.027*
Secondary	17.7%	40	24.3%	33	1.5 (1.2-1.9)	0.002*	1.7 (1.1-2.8)	0.032*	32.4%	148	24.9%	81	0.6 (0.4-0.9)	0.021*	0.6 (0.4-0.9)	0.049*
Basic/Vocational	82.3%	186	75.7%	103	*ref*		*ref*		55.4%	253	65.9%	214	*ref*		*ref*	
Living arrangements																
Unstable	43.4%	59	39.1%	88	1.2 (0.6-2.4)	0.594	1.1 (0.5-2.4)	0.791	39.5%	181	29.7%	97	0.6 (0.5-0.8)	<0.001	0.6 (0.4-0.9)	<0.001*
stable	56.6%	77	60.9%	137	ref		*ref*		60.5%	277	70.3%	229	*ref*		*ref*	
Main income source																
Irregular/illicit	4.5%	10	3.0%	4	0.6 (0.3-1.1)	0.088	0.7 (0.3-1.7)	0.405	11.4%	52	24.9%	81	2.0 (1.2-3.2)	0.006*	2.1 (1.3-3.1)	0.002*
Non-regular/dependant	34.5%	77	26.7%	36	0.7 (0.5-0.9)	0.031*	0.6 (0.4-1.0)	0.045*	45.8%	209	28.5%	93	0.6 (0.4-0.8)	0.003*	0.6 (0.4-0.9)	0.015*
Regular/salaried	61.0%	136	70.4%	95	*ref*		*ref*		42.8%	195	46.6%	151	*ref*		*ref*	

Notes Table.6.3a. (1) Column percentage (2) Unadjusted p-value using Pearson's Chi-squared test for proportions (or Fisher's exact when cells<4), t-test to test difference between means and non-parametric Mann-Whitney U test (=Wilcoxon rank-sum). (3) Reference group is opiate-single injectors. (4) Odd Ratios adjusted (aOR) for age, sex, education, main income in both cities, and for ethnicity in Kohtla-Järve and living arrangements in St Petersburg. Missing values shown in Table 4.4. CI=Confidence Intervals. * P-value ≤0.05.

Table 6.3b. Univariate and multivariate associations between context variables, sero-markers and polydrug use in opiate injectors: Kohtla-Järve (n=362), St Petersburg, (n=784)

b. Service coverage	**Kohtla-Järve - Opiate-stimulant poly-injectors** vs. opiate-single injectors								**St Petersburg Opiate-opioid poly-injectors** vs. opiate-single injectors							
by polydrug use [3]	**Opiate single**	**n** 226	**Polydrug** [1]	n 136	**Odds ratio** *(95%CI)*	[2] **p-value**	**aOR** [4] *(95%CI)*	**P-value**	**Opiate single**	**n** 458	**Polydrug** [1]	n 326	**Odds ratio** *(95%CI)*	[2] **P-value**	**aOR** [4] *(95%CI)*	**P-value**
Lifetime drug treatment																
Ever drug treatment	69.9%	158	62.5%	85	0.7 (0.5-1.1)	0.138			73.1%	335	73.6%	240	1.0 (0.7-1.4)	0.999	-	-
Never in treatment	30.1%	68	37.5%	51	*ref*				26.9%	123	26.4%	86	*ref*			
Drug/substitution treatment																
Yes *(12 months)*	15.4%	21	17.3%	39	0.9 (0.6-1.2)	0.428	-	-	10.4%	48	10.5%	34	1.0 (0.7-1.6)	0.850	-	-
No	84.6%	115	82.7%	187	ref				89.6%	409	89.5%	292	*ref*			
Needle/syringe programme																
Contact with NSP	89.0%	186	92.1%	116	1.4 (0.8-2.7)	0.236	-	-	19.4%	81	11.6%	37	0.5 (0.3-0.7)	0.001*	0.5 (0.4-0.7)	0.001*
No contact with NSP	11.0%	23	7.9%	10	*ref*				80.6%	337	88.4%	282	*ref*		*ref*	
Injections w/clean needles																
<50%	82.4%	126	88.5%	100	0.5 (0.2-1.2)	0.102			6.8%	28	12.6%	39	1.9(1.1- 3.0)	0.014*	1.9 (1.2-3.0)	0.007*
50-99%	13.1%	20	7.1%	8	0.0 (0.2-3.5)	0.874	-	-	14.3%	59	21.9%	68	2.3 (1.4-3.8)	0.002*	1.5 (1.0-2.4)	0.007*
100%	4.6%	7	4.4%	5	ref				79.0%	327	65.5%	203	*ref*		*ref*	
Source of new syringes																
other	4.3%	9	3.2%	4	0.7 (0.4-1.4)	0.331	-	-	2.6%	11	2.5%	8	1.5 (0.5-4.3)	0.394	2.4 (1.1-5.4)	0.039*
Pharmacist/chemist	6.7%	14	4.8%	6	0.7 (0.3-1.4)	0.293	-	-	77.9%	326	85.9%	274	2.0 (1.3-2.9)	0.001*	1.9 (1.4-2.8)	0.001*
Needle/syringe programme	89.0%	186	92.1%	116	ref				19.4%	81	11.6%	37	ref		*ref*	
Incarceration																
Ever in prison	74.3%	168	56.6%	77	0.5 (0.3-0.7)	<0.001*	0.5(0.3-1.8)	0.012*	32.3%	148	38.2%	124	1.3 (0.9-1.8)	0.127	1.2 (0.8-1.9)	0.276
Never in prison	25.7%	58	43.4%	59	*ref*		*ref*		67.7%	310	61.8%	202	*ref*		*ref*	
Needles/syringes (N/S) **confiscated**																
Had N/S confiscated	53.1%	119	20.0%	27	0.2 (0.1-0.4)	<0.001*	0.2(0.1-0.3)	<0.001*	29.3%	134	23.9%	78	0.7 (0.5-1.1)	0.093	0.8 (0.5-1.2)	0.260
not N/S confiscated	46.9%	105	80.0%	108	*ref*		*ref*		70.7%	324	76.2%	248	*ref*		*ref*	
c. Serological markers																
HIV positive	71.7%	162	66.9%	91	0.8 (0.5-1.3)	0.326	0.9(0.6-1.3)	0.418	54.8%	251	59.9%	195	1.2 (0.9-1.8)	0.188	1.3 (0.9-2.0)	0.138
negative	28.3%	64	33.1%	45	ref		*ref*		45.2%	207	40.1%	131	*ref*		*ref*	
HCV reactive	77.2%	105	85.8%	194	0.6 (0.2-1.4)	0.193	0.5(0.2-1.4)	0.210	Not collected		-	-	-	-	-	-
non-reactive	22.8%	31	14.2%	32	*ref*		*ref*		-	-	-	-				
HSV positive	31.6%	42	32.6%	72	1.0 (0.6-1.6)	0.849	0.7(0.5-1.1)	0.116	Not collected		-	-	-	-	-	-
negative	68.4%	91	67.4%	149	*ref*		*ref*		-	-	-	-				

Table 6.3b, c: (1) Column percentage. (2) Unadjusted p-value using Pearson's Chi-squared test for proportions, t-test to test difference between means and non-parametric Mann-Whitney U test (=Wilcoxon rank-sum). (3) Reference group is opiate single injectors. (4) Odds Ratio for HIV, HCV and HSV biomarkers adjusted (aOR) for age, sex, education, main income, injecting frequency, drug treatment and NSP in both cities, ethnicity in Kohtla-Järve and living arrangements in St Petersburg. CI=Confidence Intervals. HIV= Human Immune deficiency Virus; HCV= Hepatitis C; HSV= Herpes Virus Simplex. * P-value ≤0.05.

Table 6.3d. Univariate and multivariate association between injecting risk and polydrug use among opiate injectors in Kohtla-Järve (n=362) and St Petersburg (n=784)

d. Injecting risk variables	**Kohtla-Järve - Opiate-stimulant poly-injectors** vs. opiate-single injectors								**St Petersburg - Opiate-opioid poly-injectors** vs. opiate-single injectors							
by polydrug use [3][4]	**Opiate single**	**n** 226	**Polydrug** [1]	**n** 136	**Odds ratio**[2] *(95%CI)*	**P-value**	**aOR** [5] *(95%CI)*	**P-value**	**Opiate single**	**n** 458	**Polydrug** [1]	**n** 326	**Odds ratio** *(95%CI)*	[2] **P-value**	**aOR** [3] *(95%CI)*	**P-value**
Duration of injecting																
≤ 5 years	4.4%	10	7.4%	10	0.6 (0.2-1.5)	0.246	0.8 (0.2-2.6)	0.653	2.4%	11	1.2%	4	1.8 (0.4-7.3)	0.385	1.6 (0.3-8.6)	0.590
> 5 years	95.6%	216	92.7%	126	*ref*		*ref*		97.6%	447	98.8%	322	*ref*		ref	
Mean age at first injection																
(mean, SD)	17.8 (3.3)		18.3 (3.0)		1.1 (1.0-1.2)	0.121	1.0 (0.9-1.1)	0.751	19.3 (3.4)		17.9 (3.0)		0.9 (0.8-0.9)	<0.001*	0.9 (0.9-1.0)	0.047*
Frequency of injecting																
Daily or more	35.0%	79	25.0%	34	0.6 (0.5-0.8)	0.002*	0.5 (0.4-0.7)	<0.001*	26.9%	123	49.7%	162	2.7 (2.1-3.5)	<0.001*	2.1 (1.5-2.6)	<0.001*
Less than daily	65.0%	147	75.0%	102	*ref*		*ref*		73.1%	335	50.3%	164	*ref*		ref	
Injections last day injected																
Twice or more	45.6%	103	48.5%	66	1.1 (0.7-1.7)	0.562	1.3 (0.9-1.9)	0.220	37.6%	172	60.3%	196	2.6 (1.8-3.7)	<0.001*	2.0 (1.2-3.4)	0.012*
Once	54.4%	123	51.5%	70	*ref*		*ref*		62.4%	285	39.7%	129	*ref*			
Ever shared needles/syringes																
Yes	81.3%	183	72.6%	98	0.6 (0.4-1.0)	0.037*	0.6 (0.3-1.0)	0.068	92.1%	422	92.0%	300	1.0 (0.5-1.7)	0.893	0.8 (0.4-1.3)	0.320
No	18.7%	42	27.4%	37	*ref*		*ref*		7.9%	36	8.0%	26	*ref*		*ref*	
Injected w/used needles/syringes																
Yes	5.3%	12	11.2%	15	2.2 (1.2-4.1)	0.012*	2.4 (1.0-6.0)	0.058	56.4%	256	64.1%	207	1.3 (0.9-2.0)	0.202	1.3 (0.8-2.0)	0.242
No	94.7%	213	88.8%	119	*ref*		*ref*		43.6%	198	35.9%	116	ref		*ref*	
Gave used syringe to someone																
Yes	19.0%	43	13.3%	18	0.7 (0.3-1.4)	0.241	0.7 (0.3-1.4)	0.289	51.7%	235	62.2%	202	1.5 (1.0-2.2)	0.033*	1.4 (1.0-2.1)	0.075
No	81.0%	183	86.7%	117	*ref*		*ref*		48.4%	220	37.9%	123	*ref*		*ref*	
Filled from working syringe																
Yes	1.8%	4	15.4%	21	10 (5.4-18.5)	<0.001*	29.9 (9.3-95.0)	<0.001*	56.3%	258	51.5%	168	0.8 (0.5-1.2)	0.234	0.7 (0.5-1.1)	0.172
No	98.2%	220	84.6%	115	*ref*		*Ref*		43.7%	200	48.5%	158	ref		*ref*	
Shared drug paraphernalia																
Yes	2.7%	6	15.4%	21	6.7 (2.3-19.5)	0.001*	13.7 (1.9-98.0)	0.012*	68.3%	313	71.5%	233	1.1 (0.8-1.5)	0.371	1.1 (0.8-1.6)	0.547
No	97.4%	220	84.6%	115	*ref*		*ref*		31.7%	145	28.5%	93	ref		*ref*	
Polydrug use *(≥ 2 non-injected)*																
Yes	0.0%	0	14.0%	19	-	<0.001*	-	-	0.0%	0	16.3%	53	-	<0.001*	-	-
No	100%	226	86.0%	117					100%	458	83.7%	273				
Poly-injecting *(≥ 2 drugs injected)*																
Yes	0.0%	0	34.6%	47	-	<0.001*	-	-	100%	458	96.3%	314	-	<0.001*	-	-
No	100%	226	65.4%	89					0.0%	0	3.7%	12				

Notes Table 6.3d: (1) Column percentage (2) Unadjusted p-value using Pearson's Chi-squared test for proportions (or Fisher's exact when cells<4), t-test to test difference between means and Mann-Whitney U test (=Wilcoxon rank-sum) for non-parametric data (medians). (3) Reference group is opiate single injectors. (4) Injecting risk variables measured in the last 4 weeks, unless specified. (5) OR adjusted (aOR) for age, sex, education, main income, needle and syringe programme and drug treatment in both cities, and for ethnicity in Kohtla-Järve and living arrangements in St Petersburg. CI=Confidence Intervals. SD= Standard Deviation. * P-value ≤0.05.

Table 6.3e. Univariate and multivariate association between sexual risk and polydrug use among opiate injectors in Kohtla-Järve (n=362) and St Petersburg (n=784)

e. Sexual risk variables	**Kohtla-Järve - Opiate-stimulant poly-injectors** vs. opiate-single injectors								**St Petersburg - Opiate-opioid poly-injectors** vs. opiate-single injectors							
by polydrug use [3][4]	**Opiate single**	**n** 226	**Polydrug** [1]	**n** 136	**Odds ratio** [2] *(95%CI)*	**P-value**	**aOR** [5] *(95%CI)*	**P-value**	**Opiate single**	**n** 458	**Polydrug** [1]	**n** 326	**Odds ratio** *(95%CI)*	[2] **P-value**	**aOR** [5] *(95%CI)*	**P-value**
Any sex in 6 months																
Yes	74.6%	167	82.8%	111	1.6 (1.3-2.1)	<0.001*	1.5 (1.1-2.0)	0.007*	75.8%	347	77.4%	253	1.1 (0.8-1.4)	0.755	1.0 (0.7-1.3)	0.701
No	25.5%	57	17.2%	23	*ref*		*ref*		24.2%	111	22.6%	73	*ref*		*ref*	
Regular sex partners																
One or more	100.0%	152	99.0%	94	-		-	-	65.9%	228	54.4%	137	0.6 (0.5-0.8)	<0.001*	0.6 (0.4-0.9)	0.015*
None	0.0%	0	1.1%	1	-	0.205	-	-	34.1%	118	45.6%	115	ref		*ref*	
Casual sex partners																
One or more	100%	48	100%	39	-	-	-	-	37.8%	131	45.5%	115	0.6 (0.5-0.8)	<0.001*	1.5 (1.1-2.0)	0.020*
None	0%	0	0%	0	-	-	-	-	62.3%	216	54.6%	138	ref		*ref*	
Regular sex partner injects																
Yes	55.9%	85	62.1%	59	1.2 (0.6-2.8)	0.489	1.1 (0.5-1.9)	0.972	48.9%	110	72.3%	99	2.5 (1.7-3.7)	<0.001*	3.0 (1.9-4.8)	<0.001*
No	44.1%	67	37.9%	36	*ref*		*ref*		51.1%	115	27.7%	38	*ref*		*ref*	
Casual sex partner injects																
Yes	51.1%	24	38.5%	15	0.6 (0.3-1.4)	0.220	0.2 (0.1-0.5)	0.002*	51.3%	58	79.4%	85	3.5 (2.1-6.0)	<0.001*	2.1 (1.3-3.6)	0.005*
No	48.9%	23	61.5%	24	*ref*		*ref*		48.7%	55	20.6%	22	*ref*		*ref*	
Was ever paid for sex																
Yes	6.1%	10	5.6%	6	0.9 (0.2-4.7)	0.911	0.3 (0.1-1.4)	0.113	4.5%	14	1.8%	4	0.3 (0.1-0.8)	0.020*	0.5 (0.1-1.9)	0.298
No	93.9%	154	94.4%	101	*ref*		*ref*		95.5%	300	98.2%	214	*ref*		*ref*	
Condom with regular partner																
Yes (consistent)	26.0%	25	23.0%	35	1.2 (0.6-2.3)	0.623	1.7 (1.1-2.9)	0.035*	18.8%	43	12.3%	17	0.6 (0.2-1.6)	0.271	0.6 (0.2-1.3)	0.181
No	74.0%	71	77.0%	117	*ref*		*ref*		81.2%	186	87.7%	121	ref		*ref*	
Condom with casual partner																
Yes (consistent)	50.0%	24	61.5%	24	1.6 (0.5-5.2)	0.418	2.4 (0.7-7.7)	0.134	50.8%	66	41.2%	47	0.7 (0.4-1.1)	0.103	0.7 (0.5-1.1)	0.121
No	50.0%	24	38.5%	15	*ref*		*ref*		49.2%	64	58.8%	67	ref		*ref*	
Multiple sex partners																
multiple partners (>=2)	34.2%	53	37.6%	38	1.2 (0.8-1.7)	0.397	1.5 (1.3-1.9)	<0.001*	45.1%	155	54.0%	135	1.4 (1.1-1.8)	0.006*	1.4 (1.1-1.8)	0.020*
one sex partner	65.8%	102	62.4%	63	*ref*		*ref*		54.9%	189	46.0%	115	*ref*		*ref*	
Unprotected vaginal sex																
Yes	11.0%	17	11.6%	11	0.9 (0.3-2.7)	0.895	0.6 (0.4-1.1)	0.095	36.9%	168	47.1%	152	1.7 (1.1-2.5)	0.011*	1.5 (1.0-2.4)	0.055
No *(always used condom)*	25.3%	39	24.4%	27	*ref*		*ref*		63.1%	287	52.9%	170	*ref*		*ref*	
Had sex, did not answer	63.6%	98	60.0%	57	-	-	-	-	-	-	-	-	-	-	-	-

Notes Table 6.3e: (1) Column percentage (2) Unadjusted p-value using Pearson's Chi-squared test for proportions (STATA results). (3) Reference group is opiate single injectors. (4) Sexual risk measured in the last 6 months, unless specified. (5) OR adjusted (aOR) for age, sex, education, main income, and NSP and drug treatment in both cities, ethnicity in Kohtla-Järve and living arrangements in St Petersburg. IDU= Injecting Drug User. CI=Confidence Intervals.
* P-value ≤0.05.

ii) St Petersburg

Socio-demographic characteristics

Opiate-opioid poly-injectors in St Petersburg had greater odds of being under the age of 30 (OR=1.8; 95%CI: 1.2-2.5) and of relying on irregular or illicit sources of income (OR=2.0; 95%CI: 1.2-3.2) compared to opiate-single injectors (Table 6.3a). They also had lower odds of having completed secondary school (OR=0.6; 95%CI: 0.4-0.9), reporting unstable living arrangements (OR=0.6; 95%CI: 0.5-0.8) and of being dependent on others for income (OR=0.6; 95%CI: 0.4-0.8) compared to exclusive opiate injectors. The two groups did not differ in terms of sex or ethnicity.

HIV programmes and contextual factors

Opiate-opioid poly-injectors had lower odds of being in contact with a needle and syringe programme (NSP) in the previous month compared to opiate-single injectors (aOR=0.5; 95%CI: 0.4-0.7) after adjusting for socio-demographic factors. Consistent with their lower contact with these services, they were more likely to have obtained clean needles and syringes from a pharmacist (aOR=2.0; 95%CI: 1.4-2.8) or "other" sources (aOR=2.4; 95%CI: 1.1-5.4) rather than from an NSP. Opiate-opioid poly-injectors also reported having fewer than 50% clean needles and syringes for their injections in the last month (aOR=1.9; 95%CI: 1.2- 3.0) compared to opiate-single injectors. No other contextual differences were found between the two groups (i.e. drug treatment, needles or syringes confiscated or incarceration (Table 6.3b).

Injecting risk behaviours associated with opiate-opioid poly-injection

In univariate comparisons, opiate-opioid poly-injection was associated with several injecting risk behaviours compared to exclusive opiate injectors; associations that remained statistically significant after adjusting for age, sex, education, living arrangements, main income, needle and syringe programme, drug treatment and injecting frequency in multivariate regression (Table 6.3d).

Opiate-opioid poly-injectors were younger when they started injecting (mean: 17.9 years, SD: 3.4) than exclusive opiate injectors (mean: 19.3 years, SD: 3.0; $p<0.001$). In multivariate analysis, opiate-opioid poly-injectors were more likely to have injected more frequently in the last 4 weeks (aOR=2.1; 95%CI: 1.5-2.6) and to have injected more intensely on the last day injected (aOR=2.0; 95%CI: 1.2-3.4) compared to exclusive opiate injectors. The high injecting frequency and intensity among opiate-opioid poly-

injectors and higher odds of having under 50% clean needles and syringes for their injections compared to opiate-single injectors, suggested a high probability of re-use of needles and syringes. No differences were found between groups in sharing or lending of needles and syringes, sharing of drug paraphernalia or duration of injecting.

Sexual risk behaviours associated with opiate-opioid poly-injection

Several sexual risk behaviours were also associated with opiate-opioid poly-injection in St Petersburg in unadjusted analysis, most of which remained after adjustment for demographic and contextual variables (Table 6.3d). Opiate-opioid poly-injectors had lower odds of reporting sex with a regular partner, sex with casual sex partners or having ever been paid for sex, compared to opiate-single injectors. However, opiate-opioid poly-injectors had greater odds of reporting a regular sex partner who injected drugs, casual sex partner(s) who injected drugs, multiple sex partners and past month unprotected sex.

In multivariate analysis, the odds of opiate-opioid poly-injection in St Petersburg remained positively associated with having casual sex partners in the last 6 months (aOR=1.5; 95%CI: 1.1-2.0), multiple sex partners (aOR=1.4; 95%CI: 1.1-1.8) a regular sex partner who injected drugs (aOR=3.0; 95%CI: 1.9-4.8), casual sex partner who injected (aOR=2.1; 95%CI: 1.3-3.6) and positively but not significantly with, unprotected sex (aOR=1.4 ; 95%CI:1.0-2.4), suggesting important overlaps between injecting and sexual risks. No other differences were found after adjusting for other factors.

HIV status did not differ between opiate-opioid poly-injectors and exclusive opiate injectors, in multivariate analysis.

Box 6.3: Summary results for opiate-opioid poly-injectors in St Petersburg

Opiate-opioid poly-injectors were younger, less likely to have completed secondary or higher education, more likely to rely an illicit source of income and generally started injecting earlier than exclusive opiate injectors.

Opiate-opioid poly-injection was associated with frequent and more intense injecting, than exclusive opiate injection. Opiate-opioid poly-injection was negatively associated with contact with an NSP and positively associated with having less than half of clean syringes required for all injections. Opiate-opioid poly-injection was also positively associated with having a regular sex partner and casual sex partners who injected drugs, as well as with multiple sex partners. HIV status did not differ between the two groups.

Table 6.4 Summary of associations for "opiate-stimulant" and "opiate-opioid" poly-injection compared to opiate-single injection

Opiate-stimulant poly-injecting *Kohtla-Järve*	**Opiate-opioid poly-injection** *St Petersburg*
-	↑ < 30 years old
↑ female	-
↑ secondary education	↓ secondary education
↑ non-ethnic Russian	-
-	↑ irregular/illicit income source
↓ needles and syringes confiscated	↓ Contact with NSP
↓ frequency of injecting (daily or more)	↑ frequency of injecting (daily or more)
-	↑ intensity of injecting (> 2 times last day injected
↑ sharing injecting equipment,	-
↑ filled from working syringe	-
↑ multiple sex partners	↑ multiple sex partners
-	↑ casual sex partner
-	↑ regular sex partner injects
	↑ casual sex partner injects

Note: "↑,↓" indicate statistically significant positive and negative associations. NSP=needle and syringe programme.

6.3.4 Comparison of ATS poly-injectors and ATS-single injectors

The results are presented for ATS injectors in Kohtla-Järve. Results for St Petersburg (n=27) are not discussed due to a sample size too small to yield adequate statistical power; exploratory results are shown for completeness in appendix 6 (Table S6.3f to S6.3j).

Kohtla-Jarve

HIV related risk was compared among ATS poly-injectors (n=112) and ATS-single injectors (n=83) in Kohtla-Järve (shown in appendix Table S6.3f).

Socio-demographic, HIV programme and contextual factors

Fewer ATS poly-injectors in Kohtla-Järve reported a non-regular main source of income than ATS-single injectors in univariate analysis (OR=0.5; 95%CI: 0.3-0.8) but the two groups did not differ on other demographic characteristics (Table S6.3f).

After adjusting for demographic factors, ATS poly-injectors had higher odds of contact with a needle and syringe programme (aOR=2.1; 95%CI: 1.1-3.8) and lower odds of sourcing clean syringes from sources other than an NSP (aOR=0.5; 95%CI: 0.2-0.9) or of having needles or syringes confiscated by the police (aOR= 0.2; 95%CI: 0.1-0.5) compared to exclusive ATS injectors. Both groups reported similarly low levels of lifetime and past 12 months drug and drug substitution treatment (Table S6.3g).

Injecting and sexual risk behaviours among ATS poly- and ATS-single injectors

Few differences in injecting risk behaviours were found between ATS poly-injectors and ATS-single injectors in univariate analysis. The overall levels of sharing needles and

syringes and drug paraphernalia were generally low in Kohtla-Järve and did not differ between ATS sub-groups. The high proportion of non-injection polydrug use among ATS injectors in this city may partly explain why injecting risk did not differ between the two groups

Similar proportions of ATS poly-injectors and exclusive ATS injectors reported a regular partner who also injected drugs (45.2% vs. 52.6%, p=0.383), casual partner who also injected drugs (42.9% vs. 51.7%, p=0.536) and multiple sex partners (32.8% vs. 30.2%, p=0.731) (Table S6.3i, j). In multivariate analysis, ATS poly-injectors were more likely to report ever being paid for sex (aOR=2.6; 95%CI: 1.3-5.1) and to report consistent condom use with a casual partner (aOR=4.8; 95%CI: 1.5-15.1) compared to ATS-single injectors (Table S6.3i, j). The frequency of unprotected sex in the last 4 weeks did not differ between ATS-poly and ATS-single injectors.

After adjusting for socio-demographic and contextual variables, and injecting frequency, no differences were found in HIV, HSV or HCV status between the two ATS injector groups in Kohtla-Järve (Table S6.3h).

Box 6.4: Summary results for ATS-stimulant poly-injectors in Kohtla-Järve

ATS poly-injectors were more likely to have a regular source of income than exclusive ATS injectors. ATS poly-injectors were more likely to have been in contact with a needle and syringe programme and less likely to have obtained clean needles and syringes from sources other than an NSP and to have had needles or syringes confiscated by the police compared to ATS-single injectors (Table 6.5).

ATS poly-injectors were also more likely to report ever being paid for sex and to report consistent condom use with a casual partner than exclusive ATS injectors. HIV, HCV and HSV status did not differ between the two groups.

Table 6.5: Associations between ATS-stimulant poly-injection and ATS-single injection

ATS-stimulant poly-injection vs. ATS-single injection
↑ Regular source of income ↑ Contact with NSP ↓ Obtained clean needles/syringes from other sources ↓ Had needles or syringes confiscated by the police ↑ Kohtla-Järve
↑ Ever been paid for sex ↑ Consistent condom use with a casual partner

Note: "↑ and ↓" indicate statistically significant positive and negative. NSP= needle and syringe programme

6.4 Discussion

Polydrug use was frequent in both cities but differed in the drug combinations used, their route of administration and their associated HIV and HCV risk behaviours.

In Kohtla-Järve, most poly-injectors also injected or used other stimulants while poly-injectors in St Petersburg mostly co-injected other opiates. The majority of polydrug users were *non-injected polydrug users* in Kohtla-Järve, a practice associated with ATS injection.

In both cities opiate poly-injection was associated with unsafe injecting and sexual risk behaviours, placing opiate-stimulant poly-injectors in Kohtla-Järve and opiate-opioid poly-injectors in St Petersburg at higher risk of HIV and HCV infection, compared to exclusive opiate injectors. This first study to have analysed sub-groups of poly-injectors by drug class combinations, was able to clearly show that HIV risk behaviours associated with opiate-stimulant poly-injection (in Kohtla-Järve) and opiate-opioid poly-injection (in St Petersburg) differed from those of exclusive opiate injectors. These findings suggested distinct types of polydrug use, and consequently of exposure to HIV and HCV infection.

Opiate-stimulant poly-injection and associated HIV risk behaviours in Kohtla-Järve

Opiate-stimulant poly-injectors reported unexpectedly risky sharing practices in a setting where needle and syringe services had become widely available and where 90% of all opiate injectors reported having been in contact with needle and syringe services in the last 4 weeks. Opiate-stimulant poly-injectors injected less frequently than exclusive opiate injectors but with similar intensity on the days they injected. When they injected, they engaged in riskier injecting practices such as sharing needles/syringes or paraphernalia, filling a syringe from a working syringe (back-loading) and having multiple sex partners.

That *opiate-stimulant poly-injectors* reported injecting less often and as intensely as opiate-single injectors was consistent with the use of meth/amphetamine-type stimulants (M/ATS) [306]. The effects of M/ATS can last several hours which may explain that intensity of injecting did not differ between opiate-stimulant injectors and exclusive opiate injectors.

Furthermore, stimulants such as M/ATS are known to reduce inhibitions, affect cognition and increase sexual desire. They can also impair cognitive function, decision-making and judgment, which in social settings or in the context of intimate partnerships, may compromise the use of clean needles, syringes or injection equipment, especially when combined with addictive opiates [126, 306, 318, 319]. The high proportion of women

opiate-stimulant poly-injectors in Kohtla-Järve may account for greater vulnerability and sharing risks as studies have found women were more likely to share injecting equipment with sex partners [199, 313]. The unpredictability of stimulant- compared to heroin injection may also contribute to increased sharing of injection equipment among cocaine injectors: *The consistent daily use of heroin lends itself more than cocaine to regular injection practices, including a more predictable source of drugs and a more orderly preparation of injection paraphernalia"* [142].

Findings among *opiate-stimulant poly-injectors* were consistent with those of studies in the United States, Australia and the United Kingdom where stimulant injection among PWID who injected heroin was found to be a predictor of injecting risk, suggesting that different risks resulted from the drug combination than from stimulants alone [17, 91, 149]. PWID injecting stimulants (ATS, cocaine) and heroin were more likely to have shared needles and syringes than exclusive heroin injectors [17, 68, 127, 145, 231, 260] while PWID injecting cocaine and heroin were more likely to back-load [101, 131, 151, 243]. Several studies among heroin injectors have also found that cocaine was associated with multiple sex partners when compared to not injecting cocaine [101, 259].

The risks associated with *opiate-stimulant poly-injection* suggest an urgent need for risk reduction messages targeting these poly-injectors to emphasize the transmission risks of blood-borne infections (HIV and HCV) associated with sharing drug paraphernalia and back-loading syringes, as well as those from multiple sex partners and unprotected sex.

Opiate-opioid poly-injection and associated HIV risks in St Petersburg

Opiate-opioid poly-injection was also associated with greater injecting and sexual risk behaviours in St Petersburg but contrasted with those found among opiate-stimulant poly-injectors (in Kohtla-Järve). *Opiate-opioid poly-injectors* were younger than exclusive opiate injectors, less likely to have completed secondary or higher education, more likely to rely on an illicit source of income and had started injecting earlier.

Opiate-opioid poly-injectors injected more frequently and more intensely; they were also more likely to report multiple sex partners and to have sex partners who also injected drugs, compared to exclusive opiate injectors. This overlap of injecting and sexual risks suggest potential for multiple exposures to and transmission of, HIV and HCV infections within PWID.

The *opiate-opioid* drug combination and its association with frequent and intense injecting, suggested a substitution pattern where injectors resorted to another drug of the

same class to replace a preferred opiate (i.e. heroin) when it was not available or too costly [13, 100, 113]. Opiate-opioid combinations have been reported in east and central Asia, among PWID who injected street methadone, buprenorphine preparations or other lower potency opioids (e.g. methadone, dextro-propoxyphene, nalbuphine, codeine) as substitute for heroin when it was unavailable or unaffordable, or to manage withdrawal symptoms [12, 13, 78, 119, 123, 320]. Injection of synthetic opioids by PWID in Pakistan (e.g. dextro-propoxyphene) was associated with their lower cost and wider availability [153]. My findings are also consistent with other reports of greater injecting frequency among PWID injecting heroin with lower potency opioids and highlight the potential for elevated viral transmission of HIV and HCV from frequent and repeated exposure to contaminated injecting equipment in this group of injectors [78, 115, 321]. Poly-injecting opiates and temazepam (benzodiazepines) was also associated with sexual risk behaviours in early studies of PWID in the United Kingdom [152] [91].

It was striking that *opiate-opioid poly-injectors* had even less contact with NSPs, than exclusive opiate injectors in a setting where harm reduction coverage was already low and they were more likely to obtain supplies of clean needle and syringes from private pharmacies than from an NSP. Opiate-opioid poly-injectors were more likely to have only had clean needles and syringes for half of their injections. Given their frequent and intense injecting, there is an urgent need to reach PWID with adequate supplies of sterile needles and syringes and risk reduction messages on HIV and HCV transmission.

Although HIV prevalence did not differ significantly between opiate-opioid poly-injectors and exclusive opiate injectors, new HIV, and possibly HCV, infections resulting from higher injecting and sexual risks could be high in this group of young poly-injectors. Whether this is the case, may be determined through incidence studies.

ATS poly-injecting and HIV-related risk behaviours in Kohtla-Järve

ATS poly-injectors seemed homogeneous, with few differences between ATS poly-injectors and exclusive ATS injectors. ATS poly-injectors in Kohtla-Järve were more likely to engage in *non-injected polydrug use* and used other stimulants such as ecstasy and ATS, associated with nightlife, and dance and entertainment venues, a finding consistent with other studies among stimulant injectors [68, 96, 146].

Programme and policy implications - Why is polydrug use an issue?

The results of this study suggested important sources of heterogeneity in HIV and HCV infection risk among PWID, which could be used by programmes to differentiate and

target services to engage harder-to-reach PWID sub-groups where HIV risk behaviours are highest and engagement with services may be low [322]. Illicit drugs, their combinations, preparation methods and injection practices are central to the lives of PWID and may be elicited by trained and trusted outreach staff close to, and known by, PWID. Better monitoring drug and polydrug use practices may provide programmes with context-specific and timely information to adapt prevention and treatment interventions to changing needs and risks.

Lower engagement of poly-injectors with prevention programmes

Opiate-opioid poly-injectors in St Petersburg were less likely to have been in contact with an NSP and more likely to have obtained clean needles and syringes from a pharmacy, a result consistent with findings from Tallinn in Estonia, where drug users obtaining needles and syringes from pharmacies were more likely to be younger, at earlier stages of their injecting careers, thus not fitting the profile of an "addict" [323]. Drug use is a stigmatised behaviour and needle and syringe services may be associated with drug dependence, addiction and entrenched drug use; young PWID who do not fit the drug user "profile" and do not perceive themselves to be at risk of dependence or of acquiring blood-borne infections may therefore not engage easily with NSPs. In such settings reaching young poly-injectors may require alternative ways of providing access to clean supplies and prevention through low-threshold services or pharmacies [207, 272, 324, 325].

Multiple and overlapping risks

Poly-injector sub-groups had remarkably high injecting and sexual risk behaviours compared to exclusive opiate injectors, suggesting critical overlaps of behavioural risks and potential for HIV transmission. Delivering harm reduction services in often less than favourable, and sometimes hostile, environments may lead prevention to focus exclusively on reducing unsafe injecting practices. In this respect, NSPs and outreach services need to provide more specific information and in various forms (or media) on the risks of sharing or re-using injecting paraphernalia and back-loading syringes. More emphasis also needs to be placed on reducing sexual risk among PWID, especially in settings where stimulants such as ATS or cocaine are used, and on engaging women who inject drugs [90, 199]. Women who inject drugs have been found more likely to have a heterosexual partner who injects and to share injection equipment with an intimate partner [199].

Future research

Distinct types of polydrug use emerged from the stratification by main drug class and the specific behavioural risks associated with polydrug patterns in each setting were corroborated by findings from the literature. Further investigation would therefore help determine whether i) opiate-stimulant and opiate-opioid polydrug patterns, drug class combinations and their associated risks would apply in different settings, ii) to what extent they are generalizable and iii) how they vary over time during the life course of drug use. This generic polydrug use typology could be tested in cross-sectional studies to assess its relevance in different settings, while the validity of such a typology over time could be tested in longitudinal studies.

Strengths and limitations

Several strengths and limitations are acknowledged. The RDS surveys were conducted using comparable study methods, tools and eligibility criteria which allowed comparisons. However, the findings may not be generalizable to other PWID populations. The RDS methods used showed a satisfactory recruitment as shown in key diagnostic measures recommended in the RDS-STROBE guidelines and presented in Table 4.2 (details in Appendix 4) [293, 326]. The biases inherent to PWID self-reports and particular limitations of this study were detailed in previous chapters; they also apply to this analysis and are acknowledged [112, 310, 327-331].

As a chain referral sampling method, RDS has shown to be one of the most effective methods of recruiting "less visible" sub-groups within key populations at risk of HIV infection [332]. In both settings, RDS methods were effective in recruiting PWID sub-groups who had not been in contact with NSP or drug treatment programmes (i.e. opiate-opioid poly-injectors).

The response rate on variables of interest was satisfactory in St Petersburg but low on two sexual risk variables in Kohtla-Järve; this precluded the analysis of associations between unprotected sex and primary drug or polydrug use for example. Missing responses on variables examined were distributed randomly across demographic and drug use groups (i.e. ATS-injectors and opiate-injectors or poly-injectors and single drug injectors) but the proportion of missing data on some sexual risk variables in particular was too large (50-55%) to justify using imputation methods. This limitation highlights the challenges associated with surveying sexual risk behaviours in an already stigmatised population;

challenges that may be overlooked in the process of administering difficult and sensitive questions in this population group.

All respondents reported injecting drugs in the past month and polydrug use was defined as injecting or using additional drug(s), in addition to a primary drug in the same period. There could have been an attenuation of effect on the odds ratio due to the fact that poly-injectors included PWID who injected or used an additional (non-injection) drug in addition to the main injection drug.

A strength of this study was the use of surveys from two distinct settings to examine associations between polydrug use and HIV risk behaviours among PWID, by primary drug injected. This was the first analysis to take into account the main drug injected by polydrug users and to adjust for other factors, thus accounting for potential effects of a main drug. By investigating polydrug use separately in different primary drug groups and in two locations, the study separated the effects of distinct drug combinations or polydrug "sub-types", each associated with different behavioural risks. The sample size for these IBBS surveys was determined by the power required to detect a percentage change in HIV prevalence and was not originally designed to analyses small sub-groups. Polydrug sub-groups were defined a priori and analyses guided by my conceptual framework to reduce problems of multiple testing however an inevitable drawback of my approach was the reduction in sample size (and reduced statistical power) for certain subgroups [314, 333].

The eligibility criteria for the recruitment of PWID ensured recent drug injection and allowed comparability between sites and with other PWID surveys. The consistent timeframe of 4 weeks used to measure polydrug use and injecting risk behaviours in this study, provided more confidence in the associations reported between poly-injection and risk behaviours among PWID within the same period. However, drug questions in the survey did not provide a way of differentiating between simultaneous or sequential co-use of drugs, making it difficult to fully ascertain patterns and possible interactions between them.

Finally, this chapter used a previously unused approach to examine associations between polydrug use and injecting and sexual risk behaviours, and HIV status among PWID, after stratifying by primary drug. In doing so, it revealed significant differences in demographic profile, risk behaviours and contact with services between opiate poly-injectors and exclusive opiate injectors in both cities. The next and final chapter will use a different method to examine the same questions among PWID in Kohtla-Järve and St Petersburg and then compare the results obtained in each chapter.

Chapter 7

Polydrug use and HIV risk heterogeneity among people who inject drugs: a latent class analysis

Chapter 7 Polydrug use and HIV risk heterogeneity among people who inject drugs: a latent class analysis

7.1 Background

Few epidemiological studies of drug use and HIV risk among people who inject drugs (PWID) have taken into account the multidimensional nature of polydrug use, frequently only reported as *"using any two or more drug(s)"* [97, 109, 151, 152, 231]. In reality, different factors and motivations can lead to diverse combinations of drugs and distinct polydrug use patterns among PWID. Drug combinations may be influenced by: i) preference for specific pharmacological effects, ii) desire to experiment, iii) need to replace the use of one drug with another due to availability or cost of drugs at different times, and/or iv) to seek stronger effects from drugs as tolerance increases [2, 102, 113, 224].

Dichotomous characterisations of polydrug use therefore provide a first step in the study of polydrug use and HIV risk and risk behaviours but they may overlook important sources of heterogeneity among drug-using populations, which could usefully inform prevention and treatment programmes. Detailed characterisations of substances users have been developed in drug research studies in the United States and Canada to identify distinct patterns of substance use among young people, and types of polydrug use based on the substances used and their dependence on them [224, 334-336]. These studies found diverse forms of polydrug use, defined by a single drug, combination of drugs, routes of administration and levels of use, where the substances and administration route differed according to the population and context. However, few of these studies examined the relationship between polydrug use and HIV risk behaviours among PWID and none outside North America [17, 18, 337].

Elaborating on conventional dichotomous definitions of polydrug use by stratifying PWID by primary drug *and* polydrug use in the previous chapter, provided insights into injecting and sexual risk behaviours (and demographic profiles) associated with certain drug combinations used in Estonia and Russia. Based on comparisons using a-priori defined poly- and single drug injectors, I found that opiate-stimulant poly-injectors in Kohtla-Järve were more likely to share injection equipment and to back-load[16], compared to their single drug-injecting peers. Opiate-opioid poly-injection in St Petersburg by contrast was associated with injecting more frequently and more intensely, compared to exclusive

[16] to fill a syringe from a working syringe.

opiate injection. In both settings, opiate poly-injection was associated with multiple sex partners, compared to exclusive opiate injection. Primary ATS injectors were more homogeneous and only differed in that ATS-stimulant poly-injectors had greater odds of ever being paid for sex and having been in contact with a Needle and Syringe Programme (NSP) than exclusive ATS injectors.

This sub-group approach was useful in identifying i) generic drug class combinations and ii) differences between them in terms of behavioural risk and PWID demographic profile. Nonetheless, improving characterisations of polydrug use in populations where this practice has not been examined, yet is common, could deepen our understanding of diversity in drug and HIV-related risks associated with certain combinations of drugs. Ascertaining important polydrug sub-types or classes in particular, could contribute to understanding and identifying markers of HIV risk within heterogeneous PWID groups. In this way, different sub-groups of active drug users could be identified and targeted with suitable prevention and treatment services at the right time, to reduce harms, HIV risk and improve treatment outcomes [47].

Latent class analysis (LCA) is a statistical method that has typically been used to empirically identify distinct patterns and groups of individuals (i.e. classes) based on a set of observed characteristics [338-340]. Similar methods include factor analysis for continuous variables and cluster analysis, largely used as an exploratory method. Two LCA studies recently extended the use of LCA in the United States and Canada to uncover context-specific sub-types of PWID among people who injected opioid, cocaine and meth/amphetamine drugs to explore associations between HIV risk and polydrug sub-types [17, 18, 337]. Although these findings shed some light on patterns of polydrug use and risk in the US and Canada, their results may not be generalizable to other settings. This could be true, especially where ATS drugs (and not cocaine) or ATS combinations are injected or where illicit injected methadone is increasingly used.

To my knowledge, no study to date has either characterised polydrug use practices in Estonia or in Russia, where drug use is a major contributor to the HIV and HCV epidemics, examined the HIV risk associated with polydrug use in these settings, or identified generic classes of polydrug use. My objective in this last chapter was twofold: i) first to empirically identify classes of polydrug use in St Petersburg and Kohtla-Järve and propose a context-relevant taxonomy based on drug class and administration route using latent class analysis, and ii) second to compare HIV risk behaviours associated with different polydrug classes.

7.2 Methods

Study population and statistical analyses

The PWID population sample in this new analysis is the same as the sample described in chapter 4 and analysed in chapter 5 to 6. In a first stage, latent class analysis (LCA) was used to identify PWID subgroups (i.e. classes), based on specific drug classes and their administration route [341]. The primary goal of latent class models (LCM) is to divide a heterogeneous population into more homogenous subgroups or latent classes, by grouping observations that display similarity in response patterns on a defined set of observed variables [342]. In my study, the variables of interest were related to drug use.

In the second stage of analysis, associations between latent class and socio-demographic, HIV programmes, and injecting and sexual behaviours were examined, using univariate and multivariable multinomial logistic regression.

Observed variables selected for latent class analysis

The seven observed drug use variables[17] used in this analysis are shown in Figure 7.1. Five dichotomous and two ordinal variables described characteristics of polydrug use in the past month. They included the main drug injected, injection of additional opiate/opioid, injection of additional stimulant, use of additional opiate/opioid, use of additional stimulant, number of drugs injected and number of non-injection drugs used. These observed variables were selected to capture the possible drug class combinations identified in previous chapters, their administration route(s) and range of drugs injected and used. The assumption of conditional independence was ascertained by examining bivariate residuals for each set of variables in latent class analysis. All observed variables described drug use behaviours in the last month, with a minimum of 20% prevalence for the latent class analysis [224, 343]. The observed drug use variables were entered into a latent class model which was fitted to the data, starting with one class and increasing the number of classes progressively. Models were estimated using maximum likelihood with a minimum of 400 random starts to ensure that global maxima solutions were reached [344].

The two city samples were combined in this analysis based on i) similarities in primary drugs injected and frequency of polydrug use, and on ii) my stated objective of developing a taxonomy that could be applied across settings. However, to take into

[17] The term "observed variable" was used to differentiate variables directly reported in the study from the latent variable(s) generated in latent class analysis.

account potential unobserved differences between the two samples, a dummy variable for city was included in the model as a covariate. That is, city effects were adjusted for, but city was not included alongside the seven observed variables forming the latent classes.

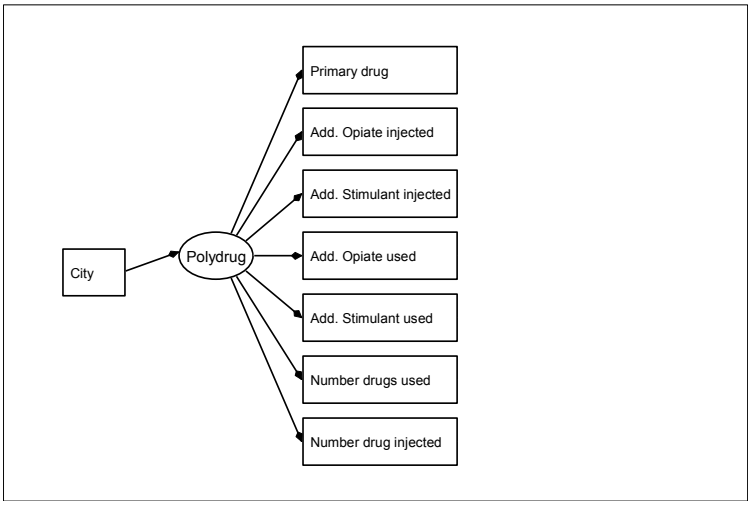


Figure 7.1: Schematic representation of latent and observed variables used in Latent class analysis
Note Figure 7.1: The oval indicates a latent variable (polydrug use) and the rectangles show the observed variables. Add. = additional.

Part 1) Determining the number of classes

The optimal number of latent classes was determined by comparing fit statistics for models with 2, 3, 4, 5 and 6 classes. The most parsimonious model was selected by considering several fit statistics including the Pearson's chi-squared and Log likelihood ratio tests (LR), Lo-Mendell Rubin likelihood ratio test for nested models (LRMT) and the Akaike (AIC) and Bayesian information criteria (BIC). A non-significant value for the LMRT suggested that the model with one fewer class better explained the data and a smaller AIC and BIC indicated a better model fit [339, 342, 345, 346].

The usefulness and value of the resulting classes were also examined using the entropy statistic with preference for values closest to +1 indicating greater entropy [342, 345]. Entropy provides a descriptive measure of the degree to which latent classes are distinct from each other, by estimating individual conditional probabilities[18] of class membership to assess the precision of class assignment. Individuals within a given class or sub-type were considered homogenous when they had similar item responses and when class-specific response probabilities for binary indicators for example were above 0.70 or below 0.30 [345]. A complete case analysis was used and observations with missing data was

[18] i.e. the probability that an individual is a polydrug user, conditional on their answer "yes" to a specific drug question. What is the probability that they are polydrug user?

disregarded (n=10). Bivariate residuals were also examined to test the assumption of conditional independence in LCA. The final selection of latent class model was also informed by current epidemiology of drug use, meaningfulness and practical implications. All latent class analyses were run using Mplus version 7.4 [344].

Part 2) Statistical analysis comparing risk across classes (models and diagnostics)

Socio-demographic, service, programme and risk behaviour variables were compared between emergent sub-types of the best fit latent class model, using chi-square tests for categorical variables. Multinomial logistic regression was then used to model class membership as the categorical outcome variable, modelling the log odds of each polydrug class as a linear combination of the predictor variables detailed below. Multinomial logistic regression is an extension of logistic regression (described in chapter 4 methods) to outcomes with more than two categories. The latent class with the largest membership was used as the referent category in order to maximise statistical power.

The variables examined for associations with the polydrug classes derived from the LCM were described in chapter 4, and were used in chapters 5 and 6 (Table 4.1). They included demographic and contextual variables such as age, sex (female/ male), ethnicity (non-Russian/ethnic Russian), living arrangements (unstable/ stable), main source of income (non-regular/salaried), contact with needle and syringe programme (yes/no), past year drug substitution treatment (yes/no) and City (Kohtla-Järve/St Petersburg), as well as injecting and sexual risk behaviours: sharing needles and syringes (yes/no), sharing drug paraphernalia (yes/no), filling a syringe from another working syringe (i.e. back-loaded yes/no), multiple sex partners (yes/no), ever paid for sex (yes/no), HIV positive status (yes/no), Hepatitis C reactive status (yes/no) and HSV positive test (yes/no) (Table 7.3). The potential correlation of observations within the recruitment chains of the Respondent Driven Sampling (RDS) was accounted for by clustering the standard errors within each recruitment seed [286]. Univariate analyses and multinomial logistic regression were performed using robust variance estimation to take into account the survey design and clustering of observations by seed, using the "svy" command in Stata version 13.1 [290]. As in the previous chapters, RDS weights were not used as sampling on background (exogenous) characteristics (not outcome variables) was not expected to influence regression results and RDS weights did not appear to influence weighted estimates when compared to unweighted estimates (chapter 4) [298, 347].

7.3 Results

The study included 1402 active PWID who had injected drugs in the previous 4 weeks, were 18 years or older and lived in St Petersburg (n=811) or Kohtla-Järve (n=591). The detailed characteristics of the study samples were previously described in chapters 5.

7.3.1 Latent class analysis and polydrug use class membership

Latent class models with 2, 3, 4, 5 and 6 classes were fit to the data and fit statistics compared (Table 7.1). Based on the different model fit indices and entropy, the five-class model was selected. Although AIC and BIC statistics were marginally lower for model 6, the Pearson's Chi-squared and Likelihood ratio tests suggested a better fit for model 5. Class assignments examined in the 5-class and 6-class model, were similar and two very small classes (not shown) in model 6 limited its relevance, interpretation and subsequent analyses. For these reasons, the 5-class model was preferred.

Table 7.1: Fit statistics for a latent class analysis of seven variables among people who inject drugs

Fit statistic	C2 Model (2 classes)	C3 Model (3 classes)	C4 Model (4 classes)	C5 Model (5 classes)	C6 Model (6 classes)
AIC	8413.9	7100.3	6388.1	6163.6	6035.8
BIC	8581.8	7357.3	6734.4	6598.9	6560.2
Pearson's X^2	<0.0001	<0.0001	<0.0001	<0.0001	0.0497
LR test X^2	<0.0001	<0.0001	<0.0001	<0.0001	0.8714
LMRT	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
LL	-4174.9	-3501.1	-3128.1	-2998.8	-2917.8
Entropy	1.000	0.998	1.000	1.000	1.000

Note Table 7.1: Latent class model with binary, categorical, nominal variables, no thresholds. Model set and replicated at 400 random starts. CZ= Z-class model. AIC= Akaike information criteria. BIC= and Bayesian information criteria. Test p-values shown for Pearson's X2, Likelihood ratio (LR) and Lo-Mandell-Rubin (LMRT) which compares current n class to n-1 class model. LL=Log Likelihood. LL was not replicated in 6- class model.

The largest class (Class 5) included 56% (n=790) of all PWID and the sizes of the four remaining classes were more similar (Table 7.2). The conditional (or posterior) probabilities of endorsing a drug indicator for an individual belonging to their most likely class in the five-class model are shown in Table 7.2.

Most class-specific response probabilities for binary indicators were above 0.70 or below 0.30, suggesting similarity in item responses for individuals in the same class and therefore homogeneity within classes. Figure 7.2 summarises the drug use characteristics of each class for the 5-class LCA model, showing qualitatively different primary and additional drug class combinations.

Table 7.2: Conditional probabilities of drug use characteristics by class membership (5-class model)

Latent Class model	**Class1:** Polydrug poly-route injection % (n)		**Class 2:** Opiate-stimulant poly-injection % (n)		**Class 3:** Non-injection stimulant co-use % (n)		**Class 4:** Opiate-opioid poly-injection % (n)		**Class 5:** Single drug injection % (n)		*All classes (%, n)*	
Class probabilities (1)	8.8%	124	6.9%	97	12.5%	174	15.5%	217	56.3%	790		
Primary drug injected												
Primarily injected opiates (2)	68.3%	69	95.8%	91	58.4%	102	93.9%	201	87.1%	689	*83.7%*	*1152*
Primarily injected ATS	31.7%	33	4.2%	4	41.6%	73	6.1%	13	12.9%	102	*16.2%*	*225*
No primary drug		22		0		0		3		0		*25*
Other drugs and route of administration												
Injected other opiate/opioid(2)	100%	41	53.6%	52	0%	0	100%	217	0%	0	*23.4%*	*310*
Injected other stimulant(s)(3)	100%	107	100.0%	97	0%	0	0%	0	0%	0	*14.7%*	*204*
Other opiate/opioid (non-injection)(4)	100%	52	0%	0	33.9%	59	0%	0	0%	0	*8.4%*	*111*
Other stimulant (non-injection)(4)	100%	104	0%	0	86.8%	151	0%	0	0%	0	*18.5%*	*255*
Number other drug(s) injected												
One	63.7%	79	46.4%	45	0%	0	97.2%	211	0%	0	*23.9%*	*335*
Two	29.8%	37	45.4%	44	0%	0	2.8%	6	0%	0	*6.2%*	*87*
Three	6.5%	8	8.2%	8	0%	0	0%	0	0%	0	*1.1%*	*16*
City *(column totals)*												
St Petersburg	33.9%	42	76.3%	74	8.1%	14	94.5%	205	60.3%	476	*57.8%*	*811*
Kohtla-Järve	66.1%	82	23.7%	23	92.0%	160	5.5%	12	39.8%	314	*42.2%*	*591*

Note Table 7.2: (1) Column totals, (2) Heroin/synthetic heroin; (3) other stimulants were Methamphetamines, ecstasy, cocaine and ketamine. (4) Non-injected use may be smoked, snorted or ingested in tablet or liquid form.

Individuals in Class 1 had 68% probability of injecting an opiate as primary drug and high probabilities of all other polydrug use indicators (i.e. injection and use); this class was referred to as *"polydrug polyroute"*. Class 2 consisted of PWID with high probabilities of i) injecting opiates as primary drug (96%) and ii) injecting additional stimulant(s) (100%), a moderate probability of injecting other opiates (54%) and a null probability of using other drugs; this class was referred to as *"opiate-stimulant poly-injection"*.

Class 3 (*i.e. "non-injected polydrug co-use"*) consisted of PWID with similar probabilities of injecting opiates or ATS as primary drug (58% and 42%, respectively), a high probability of *using* additional stimulants (87%) but low probability of *using* additional opiates (34%) and a null probability of *injecting* another drug.

Class 4 (i.e. "*opiate-opioid poly-injection*") was characterised by a predominance of primary and secondary opiate injecting (94% and 100%, respectively) and a null probability of *using* other drugs. Finally, individuals in Class 5 (i.e. "*single drug injection*") had 87% probability of injecting an opiate as primary drug but null probability on all additional (poly)drug indicators; as they did not engage in any polydrug use.

The distribution of class membership varied across cities with *"polydrug polyroute" (Class 1) and "non-injection polydrug co-use" (Class 3)* injectors having a higher probability of being from Kohtla-Järve and "*opiate-opioid poly-injection" (Class 4),* and to some degree, *"opiate-stimulant poly-injection" (Class 2)* more likely to be from St

Petersburg. Class 5 *(i.e. single drug injection)* had a higher probability of being from St Petersburg (60.3%) than Kohtla-Järve (39.8%).

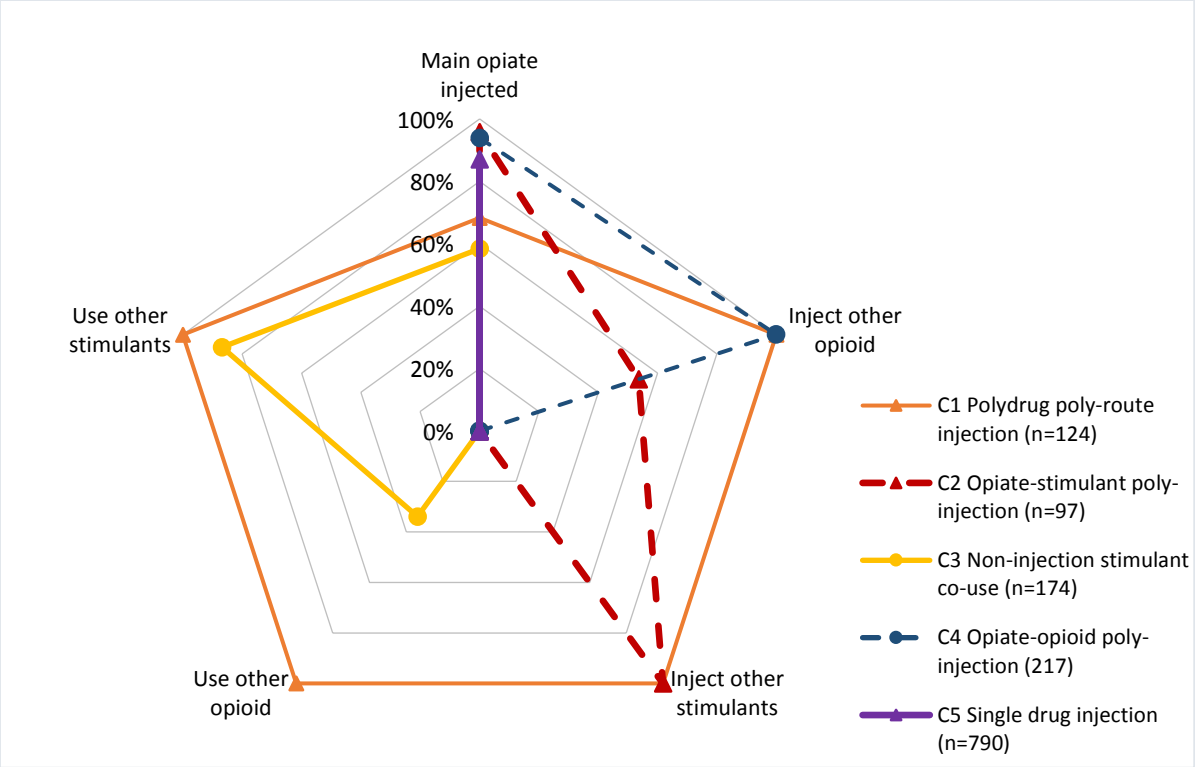


Figure 7.2: Polydrug use profiles for five-class solution of Latent Class Analysis model

Notes Figure 7.2: The estimated probabilities for past month drug use are graphed based on latent class (C1-C5) membership shown in Table 7.2. The main axis (0-100%) shows the *probability of past month use* for each drug variable. For example *opiate-stimulant injectors* (C2 - -) had a high probability of injecting an opiate as main drug (95.8%), medium probability of injecting another opiate (53.6%) and 100% probability of also injecting stimulants. The five binary variables only are shown for clarity. ATS=Amphetamine-Type Stimulant.

7.3.2 Correlates of polydrug class membership

Univariate comparisons between polydrug class and socio-demographic and contextual characteristics, and injecting and sexual behaviours are shown in Table 7.3, which presents chi-squared p-values, and indicates significant Wald p-values for coefficients in multinomial regression (i.e. log odds of each polydrug class). The chi-square p-value provides information on the overall distribution of variables across latent classes whereas the Wald p-value refers to each latent class as compared to the referent class. Multivariate multinomial regression results are shown in Table 7.4. Class 5 (single drug injection) was consistently used as the reference category.

More *polydrug polyroute injectors* (Class 1) were under the age of 30 years (45.2%) and of non-Russian ethnicity (18.6%) and from Kohtla-Järve (66.1%) than exclusive injectors (Class 5), but the groups did not differ on other demographic or contextual characteristics. A high proportion of PWID in Class 1 reported frequent injecting (daily or more in the

last month) (41.9%) and intense injecting of two or more injections daily (61.3%), and having casual sex partners who also injected drugs (62.8%). After adjustment in multivariate analysis[19], *polydrug polyroute injectors* (Class 1) reported significantly greater injecting risks than single drug injectors, but did not differ on sexual risk behaviours or HIV status. *Polydrug polyroute injectors* (Class 1) remained more likely to inject more frequently and more intensely than single drug injectors, and were also more likely to share needles and syringes, to share drug paraphernalia and to back-load.

O*piate-stimulant poly-injectors* (Class 2) and *opiate-opioid poly-injectors* (Class 4) did not differ significantly from single-drug injectors in terms of demographic characteristics in univariate analysis; Most were from St Petersburg (class 2: 76.3% and class 4: 95.5%, respectively) and both classes also reported significantly lower contact with a needle and syringe programme (Class 2: 27.7% and Class 4: 18.5%) and high, though different injecting and sexual risk behaviours.

More *opiate-stimulant poly-injectors* (Class 2) reported frequent injecting (52.6%), high injection intensity (70.1%), sharing (55.2%) or lending (56.7%) needles and syringes and back-loading in the past month (47.4%). More PWID in Class 2 also reported multiple sex partners than other classes except class 4 (Class 2: 54.2%; Class 4: 54.4%). After adjusting for age, sex, education, main income, ethnicity, contact with needle and syringe programme and city, *opiate-stimulant injection* (Class 2) remained positively associated with frequent and intense injecting, sharing needles/syringes, sharing drug paraphernalia and filling a syringe from a pre-filled syringe (back-loading) compared to single drug injection. *Opiate-stimulant injectors* were also more likely to report distributive sharing, any sex in the past 6 months and multiple sex partners than single drug injectors.

In univariate analysis, *opiate-opioid poly-injectors* (class 4) reported the highest levels of sharing of needles and syringes (57.0%) and more sharing of drug paraphernalia (64.1%) than single drug injectors. More PWID in Class 4 than in other classes reported multiple sex partners (54.4%), a regular sex partner who injected drugs (73.3%) or casual sex partners who injected drugs (78.0%). In multivariate analysis, *opiate-opioid poly-injectors (Class 4)* had higher odds of being under 30 years of age, of non-Russian ethnicity and from St Petersburg. *Opiate-opioid poly-injectors* were more likely to report more intense injecting and to have shared needles and syringes, compared to single drug injectors. They remained more likely to report multiple sex partners and to have a regular

[19] Variables adjusted for: age, sex, education, main income, ethnicity, contact with needle and syringe programme and city.

or casual sex partner who injected drugs, suggesting high levels of both injecting and sexual risk in this class.

More *non-injection stimulant co-users (*Class 3) were under the age of 30 years (51.7%), of non-Russian ethnicity (17.2%) and from Kohtla-Järve (92.0%) and fewer reported an irregular source of income (28.5%), compared to single drug injectors. *Non-injection stimulant co-users* generally reported lower injecting risk behaviours than other classes, which may reflect their generally lower injecting risks and those of PWID in the Estonian city. However more PWID in Class 3 had sex in the past 6 months (84.9%) and a high proportion reported a regular partner who injected drugs (56.9%) than single drug injectors. In multivariate analysis, *non-injection stimulant users (Class 3)* were less likely to have completed secondary education, to have a regular income and more likely to be from Kohtla-Järve. Despite seemingly lower injecting risks, class 3 had greater odds of back-loading, compared to single drug injectors, and they were more likely to have had any sex in the last 6 months.

Despite several differences found between polydrug classes in injecting and sexual risk behaviours, no statistically significant differences were found in the prevalence of HIV or HCV when polydrug classes were compared to single drug injectors

Table 7.3: Univariate comparison of socio-demographics, service characteristics and HIV risk behaviours in five-class model (cities combined)

	All PWID (n=1402) [1]		**Class 1** Polydrug poly-route injection n=124		**Class 2** Opiate-stimulant poly-injection n=97		**Class 3** Non-injection stimulant co-use n=174		**Class 4** Opiate-opioid poly-injection n=217		**Class 5** Single drug injection (ref.) n=790		**Pearson X^2 [2] p-value**
Demographic characteristics													
Female gender	23.9%	335	28.2%	35	22.7%	22	31.2%	54	20.7%	45	22.7%	179	0.082
Age < 30	38.2%	535	45.2%*	56	41.2%	40	51.7%***	90	35.5%	77	34.4%	272	0.000
Completed 2ndary school	25.6%	359	27.4%	34	25.8%	25	24.7%*	43	21.7%	47	26.6%	210	0.013
Completed higher education	6.9%	96	3.2%	4	6.2%	6	1.2%	2	10.6%	23	7.7%	61	
Non-Russian	10.4%	145	18.6%**	23	5.2%	5	17.2%*	30	6.5%	14	9.3%	73	0.000
Non-regular income†	47.1%	657	48.0%	59	46.4%	45	28.5%***	49	48.4%	105	50.8%	399	0.000
City (Kohtla-Järve)	42.2%	591	66.1%	82	23.7%	23	92.0%	160	5.5%	12	39.8%	314	0.000
Service characteristics													
Drug/substitution treatment	11.5%	161	4.8%	6	10.3%	10	14.9%	26	11.5%	25	11.9%	94	0.103
Contact with NSP	43.3%	570	53.5%	62	27.7%**	26	77.2%***	125	18.5%***	40	43.5%	317	0.000
Injecting risk behaviours													
Injecting < 5 years	6.9%	96	10.5%**	13	4.1%	4	13.8%**	24	2.3%	5	6.3%	50	0.000
Injecting daily or more	30.5%	427	41.9%	51	52.6%**	51	19.5%*	34	37.3%**	81	26.5%	209	0.000
Injected ≥ twice a day	45.9%	642	61.3%**	76	70.1%***	68	42.5%	74	49.5%*	107	40.2%	317	0.000
Shared needles/syringes	36.1%	502	31.2%	38	55.2%***	53	11.0%***	19	57.0%**	122	34.4%	270	0.000
Lent needles/syringes	37.3%	520	31.7%	39	56.7%**	55	14.5%***	25	52.8%**	114	36.5%	287	0.000
Shared drug paraphernalia	42.4%	594	34.7%	43	57.7%*	56	15.5%***	27	64.1%**	139	41.7%	329	0.000
Filled from working syringe	33.0%	462	33.1%	41	47.4%*	46	13.2%***	23	39.6%	86	33.8%	266	0.000
Sexual risk behaviours													
Any sex in last 6 months	78.1%	1092	80.7%	100	86.6%*	84	84.9%**	146	73.7%	160	76.4%	602	0.011
≥ 2 sex partners	42.7%	447	41.9%	36	54.2%**	45	32.1%*	43	54.4%***	87	40.5%	236	0.000
Regular sex partner injects	56.2%	438	60.0%	42	67.4%	33	56.9%*	70	73.3%***	63	50.9%	230	0.001
Casual sex partner injects	58.0%	218	62.8%	27	65.9%	27	52.2%	24	78.0%***	46	50.3%	94	0.003
Ever paid for sex	5.4%	54	8.5%	8	3.9%	3	5.6%	8	2.3%	3	5.7%	32	0.319
Serological markers‡													
HIV test positive	58.4%	818	53.2%	66	60.8%	59	60.3%	105	58.5%	127	58.4%	461	0.759
HCV reactive	74.4%	441	72.0%	59	65.2%	15	72.5%	116	75.0%	9	77.1%	242	0.599
HSV positive	32.1%	185	30.8%	24	39.1%	9	27.4%	43	50.0%	6	33.7%	103	0.368

Notes: [1] Column percentage (using chapter 6 categories). [2] Pearson chi-squared test and *unadjusted multinomial regression coefficient p-values (*≤0.05, **≤0.01, ***≤0.001). Reference category=Class 5. †main Income and education recoded as binary variables. ‡Hepatitis C (HCV) and Herpes Simplex Virus (HSV) for Kohtla-Järve only. NSP=needle and syringe programme. No values missing for serological markers. Missing values for demographic and injecting variables (n<7); contact with NSP (n=83); ever paid for sex (n=63) (list in table 4.4 in chapter 4).

Table 7.4: Adjusted multinomial analysis of class membership and injecting and sexual risk behaviours

	Adjusted Odds Ratios (95% CI†) *Reference group: Class 5 Single drug injection*			
	Class 1 **Polydrug polyroute injection**	Class 2 **Opiate-stimulant poly-injection**	Class 3 **Non-injection stimulant co-use**	Class 4 **Opiate-opioid poly-injection**
Demographic and services				
Female gender	1.1 (0.7-2.0)	0.8 (0.4-1.7)	1.4 (0.9-2.1)	0.8 (0.5-1.2)
Age < 30	1.3 (0.9-1.8)	1.7 (1.0-2.9)	1.5 (1.0-2.2)	1.6 (1.1-2.3)*
Non-Russian	1.8 (1.1-3.1)*	0.8 (0.3-2.1)	1.1 (0.6-1.9)	1.6 (1.1-2.4)*
Completed 2ndary school	0.8 (0.5-1.3)	0.9 (0.5-1.6)	0.7 (0.5-1.0)*	0.9 (0.5-1.5)
Non-regular income	1.0 (0.7-1.6)	0.7 (0.4-1.2)	0.6 (0.5-0.7)**	0.8 (0.5-1.1)
Contact with NSP	0.7 (0.4-1.3)	0.7 (0.4-1.3)	1.0 (0.6-1.6)	0.9 (0.6-1.3)
Drug/substitution treatment	0.3 (0.1-1.5)	0.4 (0.2-1.6)	0.7 (0.3-1.5)	0.7 (0.2-2.3)
City (Kohtla-Järve)	3.4 (1.7-6.6)**	0.5 (0.3-1.0)	14.9 (7.8-28.9)**	0.1 (0.1-0.2)**
Injecting risk behaviours				
Injecting < 5 years	1.1 (0.7-1.9)	1.6 (0.4-6.3)	0.7 (0.4-1.3)	1.8 (0.5-5.9)
Injected daily or more	2.5 (1.1-5.7)*	3.0 (1.5-5.8)*	0.9 (0.5-1.5)	1.3 (1.0-1.8)
Injected ≥ twice a day	2.7 (1.3-5.9)*	4.0 (2.3-6.9)**	1.1 (0.8-1.6)	1.6 (1.1-2.4)*
Shared needles/syringes	2.5 (1.3-4.8)**	2.3 (1.7-3.2)**	1.6 (0.7-4.0)	1.6 (1.1-2.4)**
Lent needles/syringes	1.0 (0.5-1.9)	2.4 (1.4-3.9)**	0.9 (0.5-1.7)	1.4 (0.9-1.9)
Shared paraphernalia	2.7 (1.4-4.9)**	1.8 (1.2-2.7)*	2.4 (0.9-6.9)	1.2 (0.9-1.7)
Filled from working syringe	3.6 (2.3-5.8)**	1.8 (1.1-3.1)*	3.2 (1.4-7.2)**	0.7 (0.5-1.1)
Sexual risk behaviours				
Any sex in last 6 months	1.1 (0.6-2.2)	1.9 (1.1-3.5)*	1.5 (1.1-2.2)*	0.9 (0.6-1.1)
≥ 2 sex partners	1.2 (0.8-1.8)	1.7 (1.2-2.4)*	1.1 (0.8-1.5)	1.6 (1.2-2.1)**
Regular sex partner injects	1.5 (0.8-3.2)	1.9 (0.8-4.4)	1.2 (0.9-1.6)	3.2 (2.1-4.9)**
Casual sex partner injects	1.7 (1.0-2.9)	1.3 (0.5-3.5)	1.1 (0.5-2.6)	2.1 (1.1-3.9)*
Ever paid for sex	1.0 (0.4-2.4)	0.6 (0.2-1.7)	0.5 (0.2-1.2)	0.5 (0.1-1.9)
Serological markers‡				
HIV test positive	0.7 (0.4-1.3)	1.1 (0.7-1.8)	0.9 (0.7-1.3)	1.3 (0.9-1.8)
HCV reactive	0.7 (0.2-2.3)	0.6 (0.1-2.9)	0.8 (0.5-1.3)	0.8 (0.2-4.2)
HSV positive	0.6 (0.3-1.1)	1.1 (0.5-2.8)	0.6 (0.4-1.0)	2.0 (0.6-6.6)

Note Table 7.4: Multivariate multinomial regression models adjusted for age, sex, education, income, ethnicity, contact with needle and syringe programme and city (drug/substitution treatment did not differ significantly across classes). *Regression coefficient p-value ≤0.05, **≤0.01, ***≤0.001. †Confidence Intervals. ‡Hepatitis C (HCV) and Herpes Simplex Virus (HSV) only reported for Kohtla-Järve. NSP= needle and syringe programme.

7.4 Discussion

The latent class analysis empirically classified polydrug use in St Petersburg and Kohtla-Järve into five distinct classes, or sub-types, based on the main drug injected and class of additional drugs injected and used. Among the five polydrug classes identified, the largest one exclusively injected only a main, predominantly opiate, drug (heroin in St Petersburg; fentanyl in Kohtla-Järve), two classes predominantly injected other drugs (class 2 and 4), one injected and used any other drugs and drug classes (class 1), and one mostly used other stimulant drugs (class 3). Of relevance to prevention and treatment programmes, comparisons of HIV-related risk between these classes revealed significant differences in

their injecting and sexual risk behaviours, contact with services and demographic characteristics, summarised in Table 7.5.

Polydrug-polyroute injection (Class 1) was associated with most injecting risks, being of non-Russian ethnicity and from Kohtla-Järve; this polydrug class injected significantly more frequently and intensely, shared needles and syringes, shared paraphernalia and back-loaded more often than exclusive injectors.

Table 7.5: Summary of associations for each polydrug class compared to single drug injection

Class 1 **Polydrug polyroute injection**	Class 2 **Opiate-stimulant poly-injection**	Class 3 **Non-injection stimulant co-use**	Class 4 **Opiate-opioid poly-injection**
Socio-demographic			
-	-	-	↑ < 30 years old
↑ non- Russian ethnicity	-	-	↑ non- Russian ethnicity
-	-	↓ secondary education	-
-	-	↑ non-regular income	-
-	-	-	-
↑ Kohtla-Järve	-	↑ Kohtla-Järve	↑ St Petersburg
Injecting behaviours			
↑ frequent injecting	↑ frequent injecting	-	-
↑ intense injecting	↑ intense injecting	-	↑ intense injecting
↑ shared needles/syringes	↑ shared needles/syringes	-	↑ shared needles/syringes
↑ sharing paraphernalia	↑ sharing paraphernalia	-	-
↑ back-loaded	↑ back-loaded	↑ back-loaded	-
Sexual behaviours			
-	↑ Any Sex last 6 months	↑ Any Sex last 6 months	-
-	↑ multiple sex partners	-	↑ multiple sex partners
-	-	-	↑ regular sex partner injects
-	-	-	↑ casual sex partner injects

Note: "↑ and ↓" indicate statistically significant positive and negative associations, respectively.

The two other classes also predominantly injecting other drugs, *opiate-stimulant poly-injectors (class 2)* and *opiate-opioid poly-injectors (class 4),* also reported more intense injecting and more sharing of needle and syringes than single drug injectors. In addition, *opiate-stimulant poly-injection* was also associated with frequent injecting, sharing drug paraphernalia and back-loading, compared to single drug injectors. These two classes also reported more sexual risk behaviours and both groups were more likely to report multiple sex partners, compared to single drug injectors. In addition, *opiate-opioid poly-injectors (Class 4),* who were more likely to be under the age of 30 years and from St Petersburg, also had more regular sex partners who injected and casual sex partners who injected, suggesting significant overlaps between injecting and sexual risks and a high potential for the transmission of both sexually transmitted and blood borne infections.

Non-injected stimulant co-users (Class 3) generally reported lower injecting risks but their odds of back-loading were high and similar to that of *polydrug polyroute injectors*

(Class 1) when compared to single drug injectors. *Non-injected stimulant co-users* were more likely to have had sex in the last 6 months and be from Kohtla-Järve but they were less likely to have completed secondary education or to have a non-regular income.

Despite differences in injecting and sexual risk behaviours, the prevalence of HIV and HCV were similar across polydrug classes when using single drug injectors as reference group. Since this reference group was largely composed of opiate injectors, differences in the prevalence of HIV or HCV among classes may emerge using another reference group (for example when using class 1 as reference, Class 4 was significantly more likely to be HIV positive). It is also possible that drug use patterns in the last month may be not good predictors of HIV and HCV prevalence as the polydrug taxonomy may not necessarily be consistent over time or may not reflect cumulative exposure to certain risk factors.

Differences in contact with needle and syringe programme (NSP) were no longer significant in multivariate analysis but suggested that the polydrug classes with the highest injecting frequency (i.e. *class 2 opiate-stimulant poly-injectors* and *class 4 opiate-opioid poly-injectors)* had lower access to clean needles and syringes.

The findings above were consistent with those of other latent class analyses among PWID in Canada, the United States and Australia, where 3 to 8 polydrug classes were produced from 4 to 12 drug indicators [17, 18, 224, 334, 335, 348]. Similar to the associations found above between *opiate-stimulant poly-injection* and needle and syringe sharing, frequent injecting and multiple sex partners, several studies also identified a polydrug class involving the injection of stimulants (i.e. cocaine) and opiates (i.e. heroin), which was associated with greater injecting risks [17, 224, 335]. Polysubstance users who injected heroin and cocaine in Baltimore and Tijuana were more likely to have shared needles and syringes [17, 335, 337] and to be HCV reactive [17, 224]. Other (non-LCA) studies found that PWID injecting stimulants (in addition to opiates) were more likely to share needles and syringes, inject frequently and have multiple sex partners [101, 202, 259, 337]. Combined heroin and cocaine use has also been associated with younger age, being of another ethnicity (i.e. non-Canadian), depressive symptoms, homelessness and HIV and HCV prevalence [18, 224, 335]. The existence of an opiate-opioid poly-injection class in my study differentiated it from other LCA reports and may reflect the particular drug use context in Russia. Other studies also found PWID who combined opiates with sedatives or other CNS depressants were more likely to inject frequently and to share needles and syringe [92, 122, 215].

The heterogeneity in polydrug use patterns and risk behaviours in this sample suggests i) the need for more tailored, targeted services and interventions for problematic drug users, ii) the potential for polydrug use to provide a marker of behaviours and therefore HIV and HCV risk and, iii) the importance of on-going and continuous drug monitoring in PWID populations [4]. Knowing what drugs and drug combinations are commonly injected in a PWID populations would allow prevention and treatment programmes to respond with appropriate combinations of injecting and sexual risk reduction, including clean injection and smoking equipment and promotion of safe sexual behaviours *with all sex partners*. Whereas opiate substitution modalities could be expanded (or introduced in the case of Russia) to reduce risk among opiate-opioid poly-injectors, alternative drug treatment modalities are required to reduce risk among opiate-stimulant poly-injectors in Estonia. In settings where stimulants or combinations of stimulant and opiates are injected/used, drug treatment alternatives including behavioural and pharmacological approaches for stimulant users are needed as opiate substitution may not be effective [18, 74, 75]. Improving access to primary health care services should also be encouraged to provide an entry point for different PWID with different drug use and risk profiles. Additionally, recognising and addressing polydrug use as drug combinations, in drug treatment and HIV treatment settings may help to increase PWID retention, adherence to therapy and hence, improve treatment outcomes.

Further research is needed to ascertain whether such a polydrug classification is valid and consistent across settings and whether it is stable over time. Testing polydrug classes in other PWID populations where comparable drugs are used would also help to establish whether such a taxonomy is applicable to other settings, to further our understanding of polydrug use, and to inform more accurate characterisations in support of programme implementation.

Despite significant differences in HIV-related risk behaviours, no differences in HIV prevalence were found between polydrug sub-groups; further investigation in longitudinal studies could confirm any differences in incident HIV (and HCV) infection between polydrug and single drug users. Similarly, findings from the meta-analysis of HIV incidence in PWID injecting different drugs in chapter 3 suggested non-significant differences between injectors using one (cocaine, ATS or heroin) and those injecting multiple drugs (opiate and stimulants, opiates and sedatives) but few, if any, studies adjusted for the main substance injected and polydrug practices, thus limiting both analyses and interpretation. Longitudinal studies among PWID could also contribute to

establishing whether polydrug practices and patterns evolve over time, and especially how they might change in the course of a drug injecting "career", or as a function of the drug environment [112, 346].

Several limitations were cited in the previous chapters, several of which apply to this study. Some of the strengths of this analysis were the large sample size and combination of two similar samples of PWID, surveyed using comparable methods, instruments and tools, which offered more confidence in the results. Although the drug use and HIV epidemics were similar enough for surveys to be pooled, potential unobserved differences between surveys were accounted for in the analyses.

The two samples may not be representative of all PWID in the two cities as they relied on chain referral sampling methodology. RDS has nevertheless been one of the most effective methods to recruit "less visible" sub-groups within key populations at risk of HIV infection and in this study, contributed to uncovering PWID sub-groups unreached by services [332].

Possible under-reporting of stigmatised behaviours in PWID self-reports and bias towards socially desirable answers were minimised by ensuring confidentiality during face to face interviews, in settings that were safe and familiar to PWID. Though no evidence of such bias was found, if present, it would be expected to affect sub-groups similarly, which may lead to underestimating associations.

LCA methodology was particularly useful in this context and selected above other multivariate methods such as cluster analysis or factor analysis (for continuous and normally distributed variables), for its ability to generate group characterisations based on conditional (posterior) probabilities, which cluster analysis does not provide [345, 346, 349]. LCA methods worked well due to the sample size and similarities between settings but may not be as effective in smaller samples. Integrated Bio-Behavioural Surveys (IBBS) are generally designed to have necessary statistical power to detect changes in HIV prevalence; although polydrug use was a frequent practice, such surveys may not always have sufficient power to detect differences in smaller polydrug sub-groups.

Small differences in risk behaviours and class number found in the LCA reflect a trade-off between the two methods used in chapters 6 and 7. In LCA, the latent variable "polydrug class" was determined by several variables including the main injection drug and the injection and non-injection of other drug classes. In the sub-group analysis, precedence

was given to identifying sub-groups by primary injection drug. Using latent variable modelling and multinomial logistic regression also allowed the comparison of polydrug class with a common though slightly less differentiated reference group.

Finally, while other LCA studies have developed polydrug classifications that were exclusive to a particular setting, this analysis empirically identified polydrug use classes associated with different risk behaviours and proposed a generic polydrug taxonomy, which if applicable, could be used and applied across drug use settings.

The next and final chapter discusses and compares these findings on polydrug use and how they add to drug and HIV research, places them into the broader context of implementation science and proposes several steps for future research.

Chapter 8

Polydrug use and heterogeneity in HIV risk: Discussion and conclusion

Chapter 8 Discussion and conclusions: polydrug use and HIV risk heterogeneity

New HIV infections are estimated to have stabilised globally but people who inject drugs (PWID) still accounted for significant proportions of new HIV infections in Eastern Europe and central Asia (51%), the Middle East and North Africa (28%) and Asia and the Pacific (13%) in 2014[20][350]. HIV responses have evolved in the past thirty years, from standard uniform guidance to more nuanced combination approaches that better take into account HIV prevalence, incidence and risk behaviours in different populations [351-353]. HIV transmission has effectively been reduced in several countries by focusing on high transmission foci with interventions tailored to key populations groups whose risk behaviours placed them and their partners at high risk of infection [354, 355]. Similarly, among PWID, HIV risk is not distributed equally and paying more attention to high risk sub-groups may contribute to limiting the spread of new infections [353].

8.1 Summary of new key theoretical findings

Polydrug use is increasingly cited as a source of harm and mentioned in PWID studies but its role in HIV and HCV transmission remains under-researched [1-3, 9]. In order to assess the epidemiological significance of polydrug use in HIV and HCV risk among PWID, this study (thesis) drew on several methods, and data sources from different settings to triangulate results and overcome key challenges in polydrug and HIV research. Studies of HIV in marginalised populations are often challenged by difficulties involved in reaching hidden population groups with stigmatised behaviours, comparatively small sample sizes and the absence of sampling frame in the case of PWID. By combining data from several sources and using different methods, I established that polydrug use was frequent among PWID, and generated new evidence on the biological and behavioural risks associated with injecting certain drugs and drug combinations. The key findings of my thesis are summarised in Table 8.1 below.

Considerable proportions of injectors across locations had used multiple drugs, involving diverse classes and administration routes, in contrast with the widely-held assumption that PWID mainly inject heroin (chapter 2). In chapter 3, my meta-analysis of HIV incidence studies suggested that HIV incidence rates were consistently high among PWID injecting cocaine or combinations of stimulants and heroin (opiate-stimulant), compared to those not injecting or not injecting the drug, respectively; this could indicate that these groups

[20] Eastern Europe and central Asia: 190,000 (170,000-200,000); Middle East and North Africa: 21,000 (12,000-37,000) and Asia and the Pacific: 290,000 (230,000-370,000).

have a greater risk of HIV acquisition, however wide confidence intervals and inconsistent reference categories weakened what could be said about comparisons between drug groups. Using systematic and meta-analytical methods allowed comparisons of HIV incidence across different drug groups, settings and countries but these were limited by relatively small numbers of new HIV infections in some groups which produced wide, overlapping confidence intervals and thus limited conclusions.

Chapter 4 examined HIV risk behaviour in PWID in two east European cities and found similarly high levels of polydrug use and sexual risk behaviours in both samples. Still, injecting and sharing behaviours differed and were less prevalent in Kohtla-Järve (KJ) than St Petersburg (SP), partly the result of greater availability of Needle and Syringe Programmes (NSP) and Opiate Substitution Treatment (OST) in Estonia.

In chapter 5, which compared HIV risk behaviours by primary drug, primary ATS injection in both cities was associated with later initiation, and shorter duration of injecting, being younger and lower HIV prevalence, compared to opiate injection. Of interest, ATS injectors reported lower injecting risks than their opiate peers in St Petersburg only; whereas injecting risk behaviours did not differ between drug groups in Kohtla-Järve.

Using methods previously unused to analyse sub-groups of poly-injectors by drug class combinations, chapter 6 identified different forms of opiate polydrug use in the two cities, each associated with more risky, albeit different, injecting and sexual behaviours, compared to exclusive injectors. *Opiate-stimulant poly-injectors* (Kohtla-Järve), most of whom were female, injected more intensely though less frequently, shared needles and syringes more, shared more injecting paraphernalia, back-loaded and had more multiple sex partners than did exclusive opiate injectors. By contrast, *opiate-opioid poly-injectors* (St Petersburg), who were younger than exclusive opiate injectors, injected more frequently and more intensely, were more likely to have multiple sex partners and to have regular and casual sex partners who also injected drugs. Though HIV prevalence did not differ between opiate poly-injectors and exclusive opiate injectors, difference in risk behaviours between the groups in both cities, suggested important overlaps between injecting and sexual risks and high potential for HIV and HCV transmission. Primary ATS injectors nevertheless, seemed more homogenous, with the only difference being that ATS poly-injectors were more likely to have been paid for sex than ATS-single injectors.

In chapter 7, latent class analysis was used to examine polydrug use and HIV risk and revealed five empirically categorised polydrug use classes, defined by the main drug *class* injected and *class* of additional drugs injected and used. Of these five classes, three polydrug classes (*i.e. opiate-stimulant poly-injection, polydrug polyroute* and *opiate-opioid poly-injection*) were associated with greater injecting risks than single-drug injectors, two of which were also associated with more sexual risk *(i.e. opiate-stimulant poly-injection* and *opiate-opioid poly-injection*). *Opiate-stimulant poly-injectors* and *polydrug polyroute injectors* reported more frequent and intense injecting, greater sharing of needle/syringes, more sharing of paraphernalia and back-loading, compared to single drug injectors. *Opiate-opioid poly-injectors*, who were younger and more likely to be from St Petersburg, injected as frequently, but more intensely than single drug injectors, and were more likely to share needles and syringes, and regular and casual sex partners who injected drugs. Both *opiate-stimulant poly-injection* and *opiate-opioid poly-injection* were also associated with multiple sex partners.

These results substantiated my findings in chapter 6 that polydrug use was associated with greater behavioural risks than single drug use and contributed to better understanding the epidemiological significance of polydrug use among PWID. Essentially, the different methods in chapter 7 (LCA) and chapter 6 (sub-group analysis by primary drug) agreed on four major classes of polydrug use, namely *opiate-stimulant poly-injection, opiate-opioid poly-injection*, *non-injection stimulant co-use* and *exclusive (single drug) injection*. The LCA however uncovered an additional *polydrug polyroute* class, whose levels of injecting risk were consistently higher than single drug injectors, who were largely primary opiate injectors and from both cities. Characteristics of the *polydrug polyroute* class in LCA, with significantly higher injecting risk yet no difference in sexual risk, compared to single injectors, suggested that this class emerged as a sub-group of opiate-opioid, opiate-stimulant and some ATS poly-injectors in chapter 6. Their emergence as a separate, high injecting but similar sexual risk class in LCA may explain that injecting intensity but not frequency was significantly higher for opiate-opioid injectors in the LCA. Sexual risk behaviours among opiate-opioid poly-injectors remained high using both methods. Demographic characteristics such as young age were associated with opiate polydrug injection in both analyses, as was being female and of minority ethnicity in Kohtla-Järve.

Small differences in class numbers, composition and associated risk behaviours between the two analyses reflected a trade-off between the methods used in each chapter. In LCA, the polydrug class (i.e. latent variable) was determined by several drug variables whereas

the sub-group approach gave precedence to the primary injection drug class and additional drug class. While the results were largely consistent, the selection of polydrug variables and hence sub-group characteristics are important and should also be viewed in terms of their implementation relevance, feasibility and applicability.

The polydrug combinations (classes) identified in this thesis and their associations with HIV-related risk behaviours suggested that risk heterogeneity among PWID was high and that pragmatic polydrug use characterisations based on drug class (rather than specific drugs) may contribute to targeting and adapting interventions to increase their impact.

This closing chapter discusses the importance of the thesis findings for harm reduction, their implications for HIV prevention, treatment, surveillance and research among PWID, the potential use of a drug polydrug typology and its validation in different settings. The last section acknowledges the strengths limitations of the thesis results and outlines a number of directions proposed to take this research forward.

Table 8.1: Summary of thesis aims, findings and limitations by chapter

Chapter	Aims	Findings	Limitations and gaps
2	Determine prevalence of polydrug use across settings, definitions and drug combinations; associations with HIV and HCV	Substantial proportions of PWID used multiple drugs globally (21-90% in out-of-treatment PWID in 40 cities in 19 countries). Polydrug use associated with toxicity, overdose, drug interactions, injecting risk, sexual risk and HIV, compared to non-users.	Non-exhaustive literature review; polydrug use not well defined in epidemiological studies due to inconsistent definitions and comparisons; limitations of HIV prevalence.
	Strength of evidence: Narrative review	**Conclusion**: High burden of polydrug use among PWID worldwide, may be at higher HIV risk than other PWID.	**Research gap:** role of main injection drug unclear. Review HIV incidence by main drug
3	Compare risk of HIV acquisition in PWID groups injecting different drugs or drug combinations	Consistently high HIV incidence rates among PWID injecting cocaine, or combinations of cocaine or M/ATS, and heroin (opiate-stimulant), compared to those not injecting or not injecting the drug – differences between drug groups not statistically significant.	Low numbers of incident HIV infections in drug groups, wide confidence intervals. Reference groups used not consistent.
	Strength of evidence: Systematic review	**Conclusion**: Meta-analysis supports that HIV incidence high in stimulant injectors and poly-injectors - unclear whether due to increased injecting or sexual risk	**Research gap:** Drug role in HIV varies with other drug use. HIV risk by drug combination.
4	Present study context; Describe PWID socio-demographic and drug use characteristics in KJ and SP	Injecting and sharing risks less prevalent in Kohtla-Järve (KJ) than St Petersburg (SP), partly due to expansion and availability of NSP and OST in Estonia. Polydrug use prevalence high in both cities, frequency of sexual risk behaviours high. Primary drugs: opiate, ATS. Over half PWID in both cities HIV positive. In KJ, 74.7% (95%CI: 67.3%-80.9%) HCV reactive.	Non probability samples (RDS) may not be representative of all PWID; Self-reported measures of stigmatised behaviours may lead to social desirability bias.
	Strength of evidence Epidemiological survey data analysis	**Conclusion**: Polydrug use frequent, main drugs injected similar in both cities. No OST and low NSP in SP compared to KJ. High sexual risk in both cities.	**Research gap**: HIV infection and behavioural risk in ATS and opiate injectors
5	Compare factors associated with primary ATS or opiate injection in two PWID samples (Estonia, Russia)	Primary ATS injectors were younger, had lower HIV prevalence than opiate injectors in both cities but lower injecting risks only in SP. ATS injection negatively associated with NSP and drug/substitution treatment; positive association with being paid for sex in KJ.	Cross sectional surveys – causality could not be established; Possible (non-differential) misclassification due to polydrug use would yield conservative results.
	Strength of evidence Epidemiological survey, multivariate analysis	**Conclusion**: Primary ATS injection associated with younger age and lower HIV prevalence, but not always with lower injecting risks, compared to opiate injectors.	**Research gap:** Risk behaviours and HIV differences by polydrug use (and main drug).
6	Compare HIV risk associated with poly-injection among opiate and ATS injectors in same two PWID samples (Estonia, Russia)	For opiate injectors, polydrug use positively associated with greater injecting and sexual risks in both cities: *Opiate-opioid poly-injection* associated with frequent injecting (≥ daily), intense injecting (≥ twice a day), multiple sex partners, sex partners who injected drugs, low contact with NSP, young age, lower education, illicit income (SP). *Opiate-stimulant poly-injection* associated with intense, less frequent injecting, front/back-loading, sharing drug paraphernalia, multiple sex partners, being female and from a minority ethnicity (KJ). Among ATS, injectors, ATS poly-injectors more likely to have contact with NSP, been paid for sex and used condom than PWID exclusively injecting ATS (KJ).	Same polydrug use and injecting risk period (1 month) but cross-sectional survey did not allow assessment of causal link. Association between polydrug use and HIV risk behaviours were strong, specific to drug combinations and plausible (same timeframe). Polydrug groups may include PWID injecting and using drug, thus underestimate risk. Small ATS sample size in SP.
	Strength of evidence Epidemiological survey, multivariate analysis	**Conclusion**: opiate poly-injection (opiate-stimulant, opiate-opioid) associated with different risk behaviours, compared to exclusive injectors but no difference in HIV prevalence. ATS poly-injection associated with paid sex.	**Research gap**: empirical method to model polydrug classes and associations with HIV risk.
7	Identify (i) polydrug classes defined by drug combinations and (ii) associations between polydrug class and HIV-risk	Of 5 polydrug classes, 3 associated with injecting risk, compared to single drug injection: Polydrug-polyroute (PDPR) and opiate-stimulant poly-injection (OSPI) = frequent and intense injecting, shared needles/syringes, shared paraphernalia, back-loaded. Opiate-opioid poly-injection (OOPI) = frequent and intense injecting, (regular/casual) sex partners who	Non-random sample limits generalisability, self-reported behaviours underestimated, Temporal associations with HIV could not be assessed, Polydrug use behaviour may not be stable over time.

	inject drugs. Both OSPI and OOPI associated with multiple sex partners. Non-injected polydrug use (NIPD) = more back-loading and sex in last 6 months.	
Strength of evidence Latent Variable modelling-survey data	**Conclusion:** Agreement on specific combinations of opiate polydrug use and ATS polydrug use and their associated risk behaviours. No difference in HIV prevalence between polydrug classes.	**Research gap:** Validity of generic polydrug classes and HIV risk; mixing patterns poly- and single.

Note Table 8.1: PWID= People Who Inject Drugs. M/ATS= meth/amphetamine type stimulants. HIV=Human Immune Deficiency Virus. HCV=Hepatitis C virus. HSV=Herpes Simplex virus. CAT= Computer Assisted Technology. RDS=Respondent Driven Sampling. KJ=Kohtla-Järve. SP=St Petersburg. NSP=Needle and Syringe programme. OST= opiate substitution therapy.

8.2 Practical implications for programmes: translating theory into action

8.2.1 Drug use and HIV risk behaviour among PWID are heterogeneous and may usefully inform programmes

This thesis found polydrug use to be substantial, diverse and associated with significant heterogeneity in HIV risk behaviours among PWID whereas national HIV strategies and responses have generally considered PWID as one largely homogeneous population group [356-360]. Knowledge of the drugs injected and poly-injected in a particular setting may help HIV and harm reduction programmes to identify foci where HIV and HCV transmission risks are higher, while information on the behavioural, HIV and HCV risks associated with certain drug combinations could inform setting-specific risks and programmatic needs [102, 115, 117]. Polydrug use was more common in sub-groups with certain demographic characteristics, which may also serve as proxy indicators of HIV risk to inform the development of alternative delivery modalities and reach PWID at risk who are not in contact with harm reduction services. Finally, polydrug use occurs in a complex landscape where drug use is driven by supply and availability as well as by individual, social and economic factors [50, 170]. Monitoring the availability, purity and PWID use of drugs through better drug surveillance could allow changes to be detected and programmes to prepare and address the risks associated with specific drugs or drug combinations in a timely way (i.e. HIV, HCV, overdose)[4, 80].

Rationale for generic polydrug classifications and associations with HIV risk

Beyond the apparent diversity of drugs and combinations reported, similar forms of polydrug use emerged from my analyses of PWID in Estonia and Russia and resonated with drug combinations found in the systematic and narrative reviews of literature.

A generic typology of polydrug use by drug class combination rather than specific and individual drugs may therefore offer important and sufficient data to tailor harm reduction interventions to PWID sub-groups, and risk profiles associated with local drug combinations. A generic typology such as those used in chapters 6 and 7 (i.e. opiate-stimulant and opiate-opioid) may also help programmes to monitor drug and HIV risk.

Such classifications have usefully been implemented in health care, to identify and group diagnostic and treatment needs and to help tailor, plan and provide effective prevention and treatment interventions, as well as research [314, 339, 340, 361, 362]. Similarly, diverse polydrug classes suggest specific targets for interventions, based on main drug class and drug combinations injected/used, drug dependence, injecting and sexual risk behaviours and demographic profile. Meeting the different needs of vulnerable PWID sub-groups such as young people and women, who often do not access services, is also critical to prevention and treatment efforts [199, 313].

To be useful, a typology of polydrug use would need 1) to show evidence of different risk behaviours, 2) to help identify polydrug users to be reached and targeted with services; and 3) to demonstrate how different risks require differentiated HIV prevention and drug and HIV treatment services and 4) to be generalizable to PWID elsewhere.

The generic polydrug classes to emerge among PWID in Estonia and Russia were *opiate-stimulant poly-injection, opiate-opioid poly-injection* (mostly St Petersburg), *non-injected stimulant co-use* (mostly Kohtla-Järve) and *exclusive injection* (both cities), which were comparable to drug-specific combinations detailed in two other LCA studies [17, 336]. Similar drug combinations have been mentioned in epidemiological studies among PWID whose focus was not polydrug use [92, 98, 106, 123, 152, 153, 236, 320] or reported as characterisations detailed by drug and therefore too specific to apply to other settings [17, 18, 224, 334, 335, 337, 348].

Opiate-stimulant injection in my study was associated with more intense but less frequent injections, albeit more risky sharing of injection equipment and back-loading of syringes, and increased sexual risk due to multiple sex partners. This polydrug class and the behaviours associated with it were comparable to behaviours reported by PWID injecting cocaine and heroin (speedball) in the United States and Canada [17, 91, 149]. In other studies, PWID injecting ATS and heroin, and those injecting cocaine and heroin were also more likely to have shared needles and syringes than exclusive heroin injectors [17, 68, 127, 145, 231, 260] while PWID injecting cocaine and heroin were also more likely to have back-loaded, than those exclusively injecting heroin [101, 131, 151, 243]. In addition to their stimulant and disinhibitory effects [60, 113], amphetamines were found to alter cognitive functioning and impulsivity and to impair decision-making more severely than did opiates, in studies of neurological, cognitive and behavioural effects of drugs in animals and humans [306, 318, 319, 363]. Together these factors may account

for increased sharing of drug paraphernalia and back-loading of syringes among opiate-stimulant poly-injectors, and potential overlaps with (informal) sex work.

By contrast my findings that injecting opiates with other drugs of the same class (mostly opioids) was associated with more frequent injecting and more injections per day among *opiate-opioid poly-injectors*, may result from a need to increase dosage of lower potency opioids in order to achieve the same effect. This drug combination was consistent with reports in the literature of PWID substituting or replacing heroin with other opioids when it was unavailable, too costly or lacked purity [12, 13, 78, 123, 153]. However, opiate-opioid poly-injection was also associated with multiple sex partners, an unexpected finding among opiate injectors which highlights the potential for transmission, importance of sexual risk reduction and warrants closer examination.

Despite significant heterogeneity in HIV risk behaviour between poly-and single drug injectors, differences in terms of HIV prevalence (and HCV in Kohtla-Järve) were marginal. Possible explanations could include that HIV incidence was higher in certain polydrug sub-groups but not yet reflected in prevalence due to a relatively recent epidemic and young age of the sample. Alternatively HIV prevalence may reflect past but not current risk. Indeed, polydrug use was based on past 4 week behaviours and if these were not constant over time, potential increases in HIV risk may have been diluted in studies of HIV prevalence.

At the population level, how risk behaviours influence HIV transmission also depends on the patterns of mixing between polydrug and other injectors (and other sub-groups). Dis-assortative mixing where poly- and single-drug injection (or sexual risk) occured within the same network would lead to homogeneity and similar HIV prevalence in poly- and single drug injectors [364, 365]. Conversely, assortative mixing that occurred mainly within sub-groups who are similar in terms of risk may lead to greater differences in HIV and HCV infection between poly- and single drug injectors. One study in Yunnan (China) found almost equal proportions of assortative and dis-assortative mixing between young drug users' sexual and injecting networks [366]. However little is known on the degree to which poly-injectors and other PWID inject together or not.

8.2.2 Programmatic relevance of polydrug and risk classification

From a harm reduction perspective, the different polydrug classes, their associated HIV risk behaviours and sub-group characteristics, suggested the need for differentiated HIV

prevention, drug and HIV treatment services. The relevance of my thesis findings and their implications for programmes, policy and research are discussed below.

Demographic characteristics as proxy indicators for polydrug use and HIV risk

Poly-injectors in this study were often younger and tended to be more vulnerable (ie. female, of minority ethnicity, less educated), a finding consistent with PWID studies in Australia and the United States where younger age was also associated with polydrug use [101, 131, 151, 260]. Key population sub-groups unknown to programmes have been reached using respondent driven sampling (RDS) methods which, while perhaps not fully representative of all PWID, also contributed to effectively reaching young PWID who had less contact with programmes in Kohtla-Järve and in St Petersburg (i.e. primary ATS in both cities and opiate poly-injectors in St Petersburg) [322, 332]. Polydrug use may therefore serve as marker of vulnerability as well as risk among sub-groups of PWID who are less likely to engage with programmes due to their age, gender or ethnicity. There is evidence that polydrug use is predictive of progression to drug dependency and to more severe forms of polydrug use [112, 337]. Young and female PWID therefore also constitute a critical sub-group to reach, engage and refer to appropriate services, before they progress to more severe drug dependency, polydrug injection and become infected with HCV and HIV [18, 96, 200, 204, 230, 231].

Several sub-groups of injectors reported lower contact with prevention services in both cities (i.e. ATS injectors in both cities and opiate-opioid poly-injectors in St Petersburg in chapter 6), reflecting different needs not presently being met. Interventions such as opiate substitution therapy (OST) can contribute to reducing HIV and injecting risk among opiate injectors, and being on OST can support adherence to antiretroviral treatment for PWID who are HIV positive [2, 41, 46]. However using or co-using stimulants for example may adversely affect OST outcomes and as a result, adherence to antiretroviral therapy [2, 367].

Programmatic relevance of opiate-opioid poly-injection

In settings where opiate-opioid poly-injection is common and associated with more frequent and intense injecting, significantly larger numbers of free, easily available clean needles and syringes, and other injecting equipment would need to be made available over and above standard requirements to prevent re-use. Where NSPs are uncommon, such as in St Petersburg, a significant expansion is essential to make up for greater needle and syringes requirements than usual, arising from opiate-opioid poly-injection.

Although all PWID should be informed of infection risks associated with sharing needles/syringes, drug paraphernalia and back-loading, young PWID in particular need to be reached with messages that encourage less frequent and safer injecting, OST and sexual risk reduction before they are infected with HIV or HCV.

While dependency on several drugs has been recognised as a complicating factor in drug treatment, adapting opiate substitution treatment (including methadone maintenance) to opiate and opioid poly-injection could contribute to reducing injection risk behaviours and HIV and HCV infection in these settings [41, 44, 256, 368]. Making opioid substitution treatment available in St Petersburg is essential and would provide added incentive, and a possible entry point, for young opiate-opioid poly-injectors not yet in contact with programmes, to engage with needle and syringe services.

Programmatic relevance of opiate-stimulant poly-injection

In settings where PWID reported opiate-stimulant poly-injection such as in Kohtla-Järve, clean needles and syringes need to be made available from a wider range of alternatives sources including pharmacies and other outlets in order to reach women and other vulnerable PWID sub-groups who may be more reluctant to attend NSPs. Risk reduction messages need to emphasise infection risks associated with the sharing of injection equipment, back- and front-loading and multiple sex partners and unprotected sex. Programmes in these settings would need to develop evidence-based drug treatment modalities to address the increasing co-use and possible dependency on stimulants among opiate-stimulant poly-injectors.

In cities where a third of all PWID reported multiple sex partners, opiate poly-injectors were even more likely to report multiple sex partners. However the low response rate on some sexual risk questions in Kohtla-Järve, yet high response rates on drug and injecting questions in both cities may reflect challenges in eliciting sexual behaviours from PWID. Messages that highlight infection risk from sexual transmission and promote partner reduction and condom use with all partners (sexual and injecting) are an essential, yet frequently overlooked component of HIV prevention among PWID and would benefit poly-injectors in particular.

8.2.3 Implications of polydrug use and risk heterogeneity for programmes, surveillance and research

Needle and syringe programmes

Providing clean needle and syringes has been shown to effectively contribute to reducing risk behaviours and HIV and HCV transmission among PWID [42, 353, 369, 370]. Most harm reduction programmes effectively serve a majority adult, male, opiate injecting PWID, whereas polydrug use and behavioural risk were found among PWID sub-groups who did not fit this profile and were less likely to engage with these services.

My study findings suggest that alternative methods of accessing sterile supplies and engaging with prevention services are required for PWID sub-groups such as primary stimulant and opiate poly-injectors. Primary ATS injectors in both cities and young opiate poly-injectors in St Petersburg were more likely to have obtained clean needles and syringes from a pharmacy or other sources than an NSP. For young, stimulant or early-stage injectors, NSPs may be associated with entrenched drug use and may be too stigmatised to engage those who do not perceive themselves to be at risk or fit a drug user "profile" [202, 371]. Studies of cocaine users in Australia and young opiate injectors from the former Soviet Union in New York City, found certain sub-groups of injectors reluctant to access NSP for sterile needles and syringes, preferring instead the relative anonymity of a pharmacy which was less stigmatised and not associated with drug use [202, 272, 323, 371]. Greater diversity among peer educators and outreach workers to represent young or female PWID, from ethnic or other minority sub-groups, would also help programmes reach into these networks.

Drug treatment and antiretroviral therapy

Similarly, the geographical spread of addictive substances other than opiates, including M/ATS and cocaine stimulants makes it critical that drug treatment targeted to stimulant dependency be made more widely available. Opiate substitution treatment has been an effective tool in reducing drug risks and HIV transmission among opiate-dependent PWID [41, 44, 256] and has contributed to maintaining adherence to antiretroviral therapy among HIV-positive PWID on treatment [31, 46, 48]. Stimulants such as cocaine however, negatively affect treatment outcomes (in addition to polydrug use) and despite on-going research, no medication has yet been approved to treat dependency on stimulant drugs such as ATS or cocaine [372, 373]. Drug treatment modalities therefore need be developed, and adapted to the type of drug(s) injected, polydrug use and to PWID profiles in different settings.

Stimulant injectors often overlooked in settings targeting opiate dependency

Primary ATS injectors in chapter 5, reported lower injecting risk behaviours than opiate injectors in the absence of NSP and drug treatment programmes in St Petersburg but equally risky injecting practices in the presence of harm reduction in Kohtla-Järve, which they engaged with less than did opiate injectors. This finding suggested that harm reduction in Kohtla-Järve had benefited primary opiate- but possibly not ATS-injectors. Although evidence has shown opiate substitution treatment (OST) to be effective in opiate dependency, it offers little help for stimulant dependent individuals (M/ATS or cocaine) for whom no proven medicated treatment modalities exist [31, 44, 46, 48, 256, 372, 374]. ATS injectors and those co-injecting stimulants may either not engage with prevention services targeted to opiate injectors and when they do, may not respond to drug or other treatment. To successfully increase prevention coverage and reach different risk networks, it is critical for harm reduction programmes to account for stimulant injection and dependency, to adapt interventions to stimulant use and co-use and to the different demographic profile and needs associated with these different PWID sub-groups.

Surveillance and drug monitoring at local and national levels

Polydrug combinations were associated with greater injecting and sexual risk behaviours and suggest the need to strengthen drug surveillance and monitoring at different levels (not only national), and to integrate it with HIV surveillance, to rapidly detect changes in drugs available and consumed. Changes in drug availability and injection by PWID have been associated with HIV and HCV infection in several countries with substantial rates of illicit drug use and underline the dynamic role of drug-specific factors in the spread of HIV and HCV epidemics [4, 102, 115, 142]. Drug availability, purity and consumption needs to be monitored more systematically, especially in settings close to source countries, those situated on drug trafficking corridors or where the manufacture of synthetic drugs is facilitated by ready access to precursor chemicals [4, 73, 79].

Consistent metrics to define and quantify polydrug and drug use locally need to be developed to respond to rapid changes in availability, consumption, HIV and HCV risk, and prevention and treatment needs. Local data on specific drugs and polydrug patterns in particular would provide important information for the development of drug and context-appropriate prevention and treatment interventions and may be more readily elicited than data on stigmatised injecting sexual risk behaviours [310, 375].

Finally, the differences in injecting and sexual risk behaviours (and demographics characteristics) between poly- and single drug injectors and their lower engagement with programmes suggested that differentiated HIV prevention, drug and HIV treatment services may help to reduce the behavioural and HIV risk among sub-groups of PWID. The different demographic characteristics associated with polydrug use also emphasised the need to adapt services and modes of delivery to reach different injectors not in contact with services. A polydrug use typology provides an essential starting point, and though elements of my findings were echoed in several other studies, further testing will be necessary to ensure their generalisability.

8.3 Strengths and limitations of theoretical findings and future research

The evidence generated in my thesis draws from a systematic review of the literature and in-depth analyses of complex surveys in different locations, however several limitations – previously presented in the preceding chapters – need to be acknowledged.

The use of different methods to examine associations between polydrug class and HIV risk in chapter 6 (sub-group analysis) and 7 (latent class analysis) suggested consistency between polydrug sub-groups and polydrug classes (and drug combinations in the literature), and their associations with greater risk behaviours, and reinforced my findings. Sub-group analyses were conducted using a priori-hypotheses and adjusting for possible confounders in my theoretical framework [314, 333]. LCA methods worked well due to a reasonably large sample size, use of drug classes (as opposed to individual drugs) and similarities between settings. Although some sub-groups were small and generated wide confidence intervals, a large number of very specific latent classes would have produced smaller numbers still, thus limiting class interpretability and relevance for programmes.

Second, while the magnitude of associations between polydrug use and HIV risk behaviours was reasonably strong and specific to certain drug combinations, the cross-sectional nature of these PWID surveys did not permit a causal link to be established between polydrug use, risk behaviours and HIV. The impact of polydrug use and heterogeneity in risk on HIV and HCV infection could be informed by HIV incidence studies to inform temporal associations between polydrug injection and new HIV infections among PWID.

The definitions of polydrug use in this work referred to past month practices. While recognised as optimal to minimise recall among PWID and determine associations between recent polydrug use and injecting and sexual risk behaviours, the duration of

polydrug use was not known and may have weakened associations between polydrug use and HIV. If polydrug behaviour was not constant over time, potential increases in HIV risk may have been diluted. Further research on polydrug patterns over the life course of drug use in these settings would help to understand whether and how polydrug use and associated risks evolve or remain stable over time. Similarly, the one month timeframe did not allow a detailed assessment of whether drugs were used concurrently (simultaneously) or sequentially [109], an important factor in determining possible interactions and risk behaviours.

Finally, HIV and HCV transmission in a heterogeneous PWID population is determined by exposure via injecting and sexual risk and by the extent and way in which different sub-groups (ie. polydrug and single drug injectors) mix among, and with each other. Little is known about patterns of injecting (or sexual) mixing between PWID in general and between polydrug and single drug injectors in particular and may influence HIV transmission at the population level.

These limitations also emphasize the need for future research to uncover these complex relationships. Future research directions would specifically be (i) to test and validate polydrug classes in other settings, (ii) to investigate polydrug class trajectories over time and find out timeframes during which classes remain stable and (iii) to test their use as surveillance indicators. Moreover, the influence and role of polydrug use in HIV transmission would be further informed by: iv) estimating the population fraction of HIV attributable to polydrug use among PWID, by (iv) researching sexual mixing and injecting mixing patterns among PWID and by (v) modelling HIV trajectories with, and without polydrug use.

This study proposed a generic typology of polydrug use relevant to PWID populations in Eastern Europe and Russia which would require testing in other PWID populations. Polydrug classes identified and their associations with risk behaviours could be tested in other PWID to assess their validity in different contexts of drug use and HIV epidemics. Operational research would also be essential to develop and agree on consistent (poly)drug use metrics which may be incorporated into drug and HIV surveillance and monitoring as potential markers of risk.

Further study is needed to understand the type of mixing patterns among and within PWID sub-groups (eg. polydrug classes) and the ways that injecting networks and injecting and sexual networks intersect. These findings would help to inform the degree

to which particularly high risk behaviours among polydrug users may contribute to the transmission of HIV and HCV among PWID.

Modelling studies have examined the contribution of parenteral and sexual transmission in PWID populations and found that epidemics with higher HIV prevalence in Central Europe and Asia were more likely to result from extensive sexual mixing between PWID and non-users as well as and mixing between sex workers and the general population [10, 11, 376]. Recent studies have also underscored the role of intersecting injecting and sexual risk behaviours in amplifying HIV transmission [377]. Similarly, modelling the impact of polydrug injection and associated behavioural risks may contribute to explaining the severity of HIV and HCV epidemics. More generally, modelling the impact of different polydrug use scenarios on risk behaviours, HIV and HCV transmission in PWID could improve our understanding of their potential influence on HIV epidemics [11, 376].

8.4 Conclusions

This work fills important knowledge gaps at a time when PWID continue to account for large proportions of new HIV infections globally. The need for rigorous evidence to inform prevention measures that also reach, engage and cater for, less visible PWID sub-groups who may be young and female, was recently re-emphasized at the 2016 United Nations Special session on Drugs [19, 350].

This first study to investigate sources of heterogeneity in HIV risk behaviour among PWID injecting diverse drug combinations, used different methods and data sources. My thesis results propose a pragmatic approach for HIV prevention and surveillance among PWID in increasingly complex, dynamic and integrated drug use contexts. Having established that polydrug use was frequent and associated with substantial heterogeneity in HIV risk (and demographic characteristics); I proposed a generic polydrug use typology that could serve as a marker of risk and help tailor drug and HIV prevention and treatment interventions to high risk PWID sub-groups and thus prevent the spread of new HIV and HCV infections.

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