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HIV AND HEPATITIS C PREVENTION AMONG PEOPLE WHO INJECT DRUGS IN SWEDEN

HARM REDUCTION POLICIES, RISK BEHAVIOUR INTERVENTIONS AND OUTCOMES

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THESIS FOR DOCTORAL DEGREE (Ph.D.)

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O & W

Rock Hard - Stand Tall - Show Obeisance

ABSTRACT

People who inject drugs (PWID) is a heterogeneous and hard-to-reach group due to legal implications, stigma and discrimination. PWID are vulnerable to various poor health outcomes including HIV and hepatitis due to ongoing injection and sexual risk behaviours, various forms of abuse, poor health seeking behaviours, and limited access to- and retention in prevention and care programs. General knowledge about PWID, hepatitis C (HCV) and HIV-risks is good, but less is known about certain sub-populations such as women who inject drugs (WWID). In order to reach PWID with harm reduction, primarily to reduce their risk of HCV and HIV, countries have introduced needle exchange programs (NEP). However, low NEP-availability and insufficient awareness of gender-specific and other sub-group barriers and needs challenges the coverage, uptake and effectiveness of harm reduction for PWID. The overall aim of this thesis was to analyse NEP-development in Sweden and to study determinants for injection and sexual risk behaviours among PWID over time in Stockholm, Sweden. In **paper I**, NEP-development in Sweden was analysed over time (1985–2017) in relation to Swedish drug and health policy. We found that NEP-development was obstructed for a long period because of costly time- and resource-intensive obstacles and processes, e.g. a municipal veto towards starting NEP, involving actor-coalitions, absence of evidence and ideological and individual moral dimensions on both policy and implementation levels. With renewed focus on the individual drug user-perspective, accumulation of evidence, a NEP-law, changes in actor-coalitions and removal of the veto, Sweden saw a fast NEP-development. In **paper II,** determinants for risk behaviours among PWID (n=2,150) at enrolment in remand prisons were studied over time from 2002–2012. Female sex, homelessness, young age and amphetamine injection drug use (IDU) were determinants associated with high levels of injection risk behaviours. Further, injection risk behaviours decreased over time among new enrolled PWID in remand prisons. In **paper III**, determinants and injection risk behaviours at enrolment and over time (2013–2018) were studied among PWID (n=2,860) in the first NEP in Stockholm. An overall significant reduction in injection risk behaviours was found over time and in relation to most enrolment determinants. Female sex, homelessness and amphetamine use were determinants that correlated to an increased risk of sharing needle/syringes and paraphernalia at enrolment, whereas opioid substitution therapy (OST) appeared protective. In **paper IV**, subgroup determinants for injection and sexual risk behaviours and program retention were studied among WWID (n=697) in the Stockholm NEP (2013–2018). Homelessness, amphetamine-IDU, not being in OST and a history of being sectioned (i.e. psychiatric or addiction-related compulsory care) was associated with high injection risk behaviours. Younger age, stable civil status, not in OST and being HIV-negative were associated with higher sexual risk behaviour. WWID were more likely than men to remain in the NEP over time, and previously sectioned WWID were associated with risk for being LTFU. To conclude, our findings highlight the need to better understand the needs of various sub-groups of PWID to successfully tailor harm reduction interventions and scale-up NEP-programs to prevent the spread and eliminate HCV and HIV by 2030, as proposed by the WHO and UNAIDS.

LIST OF SCIENTIFIC PAPERS

I. Karlsson N, Berglund T, Ekström A M, Hammarberg A, Tammi T. **Could 30 years of political controversy on needle exchange programs in Sweden contribute to scaling-up harm reduction services in the world?** *Submitted*

II. Karlsson N, Santacatterina M, Käll K, Hägerstrand M, Wallin S, Berglund T, Ekström A M. **Risk behaviour determinants among people who inject drugs in Stockholm, Sweden over a 10-year period, from 2002 to 2012.** Harm Reduction Journal. 2017;14:57

III. Kåberg M & Karlsson N, Discacciati A, Widgren K, Weiland O, Ekström A M, Hammarberg A. **Significant decrease in injection risk behaviours among participants in a needle exchange programme.** Infectious Diseases (2020) Feb 19:1-11

IV. Karlsson N, Kåberg M, Berglund T, Hammarberg A, Widman L, Ekström A M. **Injection and sexual risk behaviours and determinants of loss to follow-up for women who inject drugs in a needle exchange program.** *Submitted*

CONTENTS

LIST OF ABBREVIATIONS

ACF	Advocacy coalition framework
AIDS	Acquired immune deficiency syndrome
AOR	Adjusted odds ratio
ART	Antiretroviral treatment
BBV	Blood-borne virus
CHEMSEX	Chemically induced sex
CI	Confidence interval
DAA	Direct acting antiviral
DCR	Drug consumption room
ECDC	European Center for Disease Prevention and Control
EMCDDA	European Monitoring Centre for Drugs and Drug Addiction
HAT	Heroin assisted treatment
HBV	Hepatitis B
HCV	Hepatitis C
HIV	Human immunodeficiency virus
IDU	Injection drug use
IEC	Information education and communication
IQR	Interquartile range
AIRR	Adjusted incidence rate ratio
LTFU	Lost to follow-up
LTHS	Low threshold service
MARP	Most at-risk population
MMT	Methadone maintenance therapy
MSM	Men who have sex with men
MWID	Men who inject drugs
NEP	Needle exchange program
OST	Opioid substitution treatment
PDU	Problem drug use
PWID	Person/people who inject drugs
SGS	Second generation surveillance

STI	Sexually transmitted infection
UN	United Nations
UNAIDS	Joint United Nations Programme on HIV and AIDS
UNGASS	United Nations General Assembly Special Session
UNODC	United Nations Office on Drugs and Crime
VCT	Voluntary counselling and testing
WHO	World Health Organization
VS.	Versus
WSW	Women who have sex with other women
WWID	Women who inject drugs

1 INTRODUCTION

With the onset of the human immunodeficiency virus (HIV)-epidemic in mid-1980s, countries stood before a new emerging crisis. Initially, as effective treatment was lacking, the focus was directed towards prevention of both sexual and injection transmission among those considered to be most at-risk populations (MARP). Early on, it became clear that that the epidemic was following two patterns: pattern one – transmission among men who have sex with men (MSM) and people who inject drugs (PWID); and pattern two - heterosexual transmission (1). Early interventions among PWID, however uncoordinated between countries and actors, focused on testing, provision of sterile injection equipment and condom distribution. The world's first government-approved needle/syringe programme (NSP, further referred to as needle exchange program (NEP)) was opened in 1985 in Amsterdam, the Netherlands (2). With the focus of HIV and acquired immune deficiency syndrome (AIDS) among PWID in the early 1990s, new knowledge and diagnostic tools also became available to better identify so called hepatitis non-A and -B, revealing that a large number of PWID were also infected with hepatitis C (HCV) (3). This resulted in a sharp increase of globally reported HCV-cases and, by the end of the century, there were two large-scale and parallel epidemics heavily affecting the PWID-population.

1.1 The UN declaration of commitment on HIV and AIDS and the next decade surveillance system

In 2001, United Nation (UN)-members converged in a UN-General Assembly Special Session (UNGASS) on HIV and AIDS highlighting the challenge with the ongoing HCV and HIV-epidemics (4). Among efforts stipulated in a resulting Global Declaration on HIV and AIDS, special focus was put on targeting behavioural change, i.e. to reduce unsafe sexual and injection risk behaviours (further referred to as sharing of unsterile injection equipment, e.g. needle/syringes, but also paraphernalia, i.e. peripherals such as containers, filters and water used to prepare the drug injection solution (5)) At the same time, the need for interventions such as voluntary counselling and testing (VCT), male and female condom- and sterile injection equipment distribution was reaffirmed. The declaration especially pointed out the need to reach women in order to help reduce their vulnerability. In parallel, the World Health Organization (WHO) and the Joint United Nations Programme on HIV and AIDS (UNAIDS), together in 2000 released global surveillance guidelines for HIV and AIDS including sexually transmitted infections (STI) dubbed "Second generation surveillance for HIV: The next decade" (1). The joint guidelines, in line with the UNGASS-Declaration, suggested a tailored second generation surveillance (SGS)-approach comprising of data

surveillance of both biological (further related to as epidemiological infectious disease-related) and behavioural (e.g. risk behaviours) data among MARP such as PWID, sex workers and MSM. This next decade SGS-system was suggested since previous surveillance systems were considered inadequate, having rarely surveyed risk behaviours. Further, the joint guidelines suggested that risk dual behaviour and epidemiological data surveillance also could provide means for an early warning system for potential disease outbreaks and better understanding of risk-trends over time. Specifically, this meant surveillance of epidemiological indicators of HIV and STI-prevalence in combination with behavioural indicators, e.g. condom use and sharing of unsterile injecting equipment and socio-demographic determinants such as age, sex, socio-economic status, education, housing situation or civil status (1).

1.2 The European and central Asian partnership to fight HIV and AIDS

In 2004, European and central Asian governments agreed on joining forces in the so called Dublin Declaration, and preventive work with HIV and AIDS and to "break the barriers" (6). Reaffirming the UN-declaration, the Euro-Asian Declaration, among other things, underlined the importance of targeting regions affected and MARP vulnerable to HIV and AIDS infection such as PWID and their sexual partners. Compared to the UN-Declaration calling for expanded access to sterile injection equipment, the Dublin Declaration specifically called for scaled-up access for PWID to harm reduction interventions such as NEP and drug dependence treatment. Further, it suggested countries to set national targets for NEP to cover a minimum of 60% of PWID, including condom distribution, VCT and treatment for HIV and STI, but also to address the growing burden of hepatitis B (HBV) and HCV (6, 7). To survey the progress of the work, the Dublin Declaration suggested to implement adequate surveillance systems to cover MARP-size estimates and, where possible, the complex interplay between determinants and risk behaviours (7). The knowledge gap of gender disaggregated data was especially pointed out.

1.3 The early years of HIV and HCV in Sweden and among PWID

In Sweden, the first clinical AIDS-case was discovered in 1982 (3). The HIV-epidemic thereafter followed similar patterns as in other European countries, i.e. with low incidence, a slow increase over time and mostly affecting PWID and MSM. Sweden was fast in implementing intensified testing for infectious diseases and provision of health care for PWID (8, 9). Sweden's first NEP was opened in Lund, in Skåne County, in 1986 and the second in Malmö the year after despite a strict repressive-control drug policy context and

goal of a drug-free society (10), described in Figure 1 of paper I. During 1986–1989, an additional 7 of Sweden's 21 regions ran forms of NEP (11). However, after an assessment in 1988, in a missive to the government, the National Board of Health and Welfare suggested a maximum of four trial-NEP locations limited to a three-year trial period pending future evaluations. This suggestion resulted in only Malmö and Lund NEP in Region Skåne continuing (12), with no new NEP starting outside Region Skåne until 2012.

In 1985-2005, approximately 800 PWID-associated HIV cases were reported (13) and with improved HCV-testing in the early 1990s, a total of 39,000 cases of HCV were reported in 1990-2005 (14). In 2004, a government-commissioned investigation on Sweden's HIV and AIDS-preventive work, also highlighted the domestic and co-existing hepatitis epidemics (15). The investigation pointed to estimations suggesting up to 90% of PWID to be infected with HCV, a potential cause for major health problems and that HIV-treatment could be more difficult for those with an HCV co-infection. The investigation concluded that knowledge was too weak to make qualified assessments to conduct evidence-based HIV and HCV-preventive work (15). Consequently, the investigation suggested to bridge knowledge gaps: conduct both behavioural and epidemiological surveillance for PWID and subgroups, especially target women using drugs, scale-up access to harm reduction interventions such as NEP and drug dependency programs, in line with the WHO SGS-system. In 2005, the Swedish government issued national guidelines for HIV and AIDS and other blood-borne virus (BBV)-prevention, specifically targeting PWID and subgroups such as homeless and women who inject drugs (WWID) (14). The guidelines pointed to several PWID-knowledge gaps creating difficulties in understanding ongoing infection spread, e.g. group-size estimations, varying determinants and risk behaviours and sexual transmission among partners. The guidelines suggested remand prisons were a viable platform to reach PWID and a new NEP-law was proposed to counter the problem of PWID-limited access to NEP (14).

1.4 THESIS FRAMEWORK

The previously described international and domestic calls to bridge knowledge gaps regarding PWID and prevention represents the framework and guidance for this thesis. With this is meant the calls to further PWID-knowledge by conducting both biological and behavioural surveillance and analysis, i.e. to include determinants and risk behaviours. Also, to focus on both PWID and subgroups such as WWID and in relation to HCV and HIV-prevention. Because of NEP- coverage limitations in Sweden, the framework also includes an analysis into NEP-development over time, in a strict repressive-control drug policy context. This analysis aims to better understand prerequisites, factual situation and consequences of

the preventive work with the HCV and HIV-epidemics among PWID and subgroups in Sweden.

In this thesis, I have:

- analysed conditions and changes in policy surrounding NEP-development in Sweden over time, with regards to national drug and health policy and aggravating and enabling factors (**paper I**),
- investigated determinants associated with risk behaviours among PWID at enrolment in both remand prisons and NEP (**paper II-IV**),
- investigated changes in injection risk behaviours over time among PWID participating in NEP (**paper III**) and
- investigated injection and sexual risk behaviours among WWID, probability of NEP-retention over time and determinants associated with being lost to follow-up (LTFU) (**paper IV**).

Findings are discussed in the general context of harm reduction interventions and development. Further, PWID and subgroups, determinants, risk behaviours including national and global HCV and HIV-preventive work.

2 PWID AS A RISK GROUP

A person injecting drugs, e.g. opioids such as heroin or central stimulant drugs like amphetamine, is somebody who penetrates the skin of the body using a needle/syringe filled with drug solution. The aim is to infuse the drug into the body, most often directly into the bloodstream. To facilitate injection drug use (IDU), drugs are often prepared using paraphernalia. Unsterile needles, syringes and paraphernalia all constitute as potential routes of transmission of BBV among PWID when being shared with others (5, 16). PWID using drugs is a heterogeneous and often hard-to-reach group in society. This, due to laws, stigma and discrimination, all of which acts as barriers to be reached by- or for accessing harm reduction and health-related services (17-19). It is difficult to estimate the size of a partly hidden population in society however, research suggests the PWID-population aged 15-64 years to be at around 15.6 million globally, of which approximately 20% are women (20) (Figure 1). In Europe, it is estimated there are approximately 4.3 million PWID of which 26% are women (20).

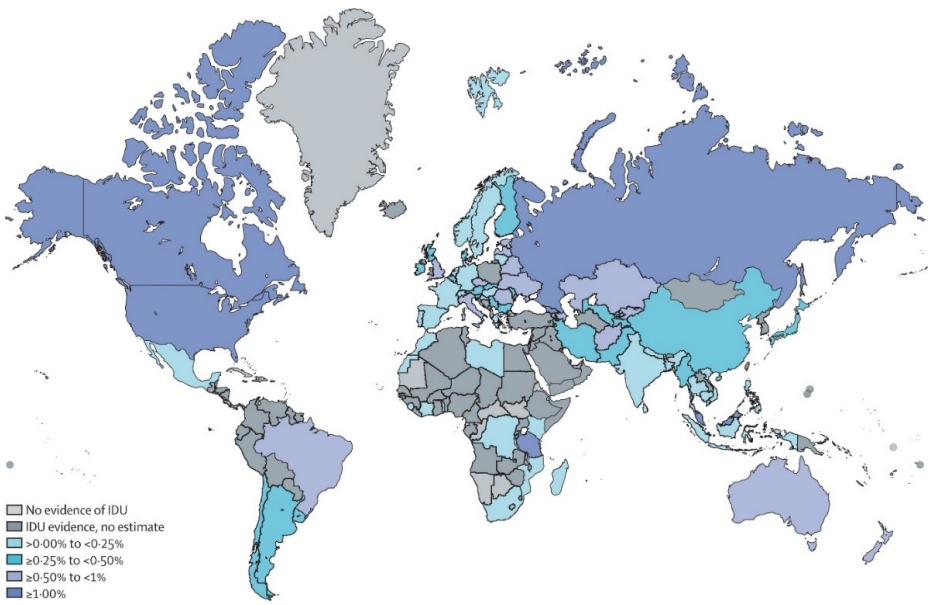

Figure 1. Estimated prevalence of IDU by country.
Source: Degenhardt L, et al., 2017 (20).

2.1 KNOWLEDGE GAPS REGARDING PWID IN SWEDEN

As in many settings, knowledge on PWID, risk behaviours and BBV-transmission in Sweden has been insufficient due to laws and policies that prevent many PWID from seeking health services. Sweden's repressive-control drug policy and historically poor provision of harm

reduction interventions such as NEP, but also inconsistencies in how to define PWID, may also have contributed to fragmented knowledge and provision of interventions (14). To fully understand the burden of infectious diseases among PWID, e.g. including PWID unaware of their infection status (21), and how to best tailor preventive interventions, the research community has called upon actors to update PWID-prevalence estimates and clear population definitions (22, 23) as research priorities.

2.2 DEFINITIONS OF PWID IN SWEDEN

Historically, several different definitions have been used to define a PWID in Sweden, while also including people not injecting drugs:

- "heavy (drug) abuse" (in Swedish: tungt missbruk) - anyone who has injected drugs at any time (i.e. regardless of frequency) during the past 12 months, or used drugs daily or virtually daily for the past four weeks (regardless of the mode of administration) and not including medical use (24),
- "serious/severe" drug abuse (in Swedish: gravt narkotikamissbruk) – using the same principal definition as for "heavy abuse" described above (25) and
- "problem drug use" (PDU) (in Swedish: problematiskt missbruk) - injection use or prolonged/habitual use of opiates, cocaine and/or amphetamines (26).

This procedure, to combine both PWID and those not injecting drugs, has resulted in a broader focus on drug user populations and risks, rather than PWID-specific characteristics (27), maintaining the knowledge gap on foremost PWID-associated injection risk behaviours and spread of BBV (17). It has additionally resulted in that other important PWID-related determinants such as the social context around drug use, type of drug injected and IDU-duration (22, 28) have been neglected.

2.3 ESTIMATIONS OF NUMBER OF PWID IN SWEDEN

Inconsistencies in how to define PWID in Sweden has resulted in different PWID-prevalence estimations, often followed by calls for caution in both interpretation and generalizability due to methodological difficulties (17, 29). A case-finding study dating back to 1998 found an estimated population of 26,000 "heavy (drug) abusers", of which 89% (23,000) were described as PWID (29). A follow-up study in 2007, this time on PDU, estimated the prevalence to 29,500 (30) with PWID estimated at around 70-90% (20,650-26,550) (3). In 2012, the National Board of Health and Welfare conducted a pilot estimation based on health care register data on PWID only, finding approximately 8,000 PWID in Sweden in 2008–

2011 (27). Just over half (57%) of PWID were found in the three metropolitan regions and approximately 1,800 PWID in the capital of Stockholm (Table 1).

Table 1. Regional and national estimates of PWID (15–69 years) 2008–2011, in relation to the general population.

Region	Estimation	Per 1,000 inhabitants	Region	Estimation	Per 1,000 inhabitants
Stockholm	1,837 [1,662 -2,051]	1.3	V:a Götaland	1,348 [1,196-1,542]	1.2
Uppsala	259 [205-351]	1.1	Värmland	318 [204-546]	1.7
Södermanland	294 [221-421]	1.6	Örebro	351 [288-453]	1.8
Östergötland	352 [274-481]	1.2	Västmanland	267 [202-382]	1.5
Jönköping	274 [234-339]	1.2	Dalarna	185 [115-342]	1.0
Kronoberg	99 [62-196]	0.8	Gävleborg	217 [143-371]	1.1
Kalmar	159 [124-225]	1.0	Västernorrland	182 [134-277]	1.1
Gotland	47 [27-122]	1.2	Jämtland	38 [22-98]	0.4
Blekinge	105 [57-249]	1.0	Västerbotten	225 [167-332]	1.2
Skåne	1,127 [996-1,298]	1.3	Norrbotten	198 [158-271]	1.1
Halland	139 [110-196]	0.7	Country total	8,021*	1.1

**Country total is summarised and confidence intervals (CI) cannot be calculated. CI are reported within brackets.*
Source: Public Health Agency of Sweden, 2015 (translated from Swedish) (17).

The estimation also included the so-called number of unknown cases, i.e. estimations built on the assumption that all persons cannot be identified through registers. This was the first time in Sweden that a direct PWID-estimation was conducted however, much lower compared to previous estimates mixing both PWID and non-injecting drug users (17).

3 PWID-DETERMINANTS, RISK BEHAVIOURS, INFECTIONS AND PREVENTION OF TRANSMISSION

Knowledge on BBV-, but also STI-transmission among MARP is generally obtained as previously described, by collecting and analysing behavioural and epidemiological data and clarifying any associations related to disease outcome. Compared to the general population, PWID are disproportionately affected and at higher risk for e.g. hepatitis, HIV but also STI (31-33). This, foremost due to risk behaviours such as sharing of unsterile injection equipment and condomless sex, but also exposure to risk environments such as incarceration (5, 17, 18, 20).

3.1 PREVALENCE AND STRATEGIES TO REDUCE HCV AND HIV AMONG PWID

Global initiatives to fight the HIV and viral hepatitis epidemics in the world are led by UNAIDS and the WHO, respectively. UNAIDS goal is to end AIDS as a public health threat by 2030, aims for 95% of people living with HIV to know their HIV-status; 95% of these to be on antiretroviral treatment (ART) and 95% of those on treatment to have suppressed viral loads (detectable HIV-virus in the blood), the so called 95-95-95 targets (34, 35). However, reaching these goals in countries with low HIV-prevalence such as Sweden, will likely mean a significant scale-up of interventions to cover PWID not already reached by existing options (36). In addition, some PWID are partly hidden in society and in need of other measures beyond NEP (37). The WHO has also set an ambitious goal for 2030, i.e. to eliminate viral hepatitis (HBV and HCV) as a public health threat (38). Among several targets and apart from providing HBV-vaccination: 90% should be diagnosed and of these at least 80% treated. The targets also include reducing the incidence of HBV and HCV by 90% and the mortality to 65%. For PWID specifically, the suggested coverage is set at 300 sterile needle/syringe-sets per person per year, i.e. based on estimations of acquired number of needle/syringes, NEP visits and individual injection frequency during a set time period (39). This level of coverage has raised concerns that it will also require a scale-up of both available and new prevention measures in contexts with poor coverage (40). Further, that actors supposed to provide prevention interventions need to acquire more comprehensive understandings of BBV-dynamics among PWID and subgroups, with calls from researchers for better surveillance and data (22).

3.1.1 HCV-prevalence and incidence among PWID

Approximately 6.1 million PWID aged 15-64 years worldwide are estimated to be HCV-infected (41) (Figure 2), with high levels of disease burden (42).

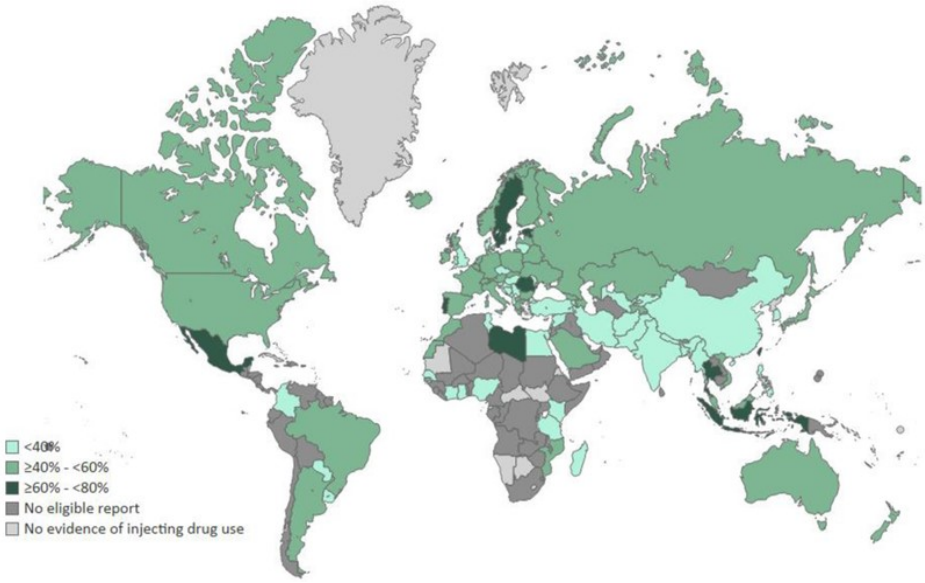

Figure 2. Estimated prevalence of HCV viraemic infection among PWID, by country.
Source: Grebely, J., et al, 2019 (41).

An estimated 4.3 million PWID live in the WHO European region, of whom 2.6 million (60%) are HCV-seropositive and 2 million live with chronic HCV (41, 43). Prevalence of HCV has been reported to vary between 7% and 95% depending on country and context (44) and in 2017, approximately 30,700 new cases of HCV were reported in the WHO European region (45). IDU is believed to account for 40-78% of all new HCV-infections (43, 45, 46), that viral hepatitis (HBV and HCV) is more prevalent among PWID than the general population (47), and suggested as a leading cause of mortality in the world (48). Research also suggests WWID to be more vulnerable to HCV compared to men who inject drugs (MWID) (49-51). In Sweden, mandatory data on drug-related infections such as HCV and HIV are collected through the statutory national surveillance system called SmiNet and case notifications are submitted from clinicians and laboratories to the Public Health Agency of Sweden and the County Medical Officer of Communicable Disease Control (one in each of the 21 regions in Sweden) (52). Up until 2015, a total of 64,200 HCV-cases had been reported in Sweden (53). In 2018, the Public Health Agency of Sweden estimated that approximately 20,000 to 30,000 people lived with HCV (excluding undiagnosed), compared to previous estimates at 43,000 (2011) and 35,000-45,000 (2015) respectively, with the majority of cases attributed to PWID (53-57).

During the past ten years (2009-2018), approximately 10,600 total domestic cases of HCV have been reported, of which approximately five percent were reported as newly infected, i.e. having an acute infection. Between the years the annual number of reported cases have dropped, down to approximately 870 in 2018, of which 600 were reported as IDU-associated (Figure 3) (57). More than half of all cases were reported in the metropolitan regions of Sweden, i.e. Stockholm, Västra Götaland and Skåne (53).

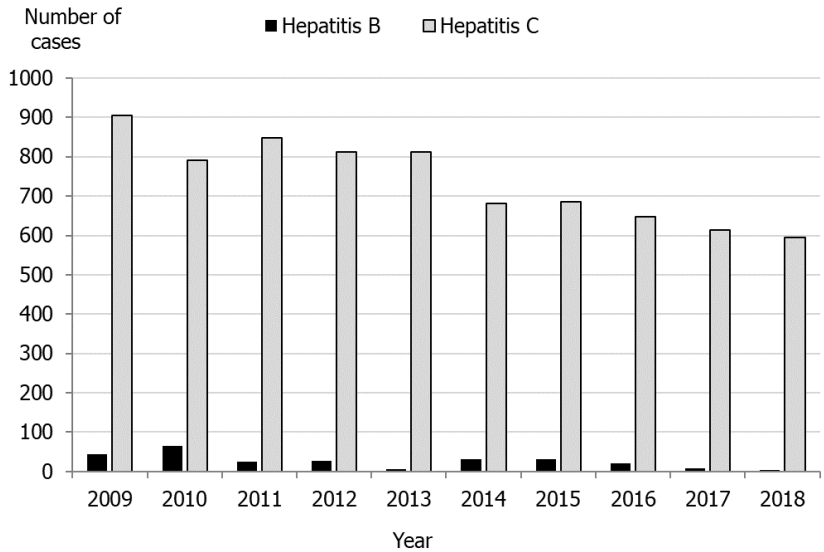

Figure 3. Number of reported cases in SmiNet 2009-2018, infected in Sweden via IDU. Source: Public Health Agency of Sweden, 2019 (57).

In Sweden, the median age at diagnosis for reported HCV-cases to SmiNet has been around 35 years (17). However, separate local reports have shown that the median age of IDU-debut is around 18-19 years (17, 58), with up to 50% of PWID infected with HCV already two years after IDU-debut (59). Further, that young women are at higher risk for HCV, altogether suggesting ongoing HCV-spread among the younger PWID-population. Few studies have investigated HCV-incidence among PWID in Sweden. However, one study among PWID in the Malmö NEP (1997-2005) found an incidence rate of 38/100 person-years compared to a study on the Stockholm NEP (2013-2016), finding an overall HCV-incidence rate of 22/100 person-years (60, 61). Even though no national data exists on PWID HCV-reinfection rates, a study on PWID in the Stockholm NEP found that 29% of respondents with a spontaneously cleared HCV-infection had been re-infected during follow-up (61).

3.1.2 HIV-prevalence among PWID

Degenhardt et al. (2017) estimates there are approximately 2.8 million PWID aged 15-64 years living with HIV worldwide (20), 28 times higher than among the general population

(62). Despite PWID being subject to sporadic HIV-outbreaks (63), e.g. in Greece in 2011 (64, 65), the number of newly reported HIV-cases among PWID in the European Union (EU), Norway and Turkey have declined during the last five-year period (45). In 2017, approximately 940 (3.7%) PWID HIV-cases were reported in the EU (excluding Germany), with a HIV-prevalence among PWID ranging from 7.5% to 20.6% (66). Research also suggests that WWID are more vulnerable to HIV compared to MWID (32, 49), and that HIV-epidemic characteristic is changing from men to women (67, 68). As with the EU, the number of domestic HIV-cases reported among PWID in Sweden has remained very low, averaging six people per year during 2014-2018 (69). The median age at diagnosis for reported HIV-cases to SmiNet, similar to HCV-reported cases, has been around 37 indicating older age for diagnosis or possibly late identification (21). However, two HIV-outbreaks have occurred among PWID in 2001 with 36 reported HIV-cases and 2007 with 70 reported HIV-cases (17, 70, 71). A study on PWID in Stockholm (2008), found that seven percent (n=50) of enrolled PWID tested positive for HIV (72). Likewise, a study on PWID in the Stockholm NEP (2013-2014) found that approximately seven percent (n=93) of newly enrolled PWID tested positive for HIV (73). However, limited research has left a knowledge gap in Sweden for HCV and HIV among PWID age 20-35, i.e. median age of IDU-debut and median age at HCV-diagnosis, and especially among the larger PWID-cohorts, WWID, and in the metropolitan regions.

3.1.3 HCV and HIV co-infection among PWID

A global systematic review estimating HCV and HIV co-infection found 2.4% (interquartile range (IQR) 0.8–5.8%) to be co-infected within the general population compared to 82.4% (IQR 55.2–88.5%) among PWID (31). Research shows that a co-infection increases the risk of liver cirrhosis and is a marker for higher risk of death, compared to those only infected with HCV (74). The goal for treating co-infected people is to eradicate HCV and reduce liver complications and all-cause mortality (75-77). HCV, unlike HIV, today have good conditions for being cured by treatment. In 2014, new effective medicines (Direct Acting Antivirals, DAA) became available, giving fewer side-effects, easier to administer and having shorter treatment time compared to previously used treatment drugs (78).

3.2 KNOWLEDGE ON STI AMONG PWID IS POTENTIALLY OVERLOOKED

Compared to the global focus on HIV and viral hepatitis among PWID, epidemiological knowledge on STI among PWID is not as prevalent. Research however show that PWID in general may be more affected by STI like chlamydia, gonorrhoea and herpes (79) than the

average population, which suggests a higher level of ongoing sexual transmission (80). In Sweden, there is scarce information on national level regarding the situation among PWID. However, in the Swedish national HIV and AIDS strategy 2006-2016, STI-prevention among PWID was pointed out as one of the main goals (14).

3.3 DIFFERENCES IN RISK BEHAVIOURS AMONG PWID

A global barrier in the preventive work with HCV, HIV and STI is the individual lack of perception of own risk behaviours and consequently routes of transmission (as previously described): awareness of infection status, one owns belonging to a risk-group (81) and lack of disease knowledge (17). The most common risk behaviours among PWID is sharing of unsterile injection equipment and having sex without a condom (61, 82, 83). However, there are knowledge gaps with regards to understanding which risk behaviour characteristics, and in what way, are driving the HCV, HIV and STI-epidemics (40).

3.3.1 Sharing of unsterile needles, syringes and paraphernalia

Sharing of unsterile injection equipment is commonly separated between the sharing of needles, syringes and/or paraphernalia (Figure 4). These injection risk behaviours have been studied to great extent and are assumed to be the leading cause for foremost HCV and HIV-transmission among PWID (5, 84, 85).

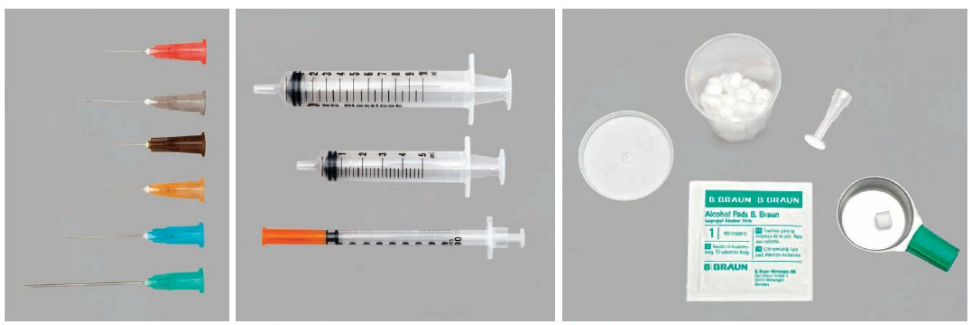

Figure 4. Needle, syringe and paraphernalia.
Source: Public Health Agency of Sweden, 2015 (17).

Further, it is common to make a distinction between people lending out (giving), or receiving already used injection equipment (86-88), since receptive sharing is considered more risk-exposed. It is also important to understand if sharing is facilitated without any direct lending or receiving, e.g. if sharing takes place via a common container, in which order and with how many people. In Sweden, studies among PWID have found needle sharing to be associated with HIV-status and paraphernalia-sharing as a stand-alone risk factor for HCV-infection (71, 72, 82, 89-91). In 2011, a study on PWID in the Malmö NEP found polydrug use of heroin

and amphetamine to be associated with HCV-seroconversion, however not investigating any underlying injection risk behaviours (60). Likewise, a study on PWID in the Stockholm NEP reached similar conclusions on higher levels of risk for sharing needles, syringes or paraphernalia among those HCV-positive (73). During the last ten years (2009-2018), most notified domestic HCV-cases (70%) in the national surveillance system SmiNet, have been reported as infected via injection risk behaviours compared to only 10% reported for HIV (Figure 5).

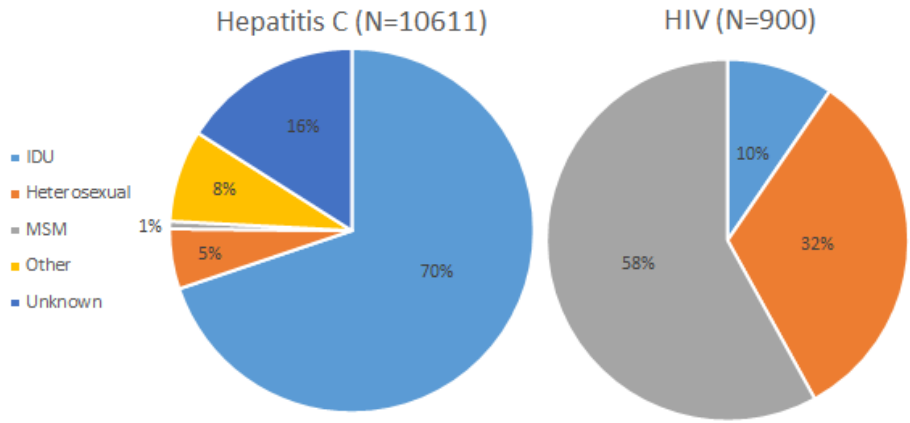

Figure 5. Routes of infection for reported domestic cases of HCV- and HIV-infection in Sweden, 2009-2018.
Source: Public Health Agency of Sweden, 2019 (57).

3.3.2 Condomless sex

Sexual risk behaviour among PWID primarily refers to having unprotected sex, i.e. vaginal intercourse without a condom, important also for both heterosexual transmission of HIV and other STI (79, 83, 92-94). Sexual risk behaviour (unprotected sex) can also refer to other forms of sexual risk practices, e.g. anal intercourse (95, 96). In the early days of the HIV-epidemic, sexual risk behaviour was a well-studied phenomenon among PWID (97). In 1990, a study in remand prisons in Stockholm, reported on widespread sexual risk behaviour among PWID (98). Later studies (1992-1995) within the same context would find low levels of self-report condom use among amphetamine-IDU (a sexual stimulant), who also reported having more sexual partners compared to heroin-IDU (99-101). A report, also on PWID in remand prisons 1987-1998, found that approximately 15% only had used a condom at last sexual intercourse (58). Over the years, research has shown that unprotected sex among PWID is highly prevalent despite targeted interventions such as risk reduction counselling and condom distribution (102, 103). It has also been established that WWID are more at risk for STI than MWID (104, 105), that sexual risk behaviour can serve as a hidden route of transmission of

both HCV and HIV and especially in the wake of reduced sharing of injection equipment (106-109). Sexual risk behaviour has also been found to function as a bridge to other populations (bridging partnerships), e.g. to also affect those in a sexual relationship not injecting drugs (49, 80). However, since 2000, few studies have investigated sexual risk behaviour among PWID in Sweden. A study in Stockholm (2005) found that sexual risk behaviour varied with the partner and their HCV- or HIV-status (82), followed by another study, also in Stockholm (2012), reporting only a third of PWID having used a condom during past month (72). Currently, there is a contemporary knowledge gap regarding sexual risk behaviour among PWID in Sweden, and WWID in particular.

3.3.3 Changes in risk behaviours over time

A key challenge in the preventive work to eliminate hepatitis and HIV among PWID and subgroups is to understand how risk behaviours, e.g. sharing of unsterile injection equipment or condomless sex, change over time. Repeated behavioural surveillance, i.e. repeated data collection with specific focus on PWID-subpopulations, with the objective to survey trends in risk behaviours over time, has been suggested by the WHO in their SGS-system since 2000 (1, 110). Some countries however, have struggled with implementing or adopting this system into their national surveillance system (111). NEP have been found to be effective in reducing injection risk behaviours (87, 112). This finding is supported by prospective cohort and longitudinal studies on PWID in NEP showing a reduction in injection risk behaviours compared to PWID not in NEP (113-120). Similar reductions in risk behaviours have also been found for PWID in opioid substitution treatment (OST) or a combination of NEP and OST (121, 122) and use of drug consumption rooms (DCR) (123, 124). However, less is known about risk behaviour change among PWID and subgroups, or PWID novel to NEP. In addition, information education and communication (IEC, sometimes referred to as a behavioural intervention (125)), or psychosocial interventions among PWID have been found useful to reduce risk of sharing unsterile injection equipment but also for having condomless sex (126, 127).

3.4 DETERMINANTS FOR RISK BEHAVIOURS AMONG PWID

Knowledge on contributing factors, or predictors (here further referred to as determinants and at an individual level), and their different associations with injection and sexual risk behaviours, provide important understanding of how risk behaviours can vary among PWID. Determinants include both those that are static, i.e. that do not vary such as gender, age at injection drug debut and those that are dynamic and can vary over time, e.g. housing situation

and so forth. Research on PWID have been inconsistent in how determinants have been used to study associations with risk behaviours, HCV, HIV and STI. In some studies, determinants have been analysed in direct connection with a health outcome e.g. associating unstable housing with risk of HIV-infection among PWID (128, 129), or type of drug being associated with HCV-seroconversion (60). Studies with this design have left out a more careful and important description of intermediate injection or sexual risk behaviours, constituting as the main routes of infection (130). On the other hand, available research on determinants for PWID risk behaviours have covered socio-demographic, drug and to some extent sexually related determinants however, not in a systematic way and especially not for WWID (60, 61, 94, 131). As a consequence, researchers have requested more in-depth research on determinants, standardisation and quality of epidemiological data, otherwise believed to constitute as barriers to effective and tailored prevention and treatment for HCV and HIV among PWID and subgroups (22, 23).

3.4.1 Socio-demographic determinants

Gender is one of the most important determinants for understanding how injection and sexual risk behaviours vary between contexts, time and geographical settings among PWID. Perception or understanding of gender-associated roles is important in understanding how this can influence people's behaviours, e.g. opportunities, expectations and demands in social contexts such as partnership roles and dynamics, parental responsibilities, education and work (132). Further, how gender roles can influence vulnerability to infection, health-seeking behaviours, an individual's sexuality or inclination to take risks such as testing drugs (133). Prevention and tailored interventions for risk behaviours and HCV, HIV and STI needs to be understood from these explanatory roles and the unequal distribution of material, resources and power related to gender in society (134). For example, studies have shown that women compared to men are more at risk for receptive sharing, or that men share in larger networks and with more people (50). Further, research suggest that women compared to men are more exposed to sexual risk behaviour (135, 136) whereas men have been associated with late HIV-diagnosis (137). International experts and organisations have highlighted gender as a future research priority in relation to ending the hepatitis and HIV-epidemics by 2030 (22, 34, 138, 139). However, even though research is growing on WWID and MWID, there is still significant knowledge gaps with regards to foremost WWID and subgroups, harm reduction interventions and HCV and HIV-prevention (32, 140). Other well established and important socio-demographic determinants are age (141, 142), housing or homelessness (60, 61, 86,

143), civil status (144-146), education level (28, 147, 148), employment status (149, 150), experience of remand prisons or imprisonment (90, 149-152).

3.4.2 Drug-related determinants

Drug-related determinants refer to determinants that in different ways can be linked to an individual or group's past or ongoing drug use and are associated with sharing injection equipment. The most common in PWID-research is type of drug or most used drug (61). Type of drug- or polydrug use, drug addiction (drug habits) and the social context in which the drugs are injected are also important to understand since they have different effects on a person's risk behaviour (153, 154). Among PWID, two groups of drugs dominate: central stimulants (especially amphetamine-like drugs) and opioids (e.g. heroin) (155). Research has also found that, for example, those injecting fentanyl (synthetic opioid) are more at risk of HIV compared to those injecting amphetamine (156). Likewise, previous research has found that amphetamine-IDU were more likely than those injecting heroin to share paraphernalia (157, 158). These determinants are especially important for understanding the risk of HCV-transmission (5, 159, 160). Other important determinants are age at drug and IDU-debut (161-163), type of drug at drug and IDU-debut (72, 164, 165), IDU-duration (163, 166) and so forth.

3.4.3 Sexual-related determinants

Sexual related determinants primarily refer to determinants that can be associated with unprotected sex, e.g. having a casual- or steady sex partner. Type of partner normally relates to being in a stable relationship or not, which in turn can indicate if one has unprotected sex or sex with one or several partners (83, 109, 167). Other important determinants is same-sex partners, e.g. MSM (168, 169), having bought sold, or exchanged items or favours for sex (68, 83, 170). Research has also found that levels of sexual risk behaviour varies with type of drug used, individual knowledge about risk of infections, preferences for sex and so forth (17, 109, 153, 171). Lately, focus has been put on chemically induced sex ("chemsex/slamming", i.e. injection of psychostimulant drugs in a sexual context (172)) prevalent among MSM, but also women who have sex with other women (WSW). The type of sex one has, e.g. high-risk traumatic sexual practices has been found to associate with transmission of HCV and HIV (108, 173, 174). Research has previously shown that sexual transmission of HIV occur among PWID (106), but research also indicate ongoing sexual transmission of HCV, foremost via anal intercourse (type of sex) among MSM IDU (109, 175, 176). There is however currently limited epidemiological data on the interplay of PWID and subgroups, MSM, WSW and sexual risk behaviour and transmission of BBV.

4 HARM REDUCTION INTERVENTIONS FOR PWID

Despite presence of harm reduction interventions such as NEP since the HIV-epidemic in the 1980s, and earlier (1966) if taking methadone maintenance therapy (MMT) into account (177), there exists no unified definition on the concept of harm reduction in the world (178). A contemporary interpretation of harm reduction has been launched by the organisation Harm Reduction International:

> *"Harm reduction refers to policies, programmes and practices that aim to minimise negative health, social and legal impacts associated with drug use, drug policies and drug laws." (179)*

When it comes to prevention of BBV and STI among PWID, harm reduction in practice normally refers to a comprehensive package of health services endorsed by the WHO, European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), European Centre for Disease Prevention and Control (ECDC) and all major UN-bodies, among others. These services (interventions) usually take the form of programs such as NEP, OST, DCR where people can inject drugs under supervision of health staff (180), or low threshold services (LTHS) incorporating many program components under one roof (181). These services usually offer program components such as IEC, VCT, vaccination for HBV, ART for HIV, DAA-treatment for HCV, treatment for STI, condom distribution (62, 182-185) and heroin assisted treatment (HAT) (186). Since effective treatments became available, firstly ART for HIV and then DAA for HCV, prevention strategies have more strongly come to focus on a treatment as prevention-approach and realised through scale-up of harm reduction services (187). Treatment as prevention has been shown to have major impact on population level and effectiveness in either stopping, or reducing, onwards linked BBV-transmission (125, 188). Current estimates suggests IDU to be present in at least 179 of 206 countries (189, 190) and despite strong support from research and international and national government agencies, access to harm reduction services such as NEP or OST is limited or non-existent in many countries because of policies or laws (18, 183).

4.1 NEEDLE EXCHANGE AND OST-PROGRAMS

Research has since long established that NEP, OST or a combination of the two, are effective in reducing injection and sexual risk behaviours as well as HIV- and HCV-incidence among PWID (70, 85, 87, 112, 117, 121, 174, 185, 191-195). However, in 2018 it was estimated that only 86 countries (of 193) were running forms of NEP and 86 countries providing OST (190). Both the WHO and UNAIDS are promoting a scale-up of

these services in order to reach their 2030 HCV and HIV-elimination goals (34, 48). The UNAIDS targets states that 90% of PWID should have access to tailored interventions such as NEP, OST, VCT, treatment and condoms (Figure 6), with recommended levels (defined as high coverage) of 200 syringes distributed per PWID and year (39). Also, that 40% of PWID should be on OST (34).

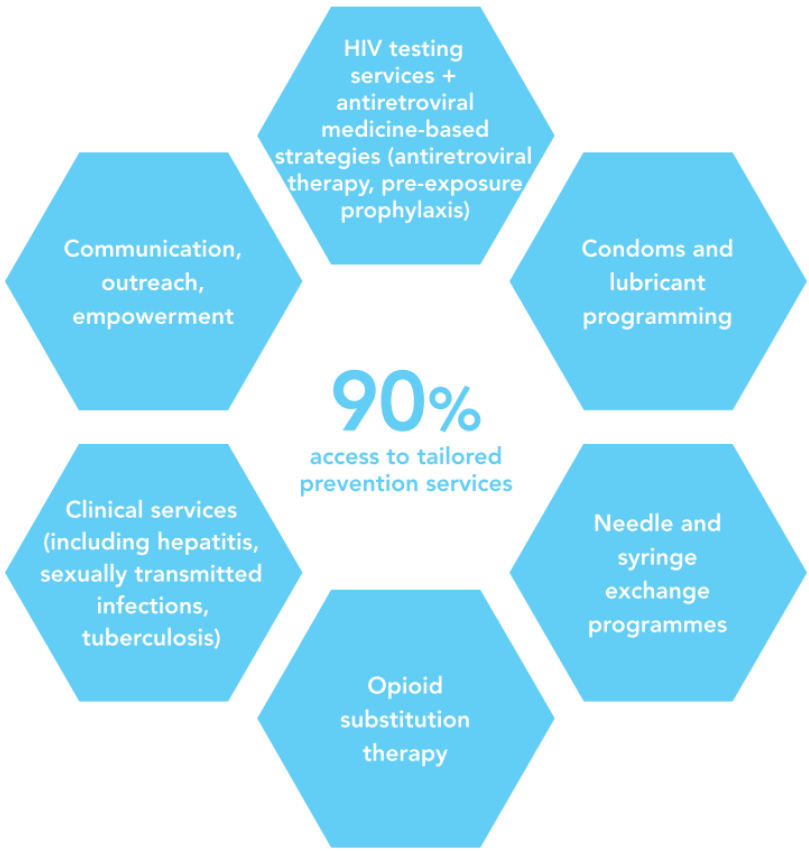

Figure 6. Illustrative combination of prevention programmes for PWID.
Source: UNAIDS, 2015 (34).

According to UNAIDS, high NEP and OST-coverage has only been found in Austria, Luxemburg and Norway, with Malta being within proximity (Figure 7) (183). Other reports have suggested Australia and the Netherlands to also have high combined coverage (189, 196).

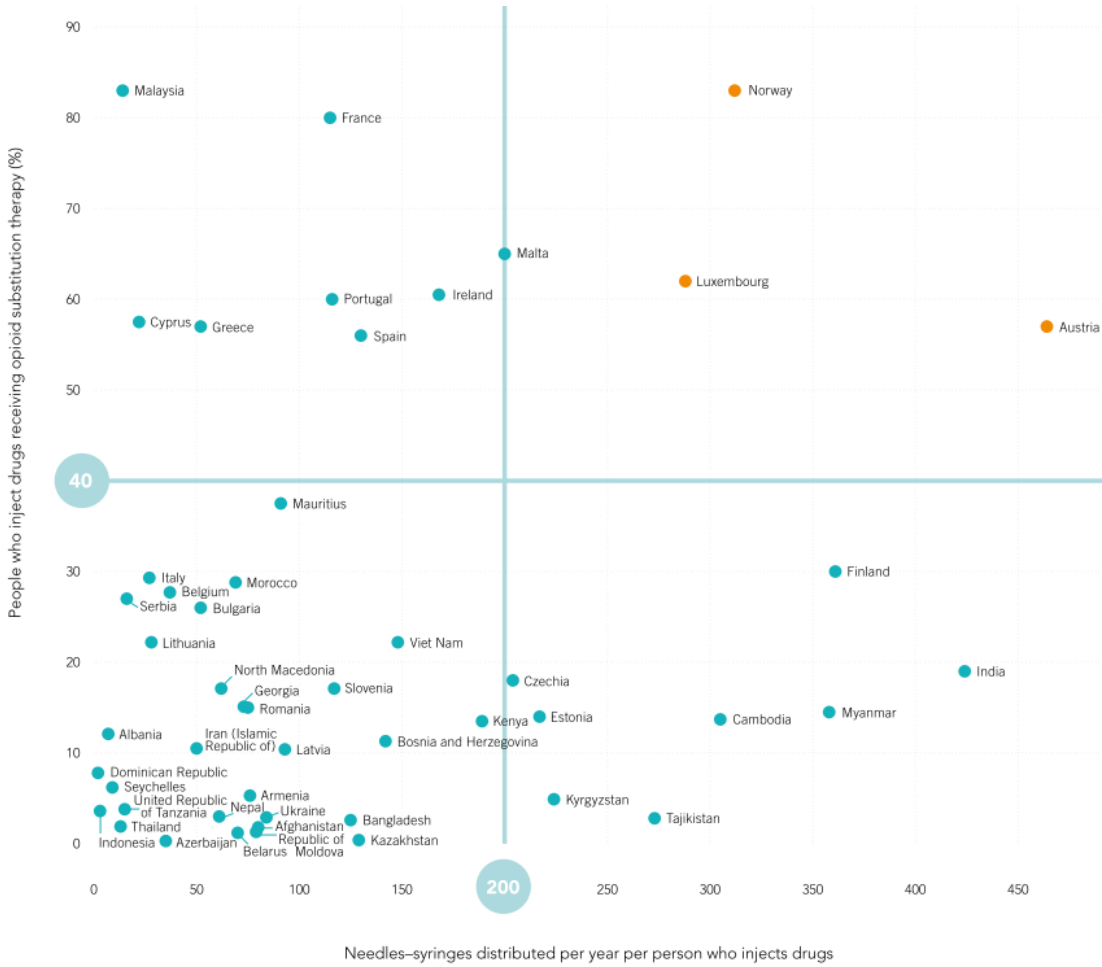

Figure 7. Coverage of NEP and OST, by country and last year available, 2013–2017.
Source: UNAIDS, 2019 (183).

The WHO target of 300 syringes distributed per person and year (as previously described) is set believing the UNAIDS' target of 200 needle/syringes is not enough to fully reduce BBV-transmission among many PWID (39, 139), risking continued spread of HIV and hepatitis (197-200). A study in UK found that scaling-up NEP and OST in three cities to an 80% coverage level (one clean needle per injection), in combination with high levels of HCV-treatment, could decrease HCV-incidence among PWID with up to 90% (201).

4.1.1 A stalled NEP-development in Sweden over time

As previously described, after early initiation of NEP in Lund (1986) and Malmö (1987), both in Region Skåne, initial NEP-development was stopped for a long period in Sweden. This stop came as a consequence of a societal climate and political decisions (202), in a strict

repressive-control drug policy era and goal of a drug-free society, captured in a government investigation report titled “We will never give up” in which it was stated,

> *”It should be difficult to be a drug addict. The more difficult it is, the more clearly the other alternative, i.e. a drug-free life will appear”. (203)*

Limited or absence of BBV-research on foremost NEP and PWID in Sweden, together with actor-coalitions, e.g. actors in terms of government agencies, researchers or politicians and how they positioned themselves around a common standpoint, being against, indifferent or for NEP, obstructed political unity (9, 204). Further, NEP-absence in the other 20 regions in Sweden during this period left an estimated 90-96% (n=7,200-22,800, from estimations previously described) of PWID in Sweden without access to formal NEP (7, 17), also seeing two HIV-outbreaks occur. Although NEP were also politically debated in other countries, they were adopted somewhat quickly in many cases and as part of official policies (205). In the Nordic countries as example, Norway, Denmark and Finland compared to Sweden have had extensive NEP-coverage for many years (181, 206, 207), despite Sweden’s NEP-law launched in 2006 (208). A study on the Swedish drug policy would come to describe this indecisive back-and-forth process as “tango politics” (9). Only in 2012 would the second region, Kalmar, start a NEP after which development took off. In 2017, the 2006 NEP-law was revised, reducing the age limit from 20 years to 18 years and removing the municipality veto towards regional decisions to start NEP (209). In 2020, 17 of 21 regions in Sweden were either running or about to start NEP (Figure 8). However, there is a knowledge gap regarding why NEP-development was stopped for such a long period of time, only to start, and then to undergo a rapid scale-up in only a few years’ time and to a near 100% regional coverage.

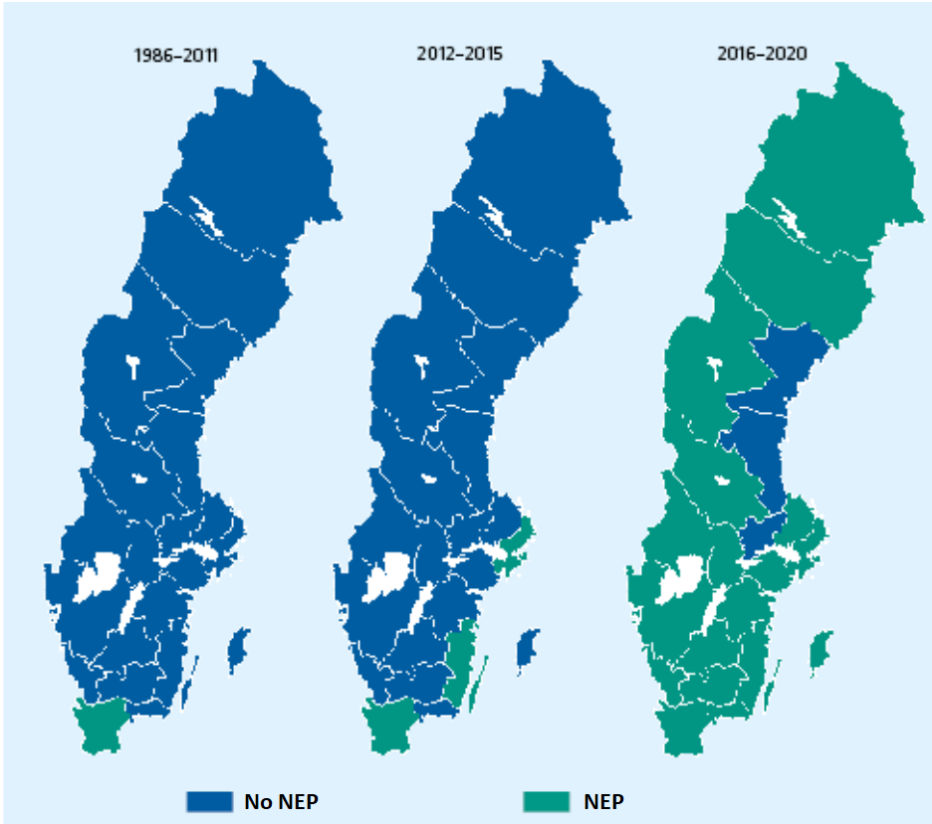

Figure 8. Development of NEP in Sweden over three periods, 1986–2020.
Source: Public Health Agency of Sweden, 2020.

4.1.2 A slow and restricted OST-development in Sweden over time

Sweden's first MMT-program for opioid users was opened in 1966 in Region Uppsala (177). For political reasons and a drug policy context similar to that of NEP, the number of individual drug treatment places were however limited to 100 in 1979 (210), and only lifted in 1984 because of the HIV and AIDS epidemic (211). Shortly thereafter, Sweden saw an additional three MMT-programs starting, in Region Stockholm (1985) and in Lund and Malmö (1990 versus (vs.) 1992) in Region Skåne, increasing the number of individual treatment places to 450. In 2004, Sweden's fifth MMT-program was started in Gothenburg, Region Västra Götaland nearly tripling the number of treatment places to 1 200 (210, 211). The first regulations (mandatory rules) issued for *opiate* substitution therapy (in Swedish: Läkemedelsassisterad underhållsbehandling för opiatberoende, LARO) came with restrictions: the age limit was set to a minimum of 20 years (212), compulsory documentation for a minimum of two year opiate dependency was needed and drug use led to program expulsion and an automatic six-month ban before being considered for re-entry. In 2009, the

two-year dependency minimum was reduced to one year, and the six-month ban for re-entry down to three months (213). In 2013-2015, there were approximately 110 programs housing 3700 clients, of which 30% were women, *opioid* dependency was included and the one-year opiate dependency requirement and three-month ban was removed (211, 214, 215). By 2020, local joint NEP and OST-collaboration initiatives were running in both Region Skåne and Stockholm and research showed that up to 80% of PWID referred to OST by the Malmö NEP, remained in treatment after one year and with an increased health-related quality of life (216, 217).

4.2 REMAND PRISONS AS AN ARENA TO REACH PWID

Remand prisons (where a person is held in custody awaiting trial) and prisons (after receiving a criminal sentence) have since long been pointed out by the WHO, UNAIDS, United Nations Office on Drugs and Crime (UNODC), EMCDDA and ECDC among others, as a well-known arena for finding and targeting PWID with health related- and harm reduction interventions (185, 218-221). It is estimated that one third of prisoners around the world have used drugs while in prison (221). Research has established that PWID in prisons, compared to the general public, are disproportionately affected by ill health (222), higher rates of injection (223-225) and sexual risk behaviours (152), HCV and HIV, and that NEP and OST in prisons are effective harm reduction measures (226-229). Further, that women in prison are at high-risk compared to men, with higher rates of drug use disorder problems (230, 231). International health agency guidelines underline the importance of interventions in prisons: condom provision, behavioural interventions, OST to reduce drug demand, VCT, treatment and vaccination for hepatitis, NEP to limit the re-use of unsterile injection equipment, safer sex promotion, to reduce risk behaviours and HIV, hepatitis and STI-transmission among PWID (232, 233). However, harm reduction interventions in prisons in the world is limited with only 11 countries reporting NEP and 56 reporting OST in at least one prison (221). In the European region, in 2017, 28 countries reported provision of OST (233), six to provide NEP and 29 to provide condoms in prisons (234). In Sweden, NEP are not available in prisons, however basic health care, condoms, VCT, vaccination and treatment for BBV, and to some extent also OST, are offered (57). In 2018, the Swedish Prison and Probation system comprised of 32 detention centres, 45 institutions and 34 outpatient centres (235) and it was estimated that 50% of the prison inmates had any form of drug dependence (236). However, research on PWID in Swedish prison has been limited resulting in a lack of understanding regarding determinants, risk behaviours and infections, especially among WWID.

4.3 SOCIAL SERVICES AS A LINK IN THE HARM REDUCTION CONTINUUM OF CARE

Each of Sweden's 290 municipalities, the administrative level below the 21 regions, constitutes of local government bodies in charge of providing social services: administering elderly care, support for PWID, people with disabilities, individuals and families, including various forms of welfare assistance. The social service arena is well-known for meeting PWID and collaborates with the Swedish National Board of Institutional Care to facilitate compulsory care and treatment of young people e.g. with drug use problems, in accordance with the Care of Young Persons (Special Provisions) Act (in Swedish: lagen med särskilda bestämmelser om vård av unga (LVU) and the Secure Youth Care Act (in Swedish: lagen om verkställighet av sluten ungdomsvård (LSU) (237, 238). Compulsory drug treatment for drug users is also facilitated under the Care of Substance Abusers (Special Provisions) Act (in Swedish: lagen om vård av missbrukare i vissa fall, LVM) (239). More than 1,000 people each year are subjected to compulsory drug treatment with support of the LVM-Act (240). Knowledge on PWID in compulsory treatment is limited. A report by Richert et al. in 2012 found that youth (15-23 years old) enrolled in an educational program while being sectioned, reported high risk for BBV, experience of IDU, high levels of sexual risk behaviour and inadequate knowledge levels of routes of infectious disease transmission (241). Research and national investigations have also shown that drug users refrain from seeking support from the social services because of presence of judgmental, ideological or moral views (242-244). Further, it is reported that only five percent preferred seeking care with the social services compared to the regional health care system (245). Health care staff in Sweden are under an obligation to report suspected child maltreatment to the social services, i.e. if a parent is using drugs. However, research show underreporting is a common issue (246-248). IDU in a context with children and parents consequent fear of losing custody, can constitute as a barrier for seeking treatment (249). Research also show that women report being less likely than men to seek treatment, citing criticism from staff, stigma and judgmental approaches to service delivery (250).

4.4 SUMMARY OF KNOWLEDGE GAPS AND CHALLENGES FOR PWID-PREVENTIVE WORK

In summary and as previously described, even though PWID have been studied at length around the world, there are still some areas where our understanding is insufficient and needs further exploration. A prioritized area is improved knowledge of risk behaviours among PWID and subgroups, and foremost WWID, largely neglected in BBV and STI-related research (22) and in countries without a developed SGS-system (111). With increased

understanding of the varying aspects of PWID and subgroups, as well as HCV and HIV-transmission, interventions and programs may become better tailored to address specific needs and to remove eventual barriers for preventive work. This also implies improving behavioural surveillance, specifically with regards to the current and limited understanding of determinants (especially gender-specific) association with injection and sexual risk behaviours, but also changes in risk behaviours over time and reasons for dropping out of NEP. To facilitate implementation of tailored harm reduction interventions, and also possible scale-up of new programs, it is also important to understand the long delay in Sweden to scale-up NEP despite strong recommendations from global health expertise. An enhanced understanding of these areas, considered and addressed in this thesis and its paper I-IV, will hopefully contribute in strengthening both behavioural and epidemiological surveillance for PWID and subgroups and especially WWID. In addition, facilitate continued scale-up of harm reduction interventions and to eliminate viral hepatitis and HIV in the world by 2030.

5 AIMS

The overall aim of this thesis was to analyse conditions for harm reduction program interventions such as NEP, including in-depth knowledge of PWID and subgroups, determinants, risk behaviours and consequent exposure to HCV and HIV, both in remand prisons and a NEP in Stockholm, Sweden.

5.1 SPECIFIC AIMS

1. To study NEP-development in Sweden over time, in an era of a repressive-control drug policy and a national goal of a drug-free society (**paper I**).
2. To study determinants for injection risk behaviours among PWID at enrolment in remand prisons in Stockholm, Sweden (**paper II**).
3. To study injection risk behaviours; receptive sharing of needle/syringes and paraphernalia at enrolment and over time in a cohort of PWID in the Stockholm NEP (**paper III**).
4. To study determinants for injection and sexual risk behaviours among subgroups to WWID at enrolment, retention in the NEP over time, and reasons for being LTFU (**paper IV**).

6 MATERIAL AND METHODS

Paper I aimed to give an overview of the national Swedish drug and harm-related policy over time, with special focus on NEP-development from the 1980s up to 2017. Paper II focused on PWID (2002-2012), using remand prisons in Stockholm as a platform to find PWID, i.e. before any NEP was available in Stockholm. Paper III-IV (2013-2018), were performed on PWID enrolled in the newly opened NEP in Stockholm, and with special focus on WWID and subgroups (Figure 9).

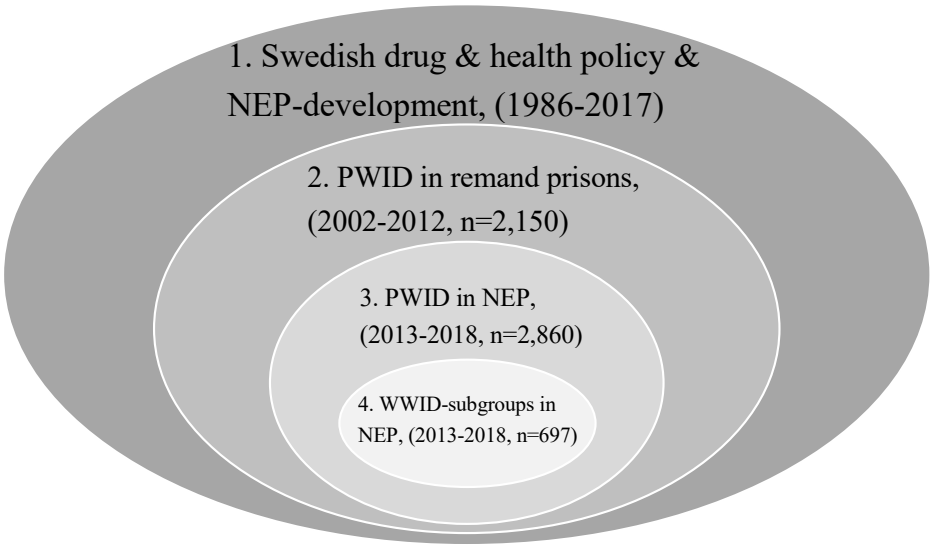

Figure 9. Overview of scope, focus and study populations for paper I-IV.

6.1 RESPONDENTS, SETTINGS AND STUDY DESIGNS

6.1.1 Paper I

This paper analysed NEP-development in Sweden over time (1986-2017) in relation to Swedish drug and health policy. The empirical material: grey literature, policy documents and research, were identified and collected using a document-snowballing sampling technique. The key sources were mostly government agency publications and foremost the National Board of Health and Welfare, the Institute for Infectious Disease Control, the National Public Health Institute, the Public Health Agency of Sweden and the Swedish Government. Data collection was complemented by a participatory approach with the research team being involved in the production of certain documents. Most documents were published 2000–2017 in Sweden. In total, 147 documents were identified based on the search terms; harm reduction, drug policy, health policy, NEP, HIV, HCV, drug abuse or use, injection, needle, syringe and PWID and the documents were read several times. Of these

documents, the research team identified 72 key documents which were analysed in-depth. Key excerpts that were associated with the search terms and for relevance to the drug and health-related NEP policy in Sweden, were extracted and the history around was deconstructed in relation to NEP development within the Swedish drug and health policy. The main events, actors and key documents for the study period are described in Figure 1 of paper I.

6.1.2 Paper II

Remand prisons in Sweden work as temporary nodes for holding arrested people for further judicial processing. All people enrolled in custody in the Swedish prison and probation system are asked about their drug use and offered a voluntary health examination which includes testing for HIV, HCV and HBV among other things. In this cross-sectional open cohort study, specifically trained staff, daily and systematically, screened newly enrolled people in remand prisons for IDU. Between 2002-2012, a total of 2,150 PWID were identified and enrolled in this study. Approximately 80 questions were asked through interviews using a semi-structured questionnaire on self-reported injection risk behaviours, i.e. having shared injection drug solution, lent out- or received already used injection equipment from somebody. The questionnaire also covered determinants which were grouped in three categories: socio-demographic determinants, drug-related determinants and time-related determinants. Enrolment characteristics of participants are described in Table 1 of paper II.

6.1.3 Paper III-IV

The Stockholm NEP, Sweden's fifth NEP since 1986 and Region Stockholm's first, started enrolling PWID in April 2013. In a NEP, PWID can exchange used injection equipment for new and sterile equipment. At enrolment, after being confirmed as an active PWID, age 18 or older (20 or older before March 2017, due to previous Swedish legislation) and ability to establish one's identity, the person undergoes testing for hepatitis A, HBV, HCV and HIV and is further offered vaccination for hepatitis A and HBV, behavioural risk reduction counselling, HCV and HIV-treatment and treatment for other diseases. PWID are also offered referral to the social services or programs for drug dependency treatment including OST. The Stockholm NEP hosts physicians and nurses with specialisation in infectious diseases, psychiatry and drug dependency, as well as counsellors and midwives. Both paper III-IV included PWID in the Stockholm NEP and all participants were followed to their last registered visit within the respective study period. Information collected from PWID-visits were recorded in the NEP-database.

Paper III

In paper III, a prospective and open cohort study, injection risk behaviours, e.g. receptive sharing of needle and/or syringe and paraphernalia at baseline and a follow-up period of five years (2013-2018) was investigated. A total of 2,860 PWID in the Stockholm NEP were identified and included in the study. Self-reported risk behaviour and information on demographic and drug-related determinants was collected through interviews using a questionnaire of 34 main questions, at baseline and follow-up visits set at: 6 months (±2 months) for early identification of changes in risk behaviour after NEP-enrolment, 12 months with a time span of ±3-5 months allowing for individual variation, 24 (±5 months), 36 (±5 months) and 48 (±5 months). Enrolment characteristics are described in Table 1 of paper III.

Paper IV

Between April 2013 and March 2018, a total of 2,909 PWID, including 697 WWID enrolled in the Stockholm NEP were included in the study. Socio-demographics, as well as determinants related to drug use and HIV- and HCV-infection among WWID were analysed for association with self-reported injection and sexual risk behaviours at enrolment. The risk behaviours considered were receptive sharing of needle/syringes and paraphernalia past month and having had sex during past month and not using a condom at last intercourse. To investigate WWID-probability of retention in the NEP, a six- and 12-month (i.e. a calendar year) time frame was used to define active NEP participation. Based on available research, reasons for being LTFU from the NEP was analysed using a selection of key socio-demographic, drug and sexual-related determinants. Enrolment characteristics are described in Supplementary Table 1 of paper IV.

6.2 METHODS

6.2.1 Policy methods in paper I

In paper I, in relation to the advocacy coalition framework (ACF) and its three levels, the deep core, the policy and secondary aspects (described below) (251, 252) and how it was used in a study on NEP-development in Switzerland (253), the concept of how NEP-development resisted or changed within the Swedish drug and health policy was analysed. This analysis was conducted using the modified hierarchical framework which included a public health-based harm reduction and health policy track, aligned side-by-side with the old repressive-control policy, the drug policy track (254), described in Figure 2 of paper I. Focus was put on analysing any competition between belief systems and their inherent and

hierarchical structural levels: firstly, the deep core holding the fundamental vision of the individual and society and secondly, the policy core containing strategies and policy positions that associate with the deep core and thirdly, secondary aspects containing the instruments on how to implement the policy core (252). A detailed within-case empirical analysis was used, i.e. conducting an in-depth exploration of a stand-alone phenomenon, to discern patterns and processes, which allowed for reconstruction of key events and decisions (255). Further, this analysis was used to trace-back, triangulate and analyse subtle and often complex multi-faceted policy and decisions-making processes, or possible triggering-events, which could influence change in NEP-development (205, 256). From an actor-coalition perspective, e.g. actors in terms of government agencies, researchers or politicians and how they positioned themselves around a common standpoint, was investigated in relation to how problems, disagreements and evidence were formulated and addressed on public platforms. Also, how actor-coalitions took part in influencing drug and health policymaking from an original and somewhat unanimous zero-tolerance approach (257, 258), to a more polyphonic health related public discussion in the new millennium (202).

6.2.2 Statistical methods in paper II-IV

Data from the Prison and Probation service and NEP were analysed using the JMP 10.0-13.0VR (SAS Institute Inc., Cary, NC, USA) or Stata 13 and 15/15.1 (StataCorp, College Station, TX, USA) statistical programs. The NEP-database (InfCare) collects data from PWID-visits to the NEP and is both a tool for clinical decision-making and analysis of data in real-time. In papers II-IV, descriptive analyses were performed to describe socio-demographic, drug, sexual or time-related characteristics for the study population and categorical data were described as percentages. All reported p-values were two-sided, and p-values <0.05 were considered as statistically significant. In paper II, multivariable logistic regression was used to study the association between 10 determinants and three injection risk behaviour outcomes described in Table 2 of paper II. Time was also considered as a determinant and the relationship between year of the interview and the three risk behaviour outcomes was modelled assuming linearity. Sensitivity analyses were also conducted, which included a quadratic form of the year of examination and polynomial b-spline with 3 degrees of freedom with no significant differences found in the estimates. The model with polynomial b-splines for the variable year of examination was used to model the predicted values for the three injection risk behaviour outcomes. Putative variables were kept in the final model. In paper III, differences in PWID NEP-enrolment characteristics were tested for using Chi-square or Fisher's exact two-tailed tests for categorical variables. For continuous values, the

Wilcoxon rank-sum test was used. Generalized estimating equation regression (259) was used to model the odds of the two injection risk behaviours at inclusion, five follow-up points and for 11 determinants. Because of the longitudinal characteristics of the data, generalized estimating equation regression was used to account for potential dependence in the injection risk behaviours and within participants over time. Firstly, associations between determinants and the injection risk behaviour odds at baseline was analysed, described in Table 2 of paper III. This was followed by an analysis into the relative change in odds of the injection risk behaviours and the five follow-up points over time, including a test for overall change over time and a p-value described in Supplementary Table 1 of paper III. Results were reported as adjusted odds ratios (aOR) with corresponding 95% CI. In paper IV, determinants at enrolment and any associations with injection and sexual risk behaviours were analysed using multivariable logistic regression described in Table 1 of paper IV. NEP retention for WWID was analysed using a 6- and 12-month time frame during the period April 2013–March 2018, and the Kaplan–Meier survival estimates, stratified for gender and compared using the 2-sample log–rank test described in Figure 3 of paper IV. Multivariable Poisson regression with estimation of cluster robust standard errors was used to study the association between selected determinants and the risk of being LTFU described in Table 2 of paper IV. The individual was used as the unit of analysis. HCV and HIV-status, given their changing status, was treated as time-variant covariates. Results were reported as aOR at enrolment and adjusted incidence rate ratios (aIRR) for the LTFU estimates, with corresponding 95% CI.

6.3 ETHICAL CONSIDERATIONS

Paper II-IV were performed in accordance with the Helsinki declaration. For paper II, ethical permissions had previously been granted (Dnr 87:90 and 88:20). However, to ensure continued validity of this grant, a new ethical permission was sought and approved in 2012 by the regional ethical review board in Stockholm, Sweden (protocol 2012/3:10). For paper III-IV, ethical permission was granted in 2013 and 2105 (2013/495-31/3 and 2015/1374-32) respectively. In paper II-IV, all interviews were conducted on a voluntary basis and after having received informed consent. The same applied for data collection from blood sampling, carried out by medical staff and following appropriate official routines of the health care system in Region Stockholm. The individual PWID did not receive any personal compensation from participating in any of the studies. However, at group and national level, all results were fed back to the NEP and remand prison staff through meetings, seminars and in local or national reports, and by extensions, to the users in terms of enhanced primary and secondary prevention.

7 RESULTS

7.1 PAPER I - NEP AND POLICY DEVELOPMENT IN SWEDEN OVER TIME

In paper I, we identified three evolutionary phases for NEP and policy development in Sweden over time: reorientation, stalemate and development, in line with finds from a policy study on the Norwegian drug context (260). The respective phase contained key events such as reports and research, actor-coalitions and policy trends and development of NEP and BBV, described in Figure 1 of paper I.

7.1.1 Phase 1: Reorientation - A change of trend in Sweden's drug and health policy and the NEP-law

Our results show that during the first phase 2000–2005, actor-coalitions for and against NEP emerged foremost on the national government agency level (14, 202) and within the research community (261, 262). This, in a time where national politics where run by a Social Democrat led government and the NEP-debate dividing political parties, with politicians voicing individual ideological arguments instead of scientific evidence (202). Sweden's first NEP (1986) was launched in a strict drug policy context with a zero-tolerance repressive-control drug policy and goal of a drug-free society, resisting the emerging concept of harm reduction in the world (263). This political and societal drug policy consensus was challenged in early 2000 when a government investigation the "Choice of path - The drug policy challenge" was published (8). The investigation reintroduced and enforced the perspective of the individual drug user's vulnerability and situational complexity around drug use, supported by similar reorientation movements in Norway and Denmark (205, 264, 265). The change in focus towards the individual drug user, was further reinforced with the reorganisation of the drug policy into a wider public health policy framework, introduction of a public health-based HIV-strategy and shift from drug substances towards environment and lifestyle determinants such as use of unsterile syringes (266, 267). The reorientation was also supported by actor-coalitions and key government agencies (15, 268), researchers, (269) and high levels of reported BBV among PWID; 800 notified HIV-cases between 1985–2005 and 39,000 HCV-cases between 1990–2005 (13). Political leadership and initiative was further demonstrated with the appointment of a special national drug coordinator tasked with investigating a possible NEP-law (266, 270), providing momentum and necessary instruments for change in NEP-development. However, despite support, key-actor opposition calls for a required strong link between NEP and the social services, resulted in an indecisive and complex political situation with arguments claiming that research on NEP-efficacy was either inconclusive or insufficient. These calls kept important key factors and adverse actors

in decisive positions, effectively hindering political unity and willingness to starting new NEP. However, despite the turmoil, national action plans for drugs and HIV were launched (271, 272), manifesting an embryo to a dual drug and health policy track structure. The national plans created enough momentum for change in which a new NEP-law was proposed and implemented, however coming with restrictions and a built in veto possibility (14).

7.1.2 Phase 2: Stalemate - The law aftermath and the dual ownership

In the second phase of 2006–2011, led by a right-wing/centre government, the NEP-law was implemented however without any new NEP starting due to the veto (208). To start NEP, the Regions needed approval from the municipality-level Social Welfare Board (social services), involving local politicians in the decision-making process and many who were against, consequently splitting the NEP-issue on both the drug and health policy track (273). Arguments have been raised that the veto was inserted out of fear of negative consequences for the Swedish drug policy, and consequently subordinating the infectious disease perspective (204). NEP-development faced opposition in terms of repeated political hindering, termination of the drug policy coordinator and creation of an intra-governmental structure which provided non-governmental organisations with ties to the repressive-control movement and critical of NEP, with direct communicative access to the government (274-277). With this reorganisation in the government structure, a political superstructure was created, and NEP-development became a non-issue when focus was shifted away from the individual drug use perspective towards other drug-related consequences, e.g. road accidents. These events and consequently changes in processes and decisions, drew strength from the balance of actor-coalitions either against or indifferent to NEP-development (278), keeping ownership under drug policy control via the veto decision-making power with local politicians. This we argue, ruled out unity around NEP-development. Sweden's shift in focus during this time was also contradictory to how the other Nordic countries were working on scaling-up harm reduction services (181, 264, 265). Despite a trigger-event such as a large HIV-outbreak among PWID in 2007–2008, and renewed support from government health agencies (279), local-level opposition remained hesitant calling for more evidence on NEP effectiveness (280), in contrast to how NEP-development took place in, e.g. Finland (181, 254). However, scientifically-grounded evidence on NEP-effectiveness kept growing (3, 70, 281-285), supported by changes in key actor-coalitions: the 21 infectious disease surveillance and control units in Sweden and the previous proponent the National Public Health Institute, promoting NEP (286-289). However, despite an ongoing HIV-outbreak, continued HCV-epidemic and harm reduction becoming mainstream policy in Europe (290), calls for NEP-

development were with counter-calls for more evidence by opposing key-actors, hindering unity and opportunity for change. Sweden's third NEP was however launched in Helsingborg in Region Skåne in 2010, after 23 years of status-quo, moving the process forward and slowly starting to eliminate space for disbelief and discrediting of NEP. In the end, we argue, these accumulated events and changes finally reclaimed the interpretative prerogative of NEP as a health policy measure, despite the active goal of a drug-free society and calls from the drug policy track for maintaining a repressive-control approach (291, 292). This slow NEP-development process would draw support from a government-commissioned investigation on Swedish drug abuse and dependence care system, concluding that NEP appeared effective while suggesting to remove the NEP-veto (245).

7.1.3 Phase 3: Development - Sweden sees the consolidation of a dual drug and health policy track

In the third phase 2012–2017, NEP-development continued to accelerate. Internationally, NEP had become mainstream policy (185) and national evidence on NEP-effectiveness continued to accumulate (17, 27, 214, 241, 293), as called for both by the international research community (22) and national key-actors in opposition. This phase also saw political leadership shifting from a right-wing/centre to a Social Democrat led government, bringing back the individual-centred focus and drug-related BBV-challenge among PWID, consequently turning the tide in Sweden regarding NEP-development (294). Despite the NEP-issue being split on both the drug and health policy track due to the veto, allowing for continued local resistance, three NEP were launched between 2012 and 2014. The shift in political leadership, new legislation on forced collaboration between regions and municipalities introduced in 2012 (294), and a continued accumulating body of evidence, provided the health policy track with a factual base, organised approach and a clear purpose. This clarification, was complemented by national public health and drug guidelines launched in 2015 and promoting NEP (17, 214). With growing additional support from international research and the Minister of Health Care and Public Health's call for a revision of the NEP-law in 2015 (295), we argue, created enough momentum for change, which this time was utilised. A new law was propose, still under a drug-free society goal however, this time without a built in veto (209, 296). As a result, by 2017, 13 NEP were operational in eight of 21 regions with a further eight regions planning for NEP launch.

7.2 PAPER II - DETERMINANTS FOR INJECTION RISK BEHAVIOURS AND CHANGE OVER TIME AMONG PWID IN REMAND PRISONS

Among remand prison-PWID in the final analysis (n=2,150), at enrolment 66% reported having shared injection drug solution, 56% to have lent out- and 62% to have received already used injection equipment from somebody during the past year, described in Figure 1, paper II. Almost 40% reported having engaged in all three injection risk behaviours. More than half (53%) of the enrolled PWID had started injecting drugs before age 18 (with a median age of injection drug debut at 19 years).

7.2.1 Socio-demographic determinants among PWID in remand prisons

When adjusting for confounders described in Table 2 of paper II, WWID had a 51% higher risk than MWID to share injection drug solution (aOR 1.51; 95% CI 1.03, 2.21). Homeless PWID were much more likely to report risky injection behaviours than those with a more stable living situation. Living with somebody was associated with a 30% reduction in risk for having shared injection drug solution (aOR 0.70; 95% CI 0.52, 0.96) and 49% reduction for having received already used injection equipment (aOR 0.71; 95% CI 0.53, 0.95), compared to being homeless. Having a housing contract was associated with a 37% lower risk of sharing injection drug solution (aOR 0.63; 95% CI 0.44, 0.90), a 43% lower risk of lending out already used injection equipment (aOR 0.57; 95% CI 0.41, 0.80), and a 59% lower risk of receiving already used injection equipment (aOR 0.41; 95% CI 0.29, 0.58), compared to being homeless.

7.2.2 Drug-related determinants among PWID in remand prisons

Those who started using drugs at age 25 or later had a 48% lower risk for having received used injection equipment (aOR 0.42; 95% CI 0.20, 0.89) compared to those starting between age 17 and 19. PWID reporting injection drug debut at older age, i.e. 30 years or older, were found to be 54% less likely to share drug solution (aOR 0.46; 95% CI 0.29, 0.76) compared to PWID reporting to have debuted with injection drug debut before age 20. Those who mainly had injected amphetamine over the past 12 months, were more than twice as likely (aOR 2.43; 95% CI 1.64, 3.62) to have shared injection drug solutions compared to those who injected heroin.

7.2.3 Time-related determinants among PWID in remand prisons

Compared to respondents having injected for five years or less, the longer time that had passed from IDU-debut until the date of the interview, the higher risk reduction, 47%-80%, was seen for all three injection risk behaviours (aOR 0.53; 95% CI 0.33, 0.86 vs. aOR 0.20;

95% CI 0.10, 0.40). Time (calendar year) was also found to have a strong effect on all three injection risk behaviours. For each observed calendar year during the study period (2002–2012), there was a decrease in the odds of having shared injection drug solutions (aOR 0.87; 95% CI 0.83, 0.92), having lent out (aOR 0.94; 95% CI 0.90, 0.99) or received (aOR 0.89; 95% CI 0.85, 0.94) already used injection equipment, described in Table 2 and Figure 2 in paper II.

7.3 PAPER III - PWID INJECTION RISK BEHAVIOURS AT ENROLMENT AND CHANGE OVER TIME IN THE NEP

Among the enrolled PWID (n=2,860) that were included in the final analysis, 29% had shared needle and/or syringe during the past month, 34.1% had shared paraphernalia and 19.8% had engaged in both injection risk behaviours, described in Table 1 of paper III. Close to half (45.2%) of PWID had started to inject drugs before age 20 (with a median age at 20 years for both WWID and MWID). When comparing between years, PWID enrolled during year five vs. year one was younger (age ≤24, 17.0% vs 10.4% p=.001) and reported later injecting drug debut (age≥20 at injecting drug debut, 63.2% vs 50.6%, p<.001).

7.3.1 Socio-demographic determinants among PWID in the NEP

When adjusting for confounders, described in Table 2 of paper III, WWID were twice as likely compared to MWID to have shared needle/syringes (aOR 1.95; 95% CI 1.61, 2.37) and paraphernalia (aOR 2.41; 95% CI 1.99, 2.91). Homeless PWID reported higher risk for sharing both needle/syringes and paraphernalia compared PWID with stable housing (aOR 1.48; 95% CI 1.20, 1.82 vs. aOR 1.50; 95% CI 1.23, 1.83). PWID with a university education had 33% lower risk for sharing paraphernalia compared to PWID with a partial or full elementary education (aOR 0.67; 95% CI 0.47, 0.94). At enrolment, PWID 34 years or older were found to have a 35% lower risk for sharing needle/syringes compared to younger PWID (aOR 0.65; CI 95% 0.53, 0.80).

7.3.2 Drug-related determinants among PWID in the NEP

PWID reporting mostly to inject amphetamine were 33% and 58% more likely to share needle/syringes (aOR 1.33; 95% CI 1.09, 1.61) and paraphernalia (aOR 1.58; 95% CI 1.31, 1.91) compared to PWID mainly injecting heroin. OST-participants were found to have lower levels of risk of sharing needle/syringes (aOR 0.66; CI 95% 0.46, 0.95) and paraphernalia (aOR 0.35; CI 95% 0.23, 0.51) compared to PWID not in OST.

7.3.3 Determinants related to BBV among PWID in the NEP

PWID living with HIV were found to have lower odds for both injection risk behaviours: needle/syringes (aOR 0.56; CI 95% 0.35, 0.92) and paraphernalia (aOR 0.62; CI 95% 0.40, 0.96) compared to HIV-negative PWID. On the other hand, HCV-positive PWID reported higher risk levels (aOR 1.31; CI 95% 1.10, 1.58 for needle/syringes vs. aOR 1.41; CI 95% 1.18, 1.68 for paraphernalia) compared to HCV-negative PWID.

7.3.4 Changes in injection risk behaviours over time among PWID in the NEP

An observed overall reduction in both injection risk behaviours (sharing needle/syringes vs. paraphernalia, p<.0001 and p<.0001) could be seen among PWID in the NEP over time, described in Figure 2 of paper III. Likewise, a similar reduction was observed for several determinants: gender, age at inclusion, education level, living situation, age at injection drug debut, duration of IDU, OST, HIV-, HBV- and HCV-status, drug at last injection and both injection risk behaviours (p<.0001), described in Supplementary Table 1, paper III. However, even though both WWID and MWID had reduction in injection risk behaviours over time (Figure 10), women compared to men consistently and at each time point, reported higher levels of risk behaviours, described in Supplementary Table 2, paper III.

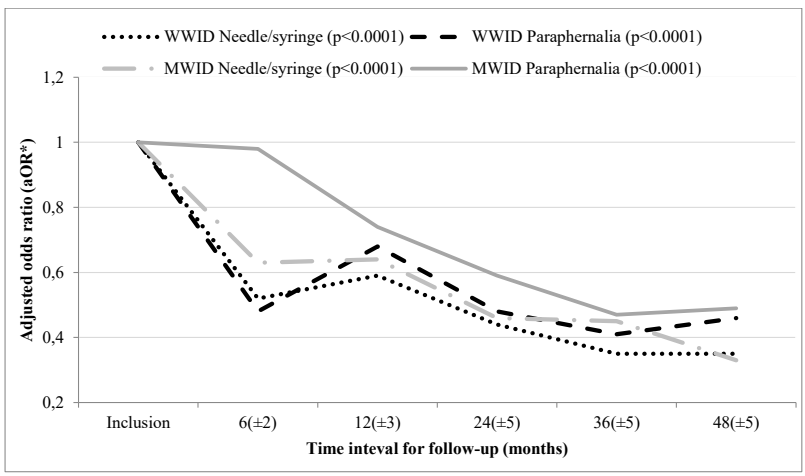

Figure 10. Changes in injection risk behaviours among WWID and MWID following inclusion in the NEP, 2013-2018.

**aOR at inclusion is set at 1 as reference value. N=2860 at inclusion. P-values represent changes in injection risk behaviours over the whole follow-up period.*

PWID reported to inject heroin or amphetamine, also reported reduction in injection risk behaviours over time in the NEP (Figure 11). As with gender, those injecting amphetamine

compared to those injecting heroin, consistently and at each time point, reported higher levels of risk behaviours, described in Supplementary Table 2, paper III.

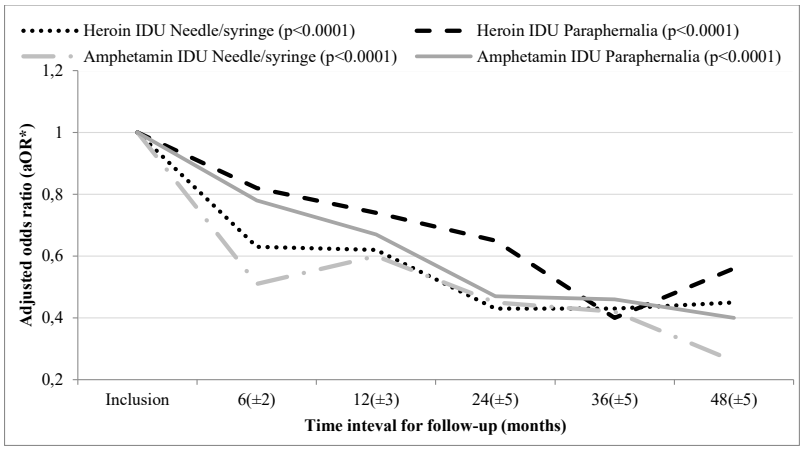

Figure 11. Changes in injection risk behaviours among heroin and amphetamine-IDU following inclusion in the NEP, 2013-2018.

**aOR at inclusion is set at 1 as reference value. N=2860 at inclusion. P-values represent changes in injection risk behaviours over the whole follow-up period.*

We also analysed differences in enrolment characteristics and injection risk behaviours between those still in the NEP at 48 months and those LTFU. No significant differences were found in either enrolment characteristics or sharing needle/syringes (p=0.53) and sharing paraphernalia (p=0.11).

7.4 PAPER IV – DETERMINANTS, INJECTION AND SEXUAL RISK BEHAVIOURS AT ENROLMENT AND LTFU AMONG WWID IN THE NEP

Among the 697 WWID in the final analysis, 43% reported to have shared needle/syringes, 50% to have shared paraphernalia and 61% having had condomless sex (sexual risk behaviour) during the past month. Twenty-five percent had engaged in all three risk behaviours, described in Figure 1 paper IV.

7.4.1 Socio-demographic determinants among WWID and MWID in the NEP

In adjusted analyses for WWID-subgroups at enrolment in the NEP, described in Table 1 of paper IV, homeless women were found to be twice as likely to share needles/syringes (aOR 2.08; 95% CI 1.25, 3.46) and paraphernalia (aOR 2.08; 95% CI 1.27, 3.42) compared to those women who had a housing contract. In separate analysis for MWID-subgroups, described in Supplementary Table 2 of paper IV, homeless men were also found at higher risk for sharing needle, syringe and paraphernalia compared to those with their own contract, although at lower risk levels than the corresponding subgroup of women. In addition, men living with

somebody were more likely to share needle or syringe (aOR 1.34; 95% CI 1.04, 1.72) and paraphernalia (aOR 1.33; 95% CI 1.04, 1.69) compared to those with their own housing contract. Age was also associated with sexual risk behaviour. WWID aged 40 or older at NEP-enrolment, were found to have lower risk of condomless sex (aOR 0.39; 95% CI 0.20, 0.78) compared to younger women. In terms of relationship status, sexual risk behaviour among co-habitant WWID and those with a partner and living-apart were three times higher (aOR 3.29; 95% CI 2.01, 5.39 vs. OR 3.20; 95% CI 1.74, 5.88) compared to single WWID. Among the corresponding MWID-subgroup, a stable civil status compared to being single was however associated with three to nearly eight times higher risk for having had condomless sex (aOR 3.24; 95% CI 2.08, 5.05 vs. OR 7.89; 95% CI 5.57, 11.18).

7.4.2 Drug-related determinants among WWID and MWID in the NEP

WWID using benzodiazepines (often prescribed for a range of psychological and neurological disorders, e.g. anxiety), cocaine or methylphenidate (used to treat attention deficit hyperactivity disorder) at injection drug debut, categorised as "other" drugs, described in Table 1 of paper IV, had double the risk of sharing paraphernalia (aOR 2.01; 95% CI 1.01, 4.01) compared to women starting by injecting amphetamine. Women who reported to have recently injected heroin had a 66% lower risk of sharing paraphernalia (aOR 0.34; 95% CI 0.17, 0.69) compared to women having injected amphetamine. Women who had used unsterile needle/syringes at their last injection (i.e. reused their own) were more likely to have received used needles/syringes (aOR 7.11; 95% CI 3.88, 13.01) or paraphernalia (aOR 2.88; 95% CI 1.62, 5.12) during the past month, compared to those having used sterile needle/syringe. Similar risk estimates were found among corresponding male subgroups. Those WWID not in OST reported almost three times the risk of sharing paraphernalia (aOR 2.57; 95% CI 1.22, 5.42) compared to those in OST. WWID not in OST were also more likely to practice condomless sex (aOR 2.37; 95% CI 1.08, 5.22) compared to those in OST. Among the corresponding MWID-subgroup not in OST compared to those in OST, similar however lower point estimates were reported (aOR 2.18; 95% CI 1.36, 3.48 for sharing paraphernalia vs. aOR 1.55; 95% CI 1.04, 2.32 for condomless sex). Furthermore, WWID with history of being sectioned (i.e. committed to compulsory psychiatric or drug dependency care), had almost double the risk for sharing needles/syringes (aOR 1.91; 95% CI 1.02, 3.57) compared to women who had not been apprehended. Similar results were found among the corresponding MWID-subgroup, however here previously sectioned men also had a 63% higher risk (aOR 1.63; 95% CI 1.07, 2.50) for having shared paraphernalia, compared to those who had not been apprehended during the past year.

7.4.3 BBV-determinants among WWID and MWID in the NEP

HIV-positive status was associated with a 63% lower risk for condomless sex among WWID (aOR 0.37; 95% CI 0.15, 0.89) compared to those who were HIV-negative. MWID living with HIV had even stronger protective effect on unprotected sex (aOR 0.18; 95% CI 0.09, 0.35) compared to HIV-negative MWID. On the other hand, an HCV-positive status among MWID was associated with a higher risk for both sharing needle/syringes and paraphernalia (aOR 1.51; 95% CI 1.19, 1.91 vs. aOR 1.41; 95% CI 1.12, 1.76) compared to being HCV-negative.

7.4.4 WWID and MWID probability of retention in the NEP over time

The Stockholm NEP first operational year 2013-2014, saw higher demand, and of newly enrolled PWID, 66% WWID vs. 60% MWID (163/248 and 519/868) remained in the program at the end of the year. For those newly enrolled the following year (2014-2015), 54% women vs. 52% men (72/133 and 205/398) remained, like the 52% women vs. 47% men (66/128 and 172/364) in 2015-2016 and 60% women vs. 51% men (55/92 and 143/283) enrolled and remaining at the end of 2016-2017 (Figure 12).

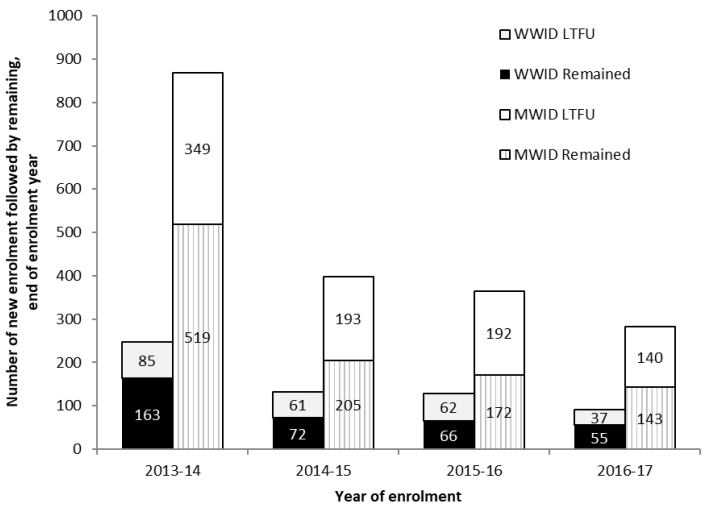

Figure 12. Number of WWID and MWID newly enrolled, remaining and LTFU per each calendar year in the NEP, 2013-2018.*

**A year equals a 12-month period, not overlapping between the years. Year 5 of enrolment (2017-2018) is not reported as no one enrolled this year had the possibility to be LTFU.*

To analyse cumulative probability of retention in the NEP, a 12- and 6-month time frame to define active participation in the NEP was used for the purpose of comparison with previous research. The respective time frames influenced the cumulative probability where it seemed like WWID compared to MWID in the 12-month scenario were significantly more likely to

remain in the NEP over time (p=0.04), however, this apparent difference disappeared when using a 6-month time frame scenario (p= 0.37) (Figure 13).

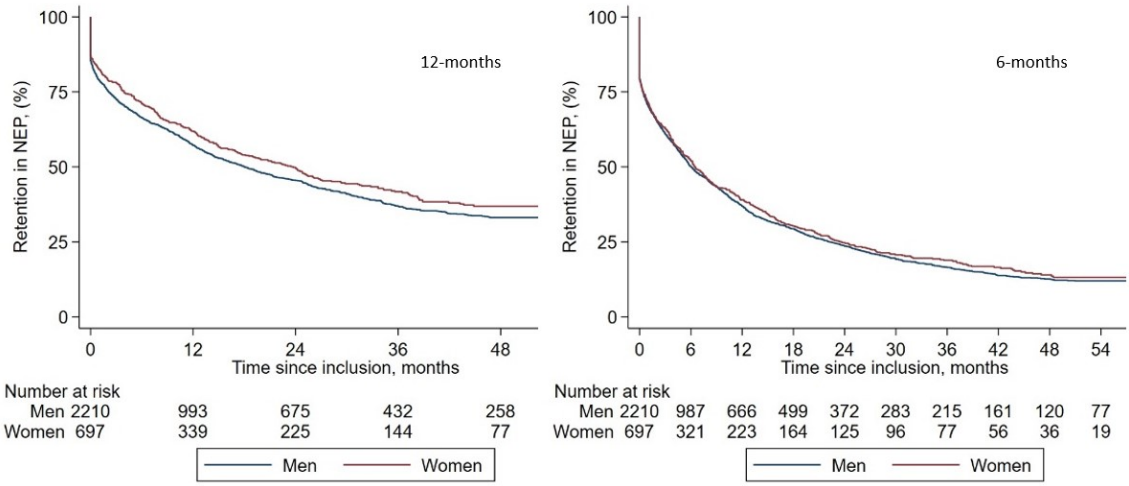

Figure 13. The cumulative probability of retention for WWID and MWID in the NEP using a 12 and 6-month time frame for the study period, 2013-2018.

Furthermore, at the first follow-up measure point (e.g. at 12 months), only 39% of WWID in the 6-month scenario vs. 62% of women in the 12-month scenario remained in the NEP. Similarly, at the second measure point (24 months), 25% vs. 50% of women remained, 19% vs. 42% after 36 months and 14% vs. 37% of women remaining after 48 months.

7.4.5 Determinants of WWID and MWID being LTFU from the NEP

Several determinants for being LTFU were analysed to understand which group that were most at risk of dropping out of the NEP. WWID with a history of being sectioned prior to NEP-enrolment, had a 48% higher risk for being LTFU in the NEP (aIRR 1.48; 95% CI 1.03, 2.13) compared to women with no history of being apprehended, described in Table 2 of paper IV. Although not statistically significant, women living with HIV had a 56% lower risk of being LTFU (aIRR 0.44; 95% CI 0.18, 1.10) compared to HIV-negative WWID. On the other hand, women who had engaged in injection risk behaviours were at 28% (not statistically significant) higher risk of being LTFU (aIRR 1.28; 95% CI 0.99, 1.65) compared to those who did not report injection risk behaviour. Among MWID-subgroups, those under age 30, had a 26% higher risk for being LTFU (aIRR 1.26; 95% CI 1.08, 1.47) compared to their older peers, described in Supplementary Table 3 of paper IV. Those men not enrolled in OST were also found at slightly higher risk (16%) to be LTFU (aIRR 1.16; 95% CI 1.01, 1.34) compared to those in OST.

8 DISCUSSION

PWID are generally hard-to-reach and therefore various settings such as harm reduction interventions, e.g. NEP or OST but also prisons, are generally used to study PWID-related determinants, risk behaviours, HCV, HIV and STI. The Swedish context is special due to its long standing zero-tolerance repressive-control drug policy, goal of a drug-free society and late introduction of NEP in most parts of the country. This is especially important for the capital of Stockholm, with the largest PWID-cohort, high HCV-prevalence and history of HIV-outbreaks. Stockholm only introduced its first NEP in 2013, seven years after the NEP-law was introduced. Thus, there was a need to further understand and analyse determinants, injection and sexual risk behaviours, HCV and HIV among PWID and subgroups in Sweden, and in relation to the Swedish drug and harm reduction policy (paper I). Since Swedish NEP-development was at a stand-still for 23 years, the options for acquiring data and knowledge on PWID and subgroups were limited. Remand prisons consequently constituted as the most viable platform for identifying and reaching PWID (in particular MWID) and to collect and analyse data for determinants and risk behaviours (paper II). WWID are considered even harder-to-reach than their male counterparts due to lower participation rates in harm reduction programmes and a lower frequency of appearing in the criminal justice system. Women have consequently been less studied compared to MWID (19, 68). As NEP-data became available also in Stockholm, we wanted to fill a knowledge gap regarding PWID-related determinants, risk behaviours and changes over time, and specifically women's risk behaviours, program retention in the NEP and reasons for being LTFU, having often been neglected in research (papers III-IV).

8.1 SWEDISH NEP-DEVELOPMENT AND IMPLICATIONS

In paper I, Swedish NEP-development over time was analysed and our results showed that unfolding events in this development had incoherent associations with our hierarchical dual drug and health policy track framework and its included structural levels (as previously described): the deep core, policy core and secondary aspects, described in Figure 2 of paper I. NEP-development events and changes took place on- and in-between the respective levels, simultaneously and in constant interaction (252). Drug policy changes leading up to NEP-implementation in European countries were typically the result of health related triggering-events (205, 297) and most scale-up occurred during the 1990s preventive work with BBV-transmission among PWID (298). Irrespective of this, Sweden continued to uphold its strict repressive-control drug policy and goal of a drug-free society for over three decades. Despite the occurrence of several key-events, the health policy was never fully

allowed to equal the drug policy with regards to NEP-development, remaining at a stand-still despite being allowed by law (264, 265, 299). However, continued development in the public health policy dimension eventually resulted in the manifestation of a separate dual drug and health policy track in Sweden (254), as had happened earlier in Finland (285, 299). This manifestation in policy tracks would later come to have effect on Swedish NEP-development. How these events unfolded and influenced change, we argue, can be associated with how the individual centred drug user perspective was emphasised in the drug policy domain in early 2000s. By this, the repressive-control drug policy and goal of a drug–free society was indirectly challenged by a complementing yet competing public health-based harm reduction approach and a reinforced health policy dimension and vision (deep core). Compared to the European NEP-development, changes in overall political leadership and key actor-coalitions in Sweden created an irregularity in how NEP-related events unfolded. But also, how they took shape, were implemented and what implications they had on NEP-development as they did not follow a clear and logical cause-effect pattern. These events rather occurred haphazardly, while a continuous underlying long-term build-up of evidence continued. With more events and data coming forward, knowledge build-up on PWID and NEP, step-by-step provided more evidence to NEP usefulness, slowly challenging the prevailing drug policy.

Prerequisites for change on vision level was realised with the introduction of separate national health and drug action plans (policy core), consequently splitting the health and drug policy tracks while bringing clarity to the respective strategy's policy position and mandate. Changes in key actor-coalitions favouring NEP, e.g. the National Public Health Institute switching its position, helped in creating wider openness to evidence and experience (secondary aspects), which continued to accumulate throughout the three evolutionary phases. Triggering-events such as HIV-outbreaks and introduction of new NEP also helped in creating momentum to remove space for disbelief and to present instrumental considerations for policy change. The accumulated effect of events created conditions to directives for change coming from a superior jurisdiction and prompting a revision of the NEP-law. These directives and sender, we argue, influenced NEP status-quo and prompted the removal of the municipality oriented veto, i.e. a forced collaboration between NEP and the social services (12). With the removal of the veto NEP-ownership was fully transferred to the health policy track (253). However, these slow changes in Sweden stood in stark contrast to how both Finland and Norway progressed more rapidly with NEP-development (264, 285).

Many countries to date still report PWID as a hard-to-reach population, despite long-term presence of harm reduction services (19). The global plans for elimination of viral hepatitis and HIV among PWID relies on high coverage of harm reductions services, consequently posing a challenge for countries struggling to reach PWID (300, 301), in many cases hindered by restrictive policies and laws (18). Reaching those high-risk PWID not already covered by existing harm reduction services, as suggested by the WHO and UNAIDS (35, 48), also poses a challenge for those countries with low prevalence of HCV or HIV. Consequently, HCV and HIV-elimination among PWID could for many countries likely involve having to start or scale-up, e.g. NEP, but also other and not as common evidence-based services like DCR and HAT (36, 302). Currently, NEP is not offered in some 120 countries and this absence of NEP could generate a forthcoming "second wave" of harm reduction scale-up and implementation, similar to the European NEP-scale-up in 1980–1990. For many national governments, this could mean facing societal and political discussion or controversy, as was demonstrated with NEP-development in Sweden (303). The Swedish NEP-development case, within its strict drug policy context (202), could provide valuable insight for countries and actors on how to circumvent costly time- and resource-intensive obstacles and processes. Further, how actors could tackle ideological and individual moral dimensions on both policy and implementation level. Contemporary examples in Denmark having introduced DCR and HAT in 2009, 23 years after their first NEP (302), Norway introducing DCR in 2004 and planning HAT in 2020 (264, 304) and Finland, where implementation of DCR is currently halted for political reasons (305), illustrate how complicated such scale-up processes may be.

Building a base of research, experience and know-how, while identifying and already early on engage with key actor-coalitions likely to be affected, might help limit opposition and especially in settings with existing veto-players, i.e. actors holding the right to block a decision (306). A solid knowledgebase will also help clarify and to remove space for disbelief and discrediting, create conditions for reaching consensus and offer opportunities for clear leadership and long-term political commitment. Proactive work on these platforms, building knowledge and engaging key-actors, can also help to capitalise on trigger-events when they occur, to promote change.

8.2 THE ROLE OF DETERMINANTS IN BRIDGING RISK BEHAVIOUR KNOWLEDGE GAPS REGARDING PWID

Acquiring baseline knowledge regarding determinants, risk behaviours and the epidemiology of HCV and HIV among PWID is important for future preventive work. Our results showed that PWID and subgroups at enrolment in remand prisons and the NEP reported varying injection and sexual risk behaviours.

Gender

Gender is one of the most important determinants to consider in research on PWID. Globally, the 3.1 million WWID are outnumbered five to one by MWID (20, 50). However, women who use drugs are at higher risk of adverse health and social outcomes such as HCV and HIV-infection and remain less prioritized in research and response efforts. We found that WWID at NEP-enrolment were more likely than MWID to report sharing needles, syringes and paraphernalia (injection drug solution) and also to display high levels of sexual risk behaviour, in line with previous research (307-309). Previous studies have also found that women are often introduced to IDU by an intimate male partner (310) and more often than men engage in direct sharing (person-to-person) of injection equipment in smaller networks, whereas men share in larger networks which often overlap with their sexual partners (50). An uneven gender balance in a relationship can also be reinforced by men mostly being in charge of acquiring or sharing the drugs (167, 311), exposure to gender-based violence, and that women in most contexts are more likely to be responsible for child care and thus more concerned to seek care for their IDU. However, these dynamics are likely to be underreported among WWID because of stigma or trust issues with government institutions and care providers (49, 93). Another challenge in acquiring knowledge could be that an IDU-lifestyle, despite its corrosive nature, can be considered to be normal among PWID (250, 312). All these factors can act as gender-based barriers in service provision (93, 101). Despite the significant importance of gender as a stand-alone determinant, gender aspects are also important to consider in relation to other determinants as described below.

Age

Those PWID who started using drugs at young age were found to display strong associations with injection and sexual risk behaviours, confirming results from previous studies (162, 308). A majority of PWID reported having begun using or injecting drugs at an age when still supposed to be in mandatory school and to start injecting drugs before age 20. Studies from the Ukraine (313), China (162) and Karachi (314) have shown young PWID, and especially subgroups of young WWID (308), to be at highest level of injection risk behaviour. A study

on PWID in Stockholm found that approximately 50% of younger PWID had HCV-antibodies only two years after IDU-debut (59), confirmed in several other studies finding young PWID-debutants at higher risk of contracting HCV and HIV (5, 166, 315). PWID with a later IDU-debut in life or showing up at NEP at and older age were found associated with lower risk behaviour levels. A later IDU-debut in life could imply a more stable life-situation, education, employment, a larger social network and an overall higher level of maturity and self-control. A study from the U.S. found that as long as a person exerted self-control with drug use, it was possible to uphold a normal social role in and lifestyle (316).

Housing

The housing situation for PWID and especially those being homeless, has since long been demonstrated as an important determinant for risk behaviours and BBV-transmission (83, 157, 317-320). For WWID, an unstable housing situation increases both injection and sexual risk behaviours (170, 321), act as a barrier for HCV and HIV-treatment (322, 323) and exposes them to multiple risks (324, 325). Previous results were confirmed in our studies finding that homeless PWID in general, but also WWID and MWID in particular, reported high injection risk behaviour levels. However, in separate analyses on MWID-subgroups, results also showed that men living with somebody were more likely than those with their own housing contract to share injection equipment.

Civil status

Compared to being single, a stable civil status was associated with high levels of injection and sexual risk behaviours among MWID whereas WWID showed higher risk for having condomless sex. Gender-based power dynamics, intimacy desire or efforts to get pregnant can influence condom use (50, 167, 326) and possibly explain the tendency of WWID in stable relationships to more frequently have condomless sex (83). Limited research suggests there to be a WWID-specific interface between sexual and drug use risk behaviours and risk of HCV or HIV-infection (51, 61, 79, 109, 170, 308, 327). This growing insight around a gender-specific interface stems from different injection equipment sharing behaviours among WWID and subgroups, and that women compared to men, share injection equipment more frequently (49, 50). Further, if sharing occurs with multiple partners, there is the likelihood that sexual transmission of HIV (93, 167, 328), but also HCV, could occur among IDU-sexual partners if there is ongoing high risk sexual behaviour such as condomless anal intercourse (109, 175).

Type of drug

Those PWID who reported amphetamine-IDU were found more likely than heroin-IDU to share injection equipment and especially paraphernalia. We also found that MWID injecting amphetamine (a sexual stimulant) were more likely to have condomless sex. These results, the demonstrated high injection risk behaviours, and specifically amphetamine-IDU high risk for sharing paraphernalia, is uncontroversial as has been previously found in studies in, e.g. Georgia, U.S. and Ontario, Canada (157, 158). However, it is especially important to understand these differences in injection equipment sharing patterns between heroin vs. amphetamine-IDU, since sharing of paraphernalia alone is a strong determinant for HCV-infection (5, 160, 329). A study on PWID in Stockholm found that own knowledge on HCV-status did not prevent injection risk behaviour (89), which strengthens the understanding of amphetamine injectors exposure to HCV. Additionally, amphetamine-IDU has also been found to associate with higher sexual frequency and risk behaviours, important in HCV and HIV-preventive work (330-332). We also found that WWID reporting benzodiazepine-IDU were at higher risk for sharing paraphernalia, results supported by a study in Vancouver, Canada, who also found that those injecting benzodiazepine were at higher risk for HCV-conversion (333).

HCV and HIV

HIV-negative and HCV-positive MWID reported higher injection risk behaviours at enrolment whereas HIV-negative WWID and MWID reported higher sexual risk behaviour. A HIV-positive status association with lower injection and sexual risk behaviour, could possibly be explained by own awareness following diagnosis, counselling and ongoing ART. On the contrary, ongoing injection risk behaviour among HCV-positive MWID suggest continued risk of transmission, where research previously has shown that own awareness of being positive or not, is not enough to change risk behaviour (89). This indicates that efforts to reduce injection risk behaviours alone, are not as an effective strategy to reduce continued spread of BBV, and therefore it is necessary to apply a combined harm reduction approach including VCT and treatment (121, 191, 301, 334-336). Altogether, this understanding of type of drug used, BBV-status, but also civil status and so forth, reinforces the understanding of women's vulnerability for HIV and hepatitis, and especially for those women injecting amphetamine (5, 160, 329).

Apprehended or enrolled in other harm reduction programs

PWID in paper II-IV, our results regarding PWID previous experience of remand prisons came out inconclusive. Approximately 70% of our study population had previous experience of remand prison, treatment or support services and 50% reported regular contact with the social services. Those PWID not enrolled in OST reported higher injection risk behaviours and WWID in relation to MWID not in OST, reported nearly three times the risk for sharing paraphernalia. This subgroup among women were also more likely to engage in condomless sex. We also found that women and men with a history of having been sectioned in compulsory care, were more likely to have higher injection risk behaviour than those without such experience. Previous research have concluded that prison experience is associated with high injection risk behaviour levels (227) and that OST-participation has been associated with sharp reduction in HCV-transmission, better if combined with NEP (85, 191). However, psychosocial vulnerability among WWID has been shown to increase risk of HIV (105, 337, 338). Further, that WWID generally are underrepresented in harm reduction interventions or seek treatment for e.g. drug dependency less often than men (339), possibly due to stronger social stigma or fear of losing custody of their children. This may altogether indicate a neglected need of targeted interventions for women, and especially those having previously been sectioned.

8.3 TIME AS A DETERMINANT FOR CHANGES IN INJECTION RISK BEHAVIOURS AND PROGRAM RETENTION

In studies II-IV, the time determinant proved important to distinguish between varying risks behaviours among PWID and subgroups.

Time as a determinant for risk behaviour among PWID in remand prisons and WWID and MWID in the NEP

In paper II, on PWID in remand prisons (2002-2012), we found that the longer time had passed between IDU-debut and enrolment in remand prison, the more protective effect could be seen on PWID injection risk behaviour. We also saw an effect of time in the sense of overall decreasing risk behaviour trends for PWID newly enrolled in remand prison each year. In the NEP (paper III), analyses showed that newly enrolled PWID year five (2018) were overall younger and with shorter IDU-duration compared to entrants' year one (2013). When analysing injection risk behaviour for PWID and subgroups over time, a reduction was observed for 11 determinants, e.g. those injecting amphetamine and heroin (as previously described) and injection risk behaviours. In terms of gender, WWID more than halved their

risk behaviours already after six months participation. However, despite women's significant reduction in injection risk behaviours, they were consistently found at higher point estimates compared to men. There are several possible explanations to perceived decreases in injection risk behaviours. One plausibility is that the longer somebody can avoid remand prisons or NEP, there more likely it is that this PWID exerts some level of IDU-control and remains socially functional (316). The overall decrease in injection risk behaviours among PWID enrolling in remand prisons over the years could have its explanation from changes in society. Since 2006, Sweden has seen the passing of a first NEP-law (273), a national strategy for HIV, hepatitis and STI specifically targeting PWID (340), Region Stockholm without a NEP suffering from a large HIV-outbreak among PWID resulting in increased efforts (70, 72) and eased OST-program restrictions. On an individual level in the NEP, the rapid and then consistent reduction in injection risk behaviour correlates with previous finds (120). However, our observed decrease of injection risk behaviours among WWID is currently unmatched. A likely explanation could be the provision of gender-sensitive services, e.g. psychological and as well as sexual and reproductive health counselling and support services, underlining the importance of understanding and promoting WWID-specific facilitators and support the needs of more gender-related studies (22, 341-343).

Time as a determinant for program retention among WWID and MWID

When analysing NEP-retention using a 12-month time frame we observed that WWID were significantly more likely and consistently on higher levels than MWID to remain in the NEP, reasons for which are unknown. Research on WWID and MWID retention in NEP over time is nearly non-existent. Those studies we found had analysed varying contexts ranging from regular NEP to NEP in prison settings, using different time frames for inclusion, e.g. six, 12 and 24-months. The use of different time frames have consequently led to reported variation in NEP-retention rates ranging from 26-75% (344, 345). Consequently, it matters which time frame is used when analysing PWID-retention in NEP, where we found a difference between WWID and MWID in our 12-month scenario but not in our six-month scenario. Care must therefore be taken to not over-interpret apparent differences that are merely dependent on the chosen time frame (definition for retention) for data analysis. Contrary to our results, one Malaysian study on PWID and subgroup retention reported MWID more likely than WWID to remain in NEP over time (346).

WWID and MWID and determinants for being LTFU from the NEP

Lastly, we found that WWID with a history of being sectioned (in compulsory care) were at high risk of being LTFU from the NEP. Non-significant results also indicated that HIV-negative women and women reporting injection risk behaviour in the past month, were at higher risk for being LTFU. In separate MWID-analyses, we found that age, type of drug and OST were associated with being LTFU. Previous and limited available studies have found that history of incarceration and PWID injecting daily were associated with being LTFU from a NEP (345, 347). Another likely explanation to HIV-negative women being LTFU, is that HIV-positive PWID can access their ART through the NEP. However, research on PWID being LTFU from NEP is scarce.

8.4 STRENGTHS AND LIMITATIONS

For paper I-IV, there are a number of limitations that needs to be considered when interpreting the results. In paper I, the study period covers a long time period extending over significant societal changes like the introduction of Internet and availability of empirical data. In Sweden, it is mandatory to preserve and make government official documents available to the public, although there is no guarantee that everything is readily accessible, especially online. However unlikely, there is the chance that key documents relating to NEP-policy development in Sweden might have been overlooked in this paper. Most of our results correlate to findings in similar contexts however, why we believe we have accumulated enough empirical material to reach saturation in findings, to support our overall conclusions. Adding to both the strength and limitation is the fact that I, as the author of this thesis, have actively worked in the policy field and development of NEP on national government level for over a decade, having had access to a significant level of material, collected and analysed in-depth and on several occasions. This could however also introduce a selection and confirmation bias leaving other important aspects of NEP-development to be overlooked. One such factor could be the importance of the non-governmental organisation movements' opposition to NEP since the beginning of the HIV-epidemic in the 1980s and up until the NEP-law in 2006. To counter this, researchers external to both the NEP-subject and Swedish policy development over time, were invited to participate in the research process. Another limiting aspect is that we mostly focused on government published documents on national level and to a lesser extent reviewed local government documents and politically produced documents and debates. On the other hand, nationally produced governments mostly serve as guidelines for local contexts and already contain or having taken into consideration local views and knowledge obtained through official referral procedures. Further, in policy research there are several policy frameworks to draw upon

depending on the focus of the study however, we believe that our used framework is suitable given that it has been used previously in similar NEP-research. Another limitation is that a majority of empirical data is in Swedish, limiting availability to international non-Swedish speaking researchers. For papers II-IV, much of the analyses are based on self-reported data from PWID in two programs, by design limited in setting and PWID-coverage compared to society as a whole. Remand prisons are confined spaces for PWID pending trial or possible release which may also limit the possibility or willingness to answer questions on sexual and injection risk behaviours and so forth. PWID in remand prisons are therefore not fully comparable with PWID in the general community. NEP-participation in Sweden is entirely voluntary but to enrol in the NEP, legislation requires a person to be 18 years or older, undergo mandatory HIV and hepatitis testing and to answer questions on drug use and without the possibility of being anonymous. Further, all health staff are under requirement to report any suspicion of harm to minors to the social services, factors all acting as potential access-barriers. PWID in remand prisons, and the NEP therefore constitutes as a sub-selection of PWID in general society, which could possibly involve selection bias. Certain questions may be very sensitive or subjected to stigma, rules and regulations, e.g. questions on illegal drug use, having children at home (in Sweden subjected to further investigation into custodial issues), injection or sexual risk behaviours, which can cause shame, guilt, aversion, all leading to the risk of underreporting or social desirability bias. Self-reported data using questions with long recall time also carry the risk of recall-bias simply because the person cannot remember exactly when or what happened, with whom and in what order, e.g. sharing of injection equipment, which in turn can lead to under or overestimations of risk. Duration of IDU was estimated as the difference between self-reported age of injection drug debut and age at enrolment (when answering the question). This leads to a risk to overestimate IDU-duration given that we did not take periods of abstinence into account. Another limitation is the risk of attrition bias, and how to interpret reasons for a PWID being LTFU in absence of data, e.g. if the person quit drugs or died.

It can also be argued that the OST-platform in Sweden could have served as a good and complementary platform to target PWID and collect data as international (191) and recent local Swedish research has shown (216). However, there are several limitations to this. The major challenge is that the availability of OST in Sweden, like NEP, has been very limited for significant periods of time, and still is to some extent in parts of Sweden. Some regions, e.g. only host one NEP however cover a vast area and several mid-size cities, foremost in the Northern part of Sweden, which forces PWID to travel longer distances in order to take advantage of harm reduction services (17, 57). OST also had an age restriction of 20 years

and strict rules for program participation, which included a zero-tolerance for drug use. Added to this was the requirement for a PWID having to prove at least two years (later one year) of ongoing drug use, acting both as a barrier and a natural sub-selection of those PWID enrolled in OST. Likewise, the decision to treat opiate addiction at first, and only later include opioid-users into the programs could also have acted as barriers to program enrolment. There are also structural challenges since OST-programs, currently around 100, can be operated by private contractors and that no national centralised and systematic regulation for program surveillance or follow-up exists.

A significant amount of PWID in our studies however had no prior experience of remand prison or NEP, were young, had short IDU-duration and some having had experience of OST and the social services, leaving us to believe we have captured a sample representative of the larger PWID-community, including those PWID who are socially functional. The strengths of the sub-studies included in this thesis, is that they include a large number of data or respondents with high response rates, over long time periods. These respondents were enrolled prospectively allowing us to collect data over time, including both program-level and individual clinical data in a data registry and readily available for analysis. All staff were also trained and experienced in question technique and how to perform interviews. Further, remand prisons hold PWID in custody and most often forward them to other locations making them function as sentinel sites, which provides a good overview of determinants, risk behaviours and BBV in the larger PWID community.

9 CONCLUSIONS AND RECOMMENDATIONS

In my four papers, I have drawn the following main conclusions:

- Costly time- and resource-intensive obstacles and processes and ideological and individual moral dimensions on both policy and implementation level, hindered NEP-development in Sweden over the last decades.
- Lack of solid research evidence, experience and presence of opposing key actor-coalitions including veto-players, hindered unity and consensus among actor-coalitions and policymakers and long-term political commitment regarding NEP-development in Sweden.
- Among PWID at remand prison enrolment, being a woman, homeless, a younger age at drug and injection drug debut, injecting amphetamine and short IDU-duration, were associated with injection risk behaviours., i.e. sharing drug solution, lending out or receiving already used injection equipment.
- A decreasing trend in self-reported injection risk behaviours among newly enrolled PWID in remand prisons each year was observed over time, 2002-2012.
- Among PWID at NEP enrolment, being a woman, homeless, at younger age, injecting amphetamine and not in OST were associated with injection risk behaviours.
- Among WWID and MWID-subgroups specifically, associated determinants for injection risk behaviours at NEP-enrolment were: a history of being sectioned and for MWID especially: living with somebody, a stable civil status and being HCV-positive.
- Among WWID and MWID-subgroups specifically, associated determinants for sexual risk behaviour at NEP-enrolment were: younger age, being in a stable relationship, not in OST and being HIV-negative and for MWID especially: injecting amphetamine.
- Injection risk behaviours among NEP-participants were reduced over time, in particular among WWID showing a 50% reduction already after six months.
- Women were more likely than men to remain in NEP over time.
- Determinants for being lost to follow-up among WWID were: being sectioned, injection risk behaviours past month and being HIV-negative and for MWID: younger age, type of drug use and not in OST.

9.1 RECOMMENDATIONS

To eliminate hepatitis and HIV among PWID by 2030, many countries will most likely have to significantly scale-up ongoing, or start new harm reduction interventions and include a wider range of PWID-tailored services, in order to reach an expected coverage among PWID. In particular, this would primarily mean to target specific needs among PWID and subgroups, especially WWID. The case of Swedish NEP-development could provide valuable insight for other countries on how to circumvent costly obstacles and processes and how to use a solid base of research, knowledge and experience to remove opportunities for disbelief and discrediting. Further, how policymakers can engage with key actor-coalitions and veto-players early on, to help promote consensus, leadership and space for long-term political commitment. With the introduction of effective treatment, ART for HIV and at later DAA for HCV, the tendency in the global health community has been to target these pandemics from a "treatment as prevention"-perspective (Figure 14). Even though such a strategy may be highly effective, there are limitations to this approach. PWID is a hard-to reach group, WWID even more so and found to refrain from seeking help due to stigma, discrimination or fear of government institutions. In addition, harm reduction programs often fail to reach MARP, here the highest-risk PWID, undermining adherence and increasing the risk for PWID being LTFU. Current harm reduction approaches may also overlook more complex conditions associated with PWID and BBV-transmission, e.g. PWID being diagnosed late after initial infection, which are important to understand if the goal is to reach higher coverage and to reach PWID with effective and tailored prevention, treatment and to reduce transmission. Even though behavioural surveillance, in the sense of targeting determinants and risk behaviours among PWID and subgroups, can be more time and resource consuming, it is only through such methods that BBV and STI-interventions can be monitored and evaluated properly. Harm reduction interventions and programs should thus be encouraged to put more emphasis on behavioural surveillance, as already suggested by the WHO in year 2000. However, it is also important to make a clear distinction between determinants and injection and sexual risk behaviours among PWID and subgroups, to more thoroughly understand subgroup-dynamics and consequent varying routes of transmission of BBV. A clear and dynamic dual (as with the Swedish NEP-case) behavioural and biological surveillance-approach (SGS), mimics the core idea of primary and secondary prevention interventions. *Primary prevention* includes several important components, e.g.: VCT, vaccination, provision of sterile injection equipment, condoms and in addition enhanced focus on IEC, psychosocial interventions including gender and subgroup-adapted approaches, OST, secured housing, targeting youths, people injecting amphetamine, WWID and MWID

with history of prison or being sectioned and so forth. Similarly, *secondary prevention* interventions are equally important, i.e. activities that target those already infected, e.g. treatment, special counselling and IEC and so forth.

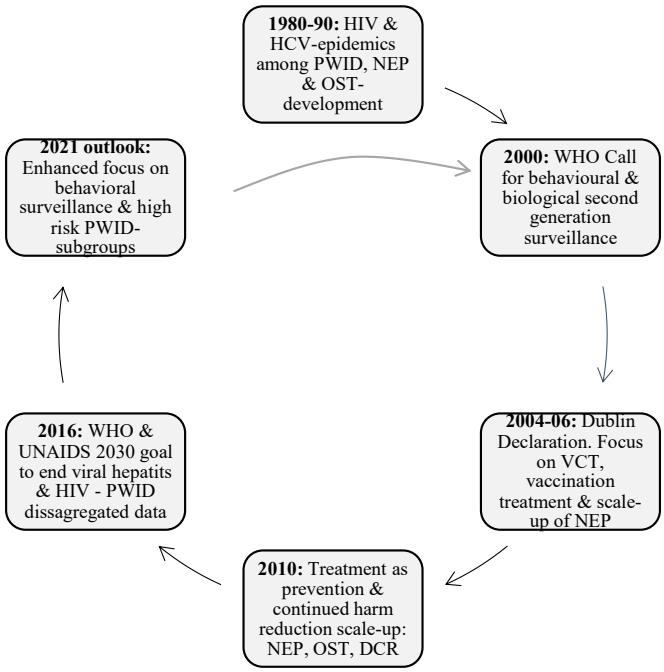

Figure 14. Important events, focus and future outlook regarding the preventive work of HCV and HIV among PWID.

A combined dual primary and secondary prevention approach may also stimulate consensus and cooperation between complementary actors and arenas frequented by PWID: OST, prisons, social services, general healthcare and DCR and so forth. Further, a strengthened dual prevention approach could support program planning and how to reduce barriers for accessing harm reduction services, reach more PWID and to share information among actors to help reduce knowledge gaps. Surveying behaviours would also make programs more susceptible to sudden changes or emerging new trends in risk behaviours, or sudden outbreaks of BBV enabling rapid adaption. A combined dual primary and secondary prevention approach could also benefit those high-risk PWID having reached an "intervention fatigue" but who still remain at risk of HCV- and HIV-transmission. A better understanding of behaviours and needs for harm reduction and other types of support and services among PWID would make it easier to tailor interventions and meet their needs, and ultimately create more favourable conditions for reducing the burden of BBV, morbidity, mortality, social stigma and discrimination, as well as reaching the global elimination goals set by the WHO and UNAIDS for 2030.

10 SAMMANFATTNING PÅ SVENSKA

Personer som injicerar droger (PID) är en heterogen grupp som på grund av lagar, stigma och diskriminering ofta är svåra att nå i samhället. PID är på grund av sitt drogbruk och sexuellt riskbeteende, extra riskutsatta för HIV och hepatit C. Kunskapen kring PID och smittsamma sjukdomar är generellt god, men eftersatt vad gäller till exempel kvinnor som injicerar droger. För att nå PID är det vanligt att gå via sjukhus och fängelser, men sprututbytesprogram riktade till PID kan nå fler och andra grupper. Begränsad tillgång till sprututbytesprogram samt lägre kunskap kring könsskillnader bland PID är en utmaning i det preventiva arbetet med att försöka adressera riskfaktorer, riskbeteenden, hepatit och HIV-överföring. Syftet med den här avhandlingen var att analysera utvecklingen av sprututbyten i Sverige över tid. Vidare att studera bestämningsfaktorer för injektions- och sexuellt riskbeteenden vid inskrivning i häkten och sprututbytet i Stockholm, men också riskbeteendens utveckling över tid. I **studie I**, analyserades sprututbytesutvecklingen i Sverige 1986–2017 i relation till svensk drog- och hälsopolicy. Expansionen av sprututbyten hindrades länge i Sverige av resurs- och tidskrävande hinder och processer, t.ex. ett kommunalt veto mot att starta dessa program. Viktiga nyckelaktörer som principiellt motsatte sig sprutbyten, ofta av ideologiska och moraliska skäl, avsaknad av kunskap, forskning och erfarenhet kring programmen bidrog till att Sverige under decennier var ett av få länder i västvärlden där majoriteten av landets PID saknade tillgång till rena sprutor. Med förnyat fokus på den enskilde droganvändaren, ackumulering av kunskap och forskning, en lag gällande byte av injektionsverktyg, samt förändringar i nyckelaktörskonstellationer och borttagandet av veto-rätten har de senaste åren lett till en skyndsam utveckling av nya sprutbytesprogram. I **studie II** (n=2,150, 2002–2012) analyserades bestämningsfaktorer för riskbeteenden hos PID vid inskrivning i häkten. Kvinnligt kön, hemlöshet, ung ålder, injektion av amfetamin var avgörande faktorer förknippade med höga nivåer av injektionsriskbeteenden. Vidare minskade injektionsriskbeteenden över tid bland nya inskrivna PID i häkten. I **studie III** (n=2,860, 2013–2018) noterades också en minskning av injektionsriskbeteendet över tid hos deltagarna på sprututbytet. Kvinnor, hemlösa och de som injicerade amfetamin visade sig ha en ökad risk att dela nålar, sprutor och andra injektionstillbehör, medan LARO-behandling var en skyddande faktor. Över tid har sprututbytet nått ett större antal individer som inte redan är infekterade av hepatit C i samband med första besöket, vilket skapar möjlighet att förebygga hepatit C i ett tidigare skede. I **studie IV** (n=2,909, 2013–2018) studerades bestämningsfaktorer för kvinnors injektions- och sexuella riskbeteenden samt vad som ökar chansen att kvinnor inte faller ur programmet. Hemlöshet, att injicera amfetamin, att inte delta i LARO samt en historia av tvångsomhändertagande, var associerat med högre injektionsriskbeteende. Yngre ålder, stabilt civilstånd, att inte delta LARO och att vara HIV-negativ, var associerat med högre sexuellt riskbeteende. Kvinnor var även mer benägna än män att stanna kvar i sprututbytet över tid. Kvinnor som tidigare tvångsvårdats var mer benägna att hoppa av sprututbytet. Våra resultat visar behovet av att skräddarsy program och att möta behoven hos både män och kvinnor som injicerar droger för att förhindra smittspridning samt för att nå de globala målen att eliminera HCV och HIV till 2030.

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