

**HIV CARE OUTCOMES AND INSTITUTIONAL STRUCTURES: PERSON-
CENTERED CARE FOR PEOPLE WHO USE ILLICIT DRUGS**

by

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Abstract

Background: Although optimal access and adherence to modern antiretroviral therapy (ART) reduces rates of HIV-related morbidity and mortality, HIV-positive people who use illicit drugs (PWUD) continue to experience suboptimal HIV treatment outcomes. This thesis sought to apply institutional perspectives to explore individual and organizational interactions in achieving person-centered care (PCC). This aim was met by first, systematically reviewing literature on medical and social service components linked to methadone maintenance therapy (MMT) in improving HIV care cascade outcomes, and second, in a series of empirical studies, assessing institutional-related structures associated with optimal adherence to ART among HIV-positive PWUD. These studies examined: 1) prescription of complex ART regimens, within a single domain of healthcare provision; 2) MMT-ART co-dispensation practices, within multiple domains of healthcare provision; and 3) the production of material insecurity through healthcare, social care and other institutional relationships. **Methods:** First, a specific search strategy was used to conduct the systematic review. Second, data from an ongoing prospective observational cohort study linked with comprehensive HIV clinical monitoring records in Vancouver, Canada was used to assess institutional-related structures. Multivariable models were built to estimate the relationships between institutional-

related variables and adherence to ART, using longitudinal analytic techniques while controlling for relevant confounders. **Results:** The systematic review found a low number of studies that described MMT service delivery in detail and a lack of information on the effectiveness of social support within MMT programs on improving HIV care outcomes. Among HIV-positive PWUD in Vancouver, complex ART regimens, as demonstrated by greater number of pills, were significantly associated with suboptimal adherence; MMT-ART co-dispensation was positively associated with optimal adherence in a low-threshold setting; and although material insecurity was associated with institutional structures, it was not significantly associated with adherence. **Conclusions:** The alignment between institutional domains may potentially enhance HIV care outcomes among PWUD as they navigate institutional structures. Public health strategies that feature PCC approaches are needed to meet the complex needs of PWUD. Thus, future research should explore the application of implementation science as a potential avenue to align treatment and care services across institutions for HIV-positive PWUD.

Lay Summary

The number of deaths caused by HIV/AIDS has declined sharply due to the development of antiretroviral therapy (ART) for HIV infection but require daily adherence to prescribed medications. HIV-positive people who use illicit drugs (PWUD) often face barriers to optimal adherence, including poverty and ongoing substance use. Efforts that depend solely on a single area of expertise can be insufficient to improve health among HIV-positive PWUD. In this dissertation, I ask: in addition to an individual's engagement with different organizational domains, how well do different health and non-health institutional configurations in which these organizations develop, support or inhibit the ability of PWUD to comply with their ART regimens? Data in this study was examined largely from an ongoing study of HIV-positive PWUD in Vancouver, Canada. Findings from the study can potentially inform the design of strategies to enhance service coordination in delivering comprehensive care for members of this key population.

Preface

This dissertation is an original intellectual product of Nur Afiqah Mohd Salleh (NA.MS). All research presented in Chapters 3 – 5 involving human participants from the AIDS Care Cohort to evaluate Exposure to Survival Services (ACCESS) study were conducted under the approval of the University of British Columbia / Providence Health Care Research Ethics Board (certificate H05-50233). The contributions made by co-authors of the manuscripts, including Dr. Lindsey Richardson (L.R), Dr. M-J Milloy (M-J.M), Dr. Jean Shoveller (J.S), Dr. Thomas Kerr (T.K), Dr. Julio Montaner (J.M), Dr. Mohammad Karamouzian (M.K), Ms. Pauline Voon (P.V), Dr. Adeeba Kamarulzaman (A.K), Dr. Nadia Fairbairn (N.F), Dr. Seonaid Nolan (S.N), Dr. Rolando Barrios (R.B), Dr. Jenna Van Draanen (J.V.D) and Dr. Ekaterina Nosova (E.N) have been made in the capacity of supervisory committee members and co-investigators. As the principal investigator of the ACCESS study, M-J.M, oversees the cohort, had access to all data and is responsible for the integrity of the results. All authors contributed the interpretation of data and the critical revision of the manuscript for important intellectual content; and approved final version of manuscripts for submission.

Specific contributions to each chapter are as follows: Chapters 1 and 6. With guidance from L.R, M-J.M and J.S., NA.MS performed the literature review,

conceptualized the research in this dissertation and wrote the draft. L.R, M-J.M and J.S reviewed and provided critical input on the final draft of these chapters. Chapter 2. With guidance from M-J.M and L.R, NA.MS and M.K designed the research and wrote the search strategy. With input from M-J.M and L.R, NA.MS and P.V conducted the screening process and determined eligible studies. NA.MS wrote the first draft. M-J.M, L.R and J.S provided critical comments and approved the final draft. Chapter 3. With guidance from M-J.M and L.R, NA.MS designed the study. M-J.M conducted the statistical analysis. NA.MS prepared the first draft of the analysis. M-J.M, L.R, J.S, T.K, J.M and A.K contributed intellectual content to this chapter and approved the final draft. Chapter 4. With guidance from M-J.M and L.R, NA.MS designed the study, wrote the analytic protocol and conducted the statistical analysis. NA.MS prepared and wrote the first draft of the analysis. M-J.M, L.R, J.S, N.F, S.N and R.B contributed intellectual content to this chapter and approved the final draft. Chapter 5. With guidance from M-J.M, L.R and J.V.D, NA.MS designed the study and wrote the analytic protocol. E.N. conducted the statistical analysis. NA.MS prepared the first draft of the analysis. M-J.M, L.R, and J.S provided critical comments to this chapter and approved the final draft.

All chapters in this dissertation were written by NA.MS and revised based on the feedback by co-authors. NA.MS was also responsible for submitting manuscripts

for publications and preparing final drafts based on the suggestions of journal editors and peer reviewers.

The following manuscripts arose from the work in this dissertation:

A version of the material in Chapter 3 has been published as: Mohd Salleh NA, Richardson L, Kerr T, Shoveller J, Montaner J, Kamarulzaman A, Milloy MJ. A Longitudinal Analysis of Daily Pill Burden and Likelihood of Optimal Adherence to Antiretroviral Therapy Among People Living with HIV Who Use Drugs in the *Journal of Addiction Medicine*, 2018 Jul 1;12(4):308-14.

A version of the material in Chapter 4 is under the review of a scientific journal, as Mohd Salleh NA, Fairbairn N, Nolan S, Barrios R, Shoveller J, Richardson L, Milloy M-J. Co-dispensation of low-barrier methadone maintenance therapy (MMT) and antiretroviral therapy (ART) linked to improved ART adherence among HIV-positive people who use illicit drugs in a Canadian setting.

A version of the material in Chapter 2 and 5 is currently being finalized for submission to a peer-reviewed publication.

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List of Abbreviations

ACCESS	AIDS care cohort to evaluate exposure to survival services
AOR	adjusted odds ratio
AIC	Akaike information criterion
AIDS	acquired immune deficiency syndrome
ART	antiretroviral therapy
CI	confidence interval
DAART	directly administered antiretroviral therapy
DTP	drug treatment program
GLMM	generalized linear mixed-effects model
HCV	hepatitis C
HIV	human immunodeficiency virus
HTC	HIV testing and counseling
IPTW	inverse probability of treatment
MAT	maximally assisted therapy
MEMS	medication event monitoring system
MMT	methadone maintenance therapy
NSEP	needle and syringe exchange program

OAT	opioid agonist therapy
OR	odds ratio
PCC	person-centered care
PLWH	people living with HIV
PWID	people who inject drugs
PWUD	people who use drugs
RCT	randomized controlled trial
STR	single tablet regimens
SUD	substance use disorder
TB	tuberculosis
UNAIDS	Joint United Nations Program on HIV/AIDS
UNODC	United Nations office on drugs and crime
VL	viral load
WHO	World Health Organization

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Chapter 1: Introduction

1.1 Problem Statement

Many countries affected by the HIV pandemic are working to reach the 90-90-90 target set by the Joint United Nations Program on HIV/AIDS (UNAIDS) by 2020. The target states that at least 90 per cent of all people living with HIV (PLWH) will know their HIV status; 90 per cent of all people knowing their status will have access to high-quality antiretroviral therapy (ART); and 90 per cent of those on treatment will have sustained viral suppression [1]. The 90-90-90 targets address progress along the HIV care cascade framework, which outlines important steps from HIV testing, linkage and retention in HIV care, initiation and adherence to treatment to HIV-1 RNA viral load (VL) suppression [2].

Despite the progress made towards achieving the goals among the general population of PLWH in recent years, a systematic review examining HIV care outcomes among key affected populations, including people who use illicit drugs (PWUD), suggests that outcomes among these groups are suboptimal [3]. In addition to low rates of HIV testing [4], data has consistently shown that PWUD experience lower rates of ART initiation and VL suppression compared to non-PWUD subgroups such as men who have sex with men [5-9]. In British Columbia, Canada, although ART

is offered to all PLWH at no cost, recent data on HIV care outcomes reported that the prevalence of suppressed VL among PWUD was 57.6%, compared to 70.1% among non-PWUD [10].

Although adherence to ART is the key determinant of virological response to treatment, PWUD often face challenges to achieve and sustain optimal levels of adherence. Common risk factors for non-adherence among PWUD include use of illicit drugs [11-14]; presence of mental illness [12, 15]; being homeless or living in unstable housing [15-18]; food insecurity [17, 19]; low socioeconomic status, as marked by low income, poor education and unemployment [20]; as well as exposure to the criminal justice system [21, 22]. These factors are barriers for HIV-positive PWUD to progress through the care cascade on par with the general population of PLWH. However, despite extensive findings regarding the important impacts of social factors on HIV care outcomes among PWUD [11-22], less is understood about the ways in which the structural features imposed by organizations and institutions play in moderating the impacts of more well-studied risk factors on poor adherence to treatment.

For HIV-positive PWUD, institutions have a potential role in structuring the delivery of a person-centered care (PCC) approach; a concept that recognizes the entirety of an individual's needs in their pursuit of health care and related support

[23]. As such, the alignment of services across multiple sectors around the needs of a patient is essential in meeting the overall needs of an individual [24]. Although typically applied in healthcare facilities, the principals of a PCC model of care are relevant to HIV care outcomes for PWUD and could be expanded to non-health institutions as well. For instance, among patients who are affected by the HIV pandemic, non-health institutions such as government agencies or service organization that promote social protection as well as the delivery of social services to marginalized populations are commonly responsible in addressing the diversified social needs of PLWH [25-27]. Thus, services that are situated beyond conventional health settings may offer key services that are relevant to the overall well-being of PWUD, such as income or housing assistance as well as vocational training to increase employment opportunities [28, 29], all of which would potentially improve health outcomes.

Of additional relevance is that the individual contacts that PWUD have with various organizations, positioned within institutions that govern core functions such as health, social protection or law, may vary. For instance, engagements with healthcare or social services can be characterized by stigma and discrimination towards HIV and SUD that are enacted formally in organizational practices or procedures [30, 31] and informally through interpersonal interactions [32], as well as

the lack of coordinated efforts between different services to properly address individual needs [33]. In addition to differing levels of engagement with specific organizations, contact with certain institutional types can also be problematic, especially when these institutions embody or interact with people based on contrasting values to those endorsed by organizations that support PWUD. For instance, the exposure of PWUD to structures within correctional facilities (e.g., prisons and jails) can produce interruptions in HIV care in the absence of adequate treatment continuity support [21, 34]. Taken together, organizational structures and the synergy within and between them may potentially explain the degree to which the institutional environments impact HIV care outcomes among PWUD. However, the lack of research in this area may indicate that significant barriers and resource gaps which could be addressed to strengthen a PCC for PWUD approach have been overlooked.

Institutional theory offers additional insights in understanding the role of institutional environments in improving health outcomes. A key principle that underpins some institutional theory frameworks is that the day-to-day activities performed by organizations are informed by the central building blocks of institutional structures: rules, norms and cultural-cognitive beliefs [35]. Using a theoretical framework that describes the alignment between different organizations

may provide a more nuanced understanding on how the institutional environments support or prohibit PCC strategies. Although the alignment of various institutional domains is crucial for the development of a PCC model in the context of HIV care for PWUD, less is known about the extent to which different organizations within institutional environments are congruent in terms of their constituent rules, norms and cultural-cognitive beliefs.

The current doctoral research project applies institutional perspectives to explore the extent to which individual and organizational interactions are aligned in achieving a PCC approach, specifically to facilitate improvements in HIV care outcomes among PWUD. Specifically, this dissertation assesses organizational practices and function within a single domain of healthcare (i.e., HIV care); within multiple domains of healthcare (i.e., treatment for substance use disorders [SUD] and ART); and across institutional domains beyond healthcare (i.e., prisons and jails, social assistance). Using institutional perspectives, this dissertation seeks to develop empirical evidence based on the theoretical constructs of institutional elements, including the rules, norms and cultural-cognitive beliefs around PCC care for HIV-positive PWUD.

1.2 Background

1.2.1 HIV among PWUD: global epidemiology and treatment patterns

The United Nations Office on Drugs and Crime (UNODC) estimates that there are 247 million PWUD globally, and out of these, 12 million are people who inject drugs (PWID) [36, 37]. Approximately 10% of HIV infections worldwide are attributed to injection drug use [38]. As a result of efficient viral transmission via contaminated injecting equipment and barriers to accessing harm reduction services, such as opioid agonist therapy (OAT) and needle and syringe exchange program (NSEP), PWID are more likely to be infected with HIV than the general population [39]. The use of non-injection illicit drugs among PWUD is likewise associated with risks of HIV infection due to overlapping social and sexual networks of PWID populations, lack of access to healthcare, or existing policing strategies that hamper HIV treatment and prevention efforts, placing the population of PWUD at high risk for adverse health outcomes [40, 41].

In response to the pandemic, substantial progress has been made in recent years to curb new infections through wide-scale implementation of ART. An effective public health tool, modern combination ART eliminates the replication of HIV in infected individuals, thus reducing population VL and rates of new HIV infections [42]. Moreover, for PLWH, timely initiation of ART prevents progression to AIDS or

death, especially among individuals with acute comorbidities [43, 44]. Despite the reduction in the number of new infections among PWUD and advances in HIV treatment through the availability of ART, gaps in treatment access and adherence among members of this key affected population pose a challenge to achieving the UNAIDS 90-90-90 target [45].

In relation to these targets, the HIV care cascade serves as an important framework to monitor progress made by PLWH in engagement in HIV care, with essential steps from diagnosis of HIV infection, treatment initiation and adherence, as well as VL suppression [2]. Patient attrition occurs at every stage, resulting in a cumulatively large gap between the number of people who are diagnosed and those who successfully achieve virologic suppression. In British Columbia, Canada, PWUD have lower VL suppression rates compared to non-PWUD populations [10], indicating that optimal ART adherence is less likely to be well maintained among PWUD.

Research has consistently shown that the success of ART among PLWH, as demonstrated by increased rates of VL suppression, is highly dependent on optimal adherence levels [46]. Adherence to treatment is defined as the degree to which patients take their medication according to prescribed treatment regimens by physicians [47]. Within the context of HIV treatment, high levels of adherence are

needed to ensure the full benefits of the medication are achieved [48]. Ultimately, through appropriate levels of adherence to ART, studies have demonstrated that the treatment is not only effective at sustaining VL suppression but also prohibiting the emergence of drug-resistant viral strains which commonly result in treatment failure, progression to AIDS and low survival rates [49, 50]. For HIV-positive PWUD, clinical care is challenging, as studies have shown that active high-intensity drug use is associated with suboptimal treatment outcomes; however, the role of prevalent social/structural exposures is becoming increasingly well recognized [51-54].

1.2.2 Social and structural barriers to optimal ART adherence

In addition to the barriers posed by active substance use, PWUD commonly experience living conditions and related exposures that may limit their engagement in HIV care. For instance, PWUD often face challenges in securing employment due to stigmatization, criminalization, and socioeconomic marginalization [55, 56]. Reduced opportunities for employment have resulted in PWUD becoming increasingly involved in illegal and informal income generation activities, such as drug dealing, theft, panhandling, and sex work, which have been associated with suboptimal treatment outcomes [57]. Additionally, studies have found that living in marginal housing among PWUD is highly associated with increased mortality,

whereas homelessness strongly predicts low VL suppression rates among PWUD initiating ART [58, 59]. In Vancouver, homelessness has been found to be negatively associated with adherence to ART through multiple potential pathways, including poor access to food, limited places to store medication and lack of privacy [16]. Collectively, these studies suggest that the ability to adhere to ART is compromised by social and structural factors and the physical environment in which members of key populations live.

While these exposures have been shown to be negatively associated with effective engagement in HIV care, they occur within institutional and policy contexts that also play central roles in HIV care outcomes. Institutional barriers, such as inadequate service delivery, may limit the effect of ART on improved health outcomes among PWUD. For instance, although SUD treatment, such as OAT, is associated with improved clinical engagement in HIV care, limited availability of OAT in many low and middle-income settings has reduced opportunities for PWUD to engage in such care [9, 60]. Specifically, the prohibition of OAT in Russia is not only a barrier to SUD care but also disrupts the effective delivery of HIV care for PWUD [60]. Nevertheless, a recent review has shown that even in regions where OAT is provided within national treatment guidelines, OAT treatment continues to be underutilized, partly due to a complex array of structural-level barriers [61]. For example, in addition to

pervasive stigma and discrimination towards illicit drug use in limiting access to OAT [62], other challenges stem from institutional practices that hamper efforts to implement low-barrier treatment strategies for both OAT and HIV care [63]. These practices may include long waiting lists or prerequisites to enter a program, the confinement of OAT treatment to specialized clinics rather than decentralized services, and inadequate OAT doses [63, 64]. Collectively, these social and structural barriers perpetuate challenges for HIV-positive PWUD to engage effectively in HIV care.

1.2.3 Person-centered care (PCC) approach in the context of HIV care

In the context of HIV care, there has been a growing trend towards structuring health programs based on a PCC approach, shifting from a disease-centered care model which often undervalues the social and structural context in which an individual lives [65]. While there are variations in how PCC is defined and conceptualized, the World Health Organization (WHO) defines PCC as consisting of “care approaches and practices that see the person as a whole with many levels of needs and goals, with these needs coming from their own personal social determinants of health.” [66]. In line with this definition, PCC is attentive to the multiple conditions that affect the overall health status of a PWUD living with HIV,

such as the complex management of both substance use and HIV infection, as well as an individual's exposure to a wide range of social and structural barriers to engagement in health care. The PCC framework is therefore an ideal conceptual framework to examine HIV care outcomes, as it focuses on a patient's needs and experiences, as determined by the broader social and structural environment of HIV and illicit drug use.

While commonly described as an individual's role in devising treatment plans and decision making processes [67], the concept of PCC also extends to the development of rapport and bonds of trust in the clinical interaction between healthcare providers and patients [68]. This relationship is essential in shaping better interpersonal experiences, which have been shown to positively impact medication-taking behaviours and retention in HIV care [69, 70]. For example, among PLWH, patient satisfaction and improved engagement with healthcare were positively associated with better adherence to ART, indicating the prominent role that interpersonal provider-patient interactions play in ensuring that patients are comfortable in accessing the services [71, 72]. However, the role of PCC in the provider-patient relationship is not equally observed among all key populations. For PWUD, the establishment of effective rapport is often challenged by previous negative experiences with the healthcare system attributed to drug use behaviours

and providers' perceptions about a person's ability to deal with intersecting issues such as untreated SUD and complex social circumstances [73, 74].

A PCC approach may shed light upon the physician-patient relationship as well as the degree to which an individual's collective needs are influenced by different levels of interaction in the wider environment. Among individuals with complexity of need in general, the exchange of interaction that occurs in the wider environment involves collaborative action in fostering partnership between health and social care systems [75]. When applied in the context of HIV care for PWUD, collaborative efforts have focused on joint service delivery between specific health domains that are closely linked to HIV, such as management of tuberculosis (TB), in conjunction with HIV care [76]. Specifically, during this interaction, the sharing of information on case detection, treatment status and outcomes occurs between HIV and tuberculosis service providers, thus enhancing service coordination and strengthening efforts to meet the overall clinical needs of a PWUD [77].

The type of interaction that promotes PCC is however not confined solely to areas of health, but interaction with non-health fields may strengthen a PCC model of care. For example, in Canada, the Housing First program is supplemented with a harm reduction service component to assist PWUD in meeting their housing and SUD treatment needs [78]. The interaction between different service providers may yield

benefits not only in promoting housing stability and reducing the negative impact of substance use but also in improving health [79]. Among HIV-positive PWUD who were homeless in the US, case managers from a hospital social work staff and non-profit agencies facilitated individual access to supportive housing, resulting in improvements in HIV clinical outcomes [80]. Thus, the delivery of services to achieve PCC for HIV-positive PWUD involve an array of organizations that include not only health-related facilities but also community-based or cultural organizations and different bodies of government that operate within an institutional environment.

In the current literature, a PCC model of care has been typically described as the physician-patient relationship, with significant impacts on HIV-related outcomes among PLWH [68, 71, 72]. However, the extension of a PCC approach into the role of institutions, particularly in exploring how different levels of interaction between organizations/institutions are linked with HIV care outcomes among PWUD, remains limited. Current knowledge gaps on the implementation of PCC in this area may stem from the lack of exploration of underlying theories to explain the relevance of institutional structures across multiple contexts. While collaborative exchange between multiple providers have been incorporated as an essential element in several existing frameworks on PCC [66, 81], further conceptualization of the relationships between institutions is needed to bridge the theory-practice gaps in delivering PCC-

oriented care. In addressing these gaps, an application of social scientific approaches may increase understandings of the role of institutions in meeting the complex needs of PWUD and to establish the definition of institutional relationships.

1.2.4 Sociological perspectives on organizational/institutional function

In sociology, social interaction is based on the conceptualization of “social action”, which Blumer elaborated as “consisting of the individual and collective activities of people who are engaged in social interaction — that is to say, activities whose own formation is made in the light of the activity of one another” [82]. In this sense, individual actors enter a situation in which they encounter different actors or groups, and the other party responds, together producing a reciprocal action. The “collective activities of people” refer to aggregated actions or practices, often originating from organizations and institutions [82], which thus become central elements of the social interaction. When applied in the context of healthcare’s institutional environments, social interaction is characterized first as the relationship between service providers and patients, and second, the interaction between organizations or institutions, across multiple service providers in different domains [83]. Exploration of social actions embedded in institutional relationships may allow researchers to determine the extent to which health outcomes are impacted by

synergies or incongruence between organizations, within and beyond institutional healthcare contexts. Specifically, the interactions between multiple sectors may determine whether certain health and social needs are met, and in turn, impact health outcomes.

Although PCC requires the consideration of institutional relationships that include an array of social institutions, there is a paucity of studies assessing institutional functions and interactions in relation to PWUD experiences in engaging in HIV care. In the tradition of sociologists Durkheim and Parsons, social systems are maintained by institutions which manage core functions such as health, labour, law, and education [84]. Each social institution is governed by distinct values that, in theory, seek to serve the entire social system and, by extension, influence an individual's interaction with a given institution [85]. In a Durkheimian conception, the function of an institution is to provide a high degree of stability by retaining its core values. Further, institutional subsystems are viewed as "organs" with specialized functions that apply a set of key actions and practices in daily operations [86, 87]. These organs are comprised of "organizations" governed by rules, regulations and policies that are shaped by the values of the institution in which these organizations developed [86, 87].

As organizations exhibit patterns of operation that are oriented around specific rules and regulations, these organizations develop into normative systems, in which work practices or key actions are designed to pursue a certain goal or objective [35]. Further, as institutions form an integral part of societies, Parsons argued that individuals become accustomed to a normative system when the goals of an organization are connected to wider cultural values within societies, such as support for well-being, knowledge or skills development [88]. Given their position in society, institutions additionally exhibit cultural-cognitive beliefs; a hyphenated label which recognizes that cognitive (i.e. conceptual beliefs and values, shaped by how certain information are interpreted and retained, are internalized within institutions) and cultural (i.e. the external influence specifically the cultural context in which an institution is embedded) beliefs, can be mutually reinforcing [35, 89, 90]. Collectively, these elements – rules, norms and cultural-cognitive beliefs – are central ingredients of institutions that guide their core function. Thus, the alignment between institutional elements and societal values, and whether different institutional goals are congruent with one another may determine the extent to which these institutions operate in delivering a PCC care.

Meanings and values that are expressed by institutional functions and practices shape individual experiences as these individuals navigate through the

institutional environments [91]. Health institutions, for instance, are composed of an array of organizational units, such as hospitals, clinics and other care facilities, across public and private sectors, each with their own management practices [92]. Smaller units can also be differentiated according to disease specialty. In the context of HIV care for PWUD, relevant institutional domains extend beyond the provision of ART to include treatment for SUD (e.g., methadone maintenance therapy [MMT] or buprenorphine/naloxone), management of other common viral infections and co-morbidities (e.g., mental health, TB and hepatitis C), as well as public health promotion or harm reduction services. Each domain is responsible for a certain component of care within their respective organizational units, and typically deliver specific material resources or technical services to individuals who are likely to benefit from these services. In some instances, different health domains intersect with one another through an integrated approach, in line with a PCC concept to provide a broader set of services to PWUD. A much-publicized example of an integrated approach is the implementation of HIV care through directly administered therapy in which ART is provided and ingested under direct supervision along with MMT doses [93, 94]. The healthcare system consists of a range of diverse domains to improve and protect the health of HIV-positive PWUD, thus, with respect to this aim, health institutions lie at the core of the institutional environments.

Although the health sector is a significant element of the institutional service delivery landscape, non-health institutions are also essential in providing complementary resources to address a wide range of unique needs among PWUD. When provided in a complementary and integrated fashion, these health services constitute the comprehensive care package for the prevention, treatment, and care of HIV among PWUD—a strategy endorsed by UNAIDS, WHO and UNODC [95]. For example, housing assistance may be provided by a non-health institution through the provision of a housing allowance or housing supply programs to support individuals who experience socioeconomic marginalization [28]. One study has demonstrated that close collaboration between a health institution and the governmental agencies responsible for housing has resulted in improved health outcomes among PLWH receiving rental assistance [28]. In addition to housing security, labour supports to increase employment options are also imperative in improving health outcomes [29, 96]. Engagement with vocational services, for instance, has been shown to increase opportunities for employment and improve health services uptake among the general population of PLWH [97]. Thus, in addition to the health sector, different institutions within the social system can feature prominently in providing supplementary resources.

In the above examples, social institutions share the common objective of providing services or goods to individuals through specific organizational units, independently or jointly. However, individuals, and specifically PWUD living with HIV, may interact with institutions that may have contrasting values with institutions that are engaged in service delivery. Correctional institutions, for example, do not aim to deliver services that can benefit individuals per se but function as a physical constraint to eliminate or deter crime or punish people convicted of crimes, with key practices to promote rehabilitation among offenders [98]. Due to policing practices related to drug offenses, correctional institutions —through prisons, jails and compulsory detention settings—have housed a disproportionate number of PWUD [99]. Despite having different basic functions from those of health or social welfare promoting institutions, in previous research, the highly-structured environments have been characterized as a potential platform to engage PWUD in HIV care, thus opening opportunities to monitor compliance to HIV treatment and achieve optimal treatment outcomes [100]. In this regard, the capacity of correctional facilities could stretch beyond its core functions to facilitate the engagement of people who are imprisoned into clinical care.

Although there is a mandate to provide essential healthcare for incarcerated individuals across Canada [101], unfortunately, in many settings including British

Columbia, periods of incarceration evidence indicate incarceration can hamper efforts to retain individuals in treatment. For instance, several studies have demonstrated the deleterious effect of incarceration on ART continuity and treatment outcomes, with increasingly negative outcomes as the number of incarceration events increases [21, 102]. Cycles of incarceration may impede the continuity of ART delivery, with more adverse effects among PWUD released into community settings due to a lack of effective linkage strategies with community organizations [103]. Therefore, individuals' engagement with correctional institutions can either be beneficial or restrictive in influencing health outcomes, depending on the types of services offered in these settings and the linkages with other organizations that are able to facilitate transitions in care upon release to the community. Further, the discontinuity in care may be attributed to incongruent interactions between healthcare settings that provide ART treatment and the criminal justice systems, as well as other relevant organizations that facilitate re-entry.

The notion of individual and organizational interaction coincides with socioecological perspectives outlining the different institutional layers that impact HIV care engagement, specifically at the community level where individuals navigate multiple systems simultaneously [104]. In particular, Bronfenbrenner in his ecological model described the evolving interaction between an individual and the environment,

comprising of nested social systems with specific functions that influence health outcomes [105]. These nested social systems comprise of micro-, meso- and macro-systems that describe an individuals' relationship with their immediate surroundings and expand into wider forms of interaction, specifically between institutions [105]. In a more general sense, interaction within institutional environments occurs at three different levels: at the micro-level, the interaction between service delivery providers and individuals; meso-level, the interplay between organizational units within the same institution (e.g., HIV and substance use disorder within health institutions); and macro-level, the coordination between institutions beyond healthcare, within a larger system [106]. Not only do these levels of interaction highlight the connection between organizations and individuals, but also the pathway in which different infrastructures interact and communicate with each other. In this respect, these levels of interaction represent different potential frames of reference through which the relative adherence to the principles of PCC may support or interfere with the complex needs of a PWUD. This support or interference will, in part, be determined by considerations surrounding the institutional environment in which these individuals come into contact with different organizations.

1.2.5 Theoretical and conceptual framework

1.2.5.1 Application of organizational theories

In the current literature, the application of organizational theories has been useful to describe organizational performance and structures in the fields of HIV and SUD treatment. Resource dependence theory, for example, offers an explanation on the influence of external organizations on resource allocation for a particular organization, thus supporting the delivery of key services and enhancing collaborative efforts across organizations [107]. A previous study has demonstrated that SUD treatment units with greater dependence on government funding were more likely to adopt health services that are tailored around the needs of women such as reproductive services [108]. Although this theory supports strategic coordination across organizations and can be useful in structuring a PCC approach, the use of this theory can be limited by the overreliance on external actors for resources and the overemphasis on material forces in shaping the interaction between organizations [107, 109]. When examining organizational relationships, the limited inclusion of agencies responsible for funding may undermine the role of other organizations whose conceptual beliefs and cultural values can be influential in meeting the complex needs of PWUD.

Shifting from a material theoretical framework, the diffusion of innovation theory is centered around newly emerging ideas, practices or technological advances, as well as the organizational environment as adopters [110]. The application of this theory in HIV research has been demonstrated in studies investigating the availability of HIV-related services across a range of organizational settings, including community-based organizations and SUD treatment facilities [111, 112]. For example, one study has found that organizational characteristics, including care philosophies around HIV prevention, organizational resources, levels of experience and targeted populations, were associated with the adoption of HIV preventive measures within community-based organizations [111]. Despite its strengths in analyzing an organizational capacity to adopt new practices, one limitation of the diffusion of innovation theory is that there is lack of consideration of the external environment, particularly the influences of institutional networks in decisions regarding the adoption process [113]. Thus, the limited focus on other organizational domains may hamper efforts to meet the objective of PCC in aligning multisectoral services.

While existing organizational theories are grounded in economic principles or tend to focus on the adoption of new innovations and internal characteristics of the organization as the adopter, institutional theory offers an added-value by taking a sociological view to explain organizational structures through the acknowledgement

of basic constituents of institutional structures [114]. As such, institutional theory posits that institutions possess rules, norms and cultural-cognitive beliefs, all which may be represented or reflected through the actions or functions of organizations [84]. Further, the use of institutional theory may shed light on the relationships between organizations across multiple institutional contexts relevant to a PCC approach in acknowledging within- and between-institution relationships. The synergy between organizational units within and across institutions is determined by the extent to which institutional elements (i.e. rules, norms and cultural-cognitive beliefs) are congruent with one another, and in turn influence the structure of an organization as these elements become institutionalized within an organization. The term *institutionalization* was coined by institutional theorists to capture the process by which these elements are embedded within organizations [115]. In the institutionalization processes, the occurrence of organizational changes results in certain practices becoming internalized within the structure of an organization, driven by three major pressures—regulative, normative and cognitive. This concept provides a theoretical basis for understanding how the interplay of rules, norms and cultural-cognitive belief elements could contribute to changes that occur within organizational structures and practices that reinforce HIV service coordination among PWUD [116].

First, in a regulative process, organizations comply with policies, rules and regulations that are imposed by higher levels in the institutional structure [84]. This process highlights the capacity of a higher-level organization to influence the process of institutionalization by developing and setting standards, as well as enforcing conformity to those standards among the institutional components under their jurisdiction. In the context of HIV treatment among PWUD, guidelines for the delivery of care contain a set of information on ART therapeutic guidelines, including treatment initiation and the selection of ART regimen [117, 118], as well as the use of OAT for opioid-dependent users living with HIV to optimize ART [119]. With reference to medication-related policies and procedures, in British Columbia, the safe and effective practice of OAT prescription is shaped by guidelines developed by regulatory bodies such as the College of Physicians and Surgeons of British Columbia (CPSBC) and the College of Pharmacists of British Columbia (CPBC) [120]. Optimal dose guidelines, as put forward by CPSBC and CPBA, have been incorporated as part of a low-barrier OAT approach which entails efforts to remove programmatic barriers for PWUD to access OAT services and maintain treatment enrolment. These organizational units (i.e., CPSBC and CPBA) thus play a prominent role, through regulation and policy reform, in ensuring that the clinical needs of PWUD are achieved.

Second, the normative source of change arises from social expectations, as reflected in norms or work policies aimed at the pursuit of valued ends. A normative process emphasizes the role of professionals in influencing the type of activities or key actions to take [116]. Institutional theorists, such as DiMaggio and Powell, have embraced the idea that professionals are in positions to determine certain practices for a group of individuals, based on what these experts consider the “proper” way of doing things [116]. Within treatment settings, physicians are commonly the professionals who determine the selection of clinical practices they perceive as appropriate and could incorporate normative change between types of care providers [121]. For example, current calls for service coordination lead to expectations that multiple providers of care (ie. HIV care and SUD treatment) would collaborate [95]. The expansion of professional networks that span organizations allows robust exchange of information between experts and increases exposure to different work roles. New forms of service delivery practices may emerge from this interaction to meet the social expectations of enhanced service coordination. For instance, the incorporation of SUD treatment, HIV care and treatment for other comorbidities in a single facility not only broadens access to a range of services for PWUD, but it also highlights normative contents in the interaction between health professionals [122].

Thus, the institutionalization of this practice is said to be institutionalized in organizations through a normative pressure, as a product of social obligation.

Third, cognitive elements influence institutional change through prevailing values and conceptual beliefs [123]. Academic and research institutions can and do play a considerable role in the institutionalization process through the production of knowledge and recommendations for evidence-based practices that are informed by clinical expertise and patient values [124]. For instance, in Vancouver, British Columbia, academic and research institutions' efforts to translate research into knowledge by disseminating study findings to the public were integral to securing the ongoing operation of Insite, North America's first sanctioned supervised injection facility, as part of a harm reduction initiative to prevent new HIV transmissions among PWUD [125]. These facilities are now embedded within community institutions across Canada, supported by evidence that demonstrate the provision of such services do not promote initiation of injection but rather seeks to reduce HIV infections and overdose incidence [126]. The establishment and maintenance of such interventions highlights the role of academic and research institutions in providing evidence that other institutions can utilize to address health-related risks, particularly in relation to organizations that are responsible for regulating or delivering these services. Conceptual beliefs are internalized by these organizations, because such

beliefs are valued by organizational members and, more importantly, by affected populations, rather than reinforced through policies and work norms [90]. Thus, knowledge translation activities serve as a pathway in which the influence of research institutions lead to the transmission of new ideas or beliefs across various organizations.

The integration of institutional perspectives in a PCC approach could be used as a framework for empirical research to view the role of institutions in determining HIV care outcomes among PWUD. However, institutional frameworks have been underutilized in HIV research, particularly in research among members of key affected populations, with most research focused on the adoption of empirically proven HIV testing practices in SUD treatment facilities [127-131]. For example, existing research shows that smaller units have been obliged to adopt practices that are accepted by a broader institutional system, resulting in the integration of HIV testing in SUD treatment facilities as a result of directives from higher-level organizations such as accreditation bodies [131]. With the power to set standards for the implementation of health interventions and provide resources to ensure such interventions were in place, accreditation bodies play a key role in determining public health strategies to improve HIV care among PWUD. Further, private-for profit SUD treatment facilities were less likely to conduct HIV testing for their attendees,

compared to public-owned facilities [132], indicating that public facilities may exhibit rules, norms and cultural-cognitive beliefs that are more congruent with the broader institutional bodies as compared to private facilities. Collectively, these studies provide evidence that the institutionalization of HIV testing practices in SUD treatment facilities can be shaped by regulations imposed by higher-levels organizations that are linked to these facilities, and the nature of the organizational structure. Moreover, this collection of evidence highlights the practicality of an institutional theory in offering additional insights on the interdependence of organizations operating at multiple levels, and its potential impact on HIV care outcomes.

Although institutional theories have the potential to advance understandings of opportunities to increase connectedness and alignment of institutional elements in support of optimized HIV and SUD care, there is very little understanding on how these elements—rules, values, norms and beliefs—shape institutional function and structures. Additionally, there is little knowledge on how the alignment of these elements, in turn, have an impact on an individual’s HIV care outcomes, specifically adherence to ART. Unlike most theoretical frameworks that have conceptualized HIV care within social and structural environments [31, 133], the focus on an institutional framework seeks to specifically identify the role of the constituent elements of

institutions in promoting HIV care [84]. Subsequently, these components are reflective of the overall function of an institution in determining whether they can support a PCC model of care. Considering the often complex clinical, social, economic and material needs of PLWH, especially PWUD living with HIV, more conceptual and empirical work is needed to map the components and qualities of institutional environments in which HIV-positive PWUD interact with different organizations. The application of institutional theories in the field of HIV, substance use and social assistance may improve understandings of how the interplay of institutional elements that underpin the function of organizations, especially the degree to which these elements are congruent within and between organizations, impact individual-level outcomes.

The rationale for selecting institutional theory as a key theoretical lens for this dissertation is therefore to broaden current understanding of the capacity of different organizational/institutional domains to enshrine a PCC approach. Ultimately, the interplay of institutional elements (i.e., rules, values and cultural-cognitive beliefs) helps to uncover the ways the interaction between service delivery providers and individuals (micro-level interaction) are also influenced by macro- and meso-level organizational/institutional dynamics. In short, institutional theory can be used to establish the underlying mechanism through which multiple organizations and

institutions are aligned and congruent with one another; an important concept of PCC. Specifically, in this dissertation, institutional congruence is theorized to be the alignment of regulation, normative standing and cultural-cognitive beliefs between organizations across institutional contexts.

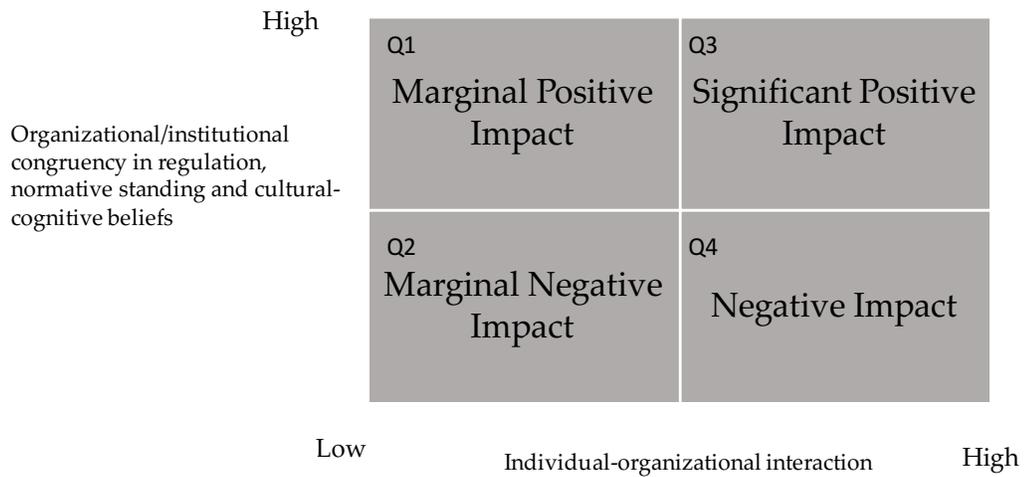
1.2.5.2 Conceptual framework

In line with the principles of PCC, the congruence between organizations and institutions in terms of their overall objectives, practices and service coordination may strongly influence the support and care experiences of individuals via institutionalization processes. However, there is little acknowledgement of the two-fold interaction that occurs in the institutional context of HIV treatment among PWUD: one, an individual's direct engagement or exposure to different organizations; and second, the relationship between organizations, within and beyond institutions. Thus, there is a need to identify areas that reflect the values of PCC within institutional environments by empirically testing the association between interactions with different institutions and HIV care outcomes among PWUD.

In the context of the current project, a conceptualization of social institutions will support evaluations of how the interactions between individuals and the institutional environments impact key HIV treatment outcomes. To understand the

potential configurations, it is conceptualized that there are two key dimensions of interest: First, individuals' exposure to a given organization (individual-organizational interaction) and second, the alignment of regulation, normative standing and cultural-cognitive beliefs between organizations with which an individual may interact, or institutions within which these organizations operate. This dissertation is conceptualized using a four-quadrant diagram which describes levels of individual and organizational/institutional interactions, as well as the potential impact on HIV care outcomes, as depicted in Figure 1.1. below.

Figure 1.1 Conceptual framework illustrating the different levels of individual and organizational/institutional interactions that occurs within institutional environments



The relationship between the different levels of interactions and adherence to ART is examined empirically by including key practices and function that, in theory, capture the following four patterns of interaction:

The first quadrant (Q1) demonstrates high organizational/institutional congruence, but low individual-organizational interaction levels. Although there is a high congruence between organizational/institutional domains, PWUD may have low levels of interactions with organizations (e.g. poor access to a specific organization) that could potentially support their needs. This configuration may lead to a “marginal positive impact” on HIV care outcomes.

The second quadrant (Q2) demonstrates low organizational/institutional congruence and low individual-organizational interaction levels. This configuration results in “marginal negative impact” on HIV care outcomes, as such that the impact will be less relevant because of the lower levels of interaction individuals have with unaligned organizations/institutions.

The third quadrant (Q3) demonstrates high organizational/institutional congruence and high individual-organizational interaction levels. PWUDs’ interaction with organizations that are closely aligned in serving members of this key population may yield “significant positive impact” on HIV care outcomes, as PWUD needs are sufficiently addressed. With respect to organizational/institutional

congruence, different organizational or institutional domains may share the same values or even collaborate at a certain level and coordinate activities for a common cause.

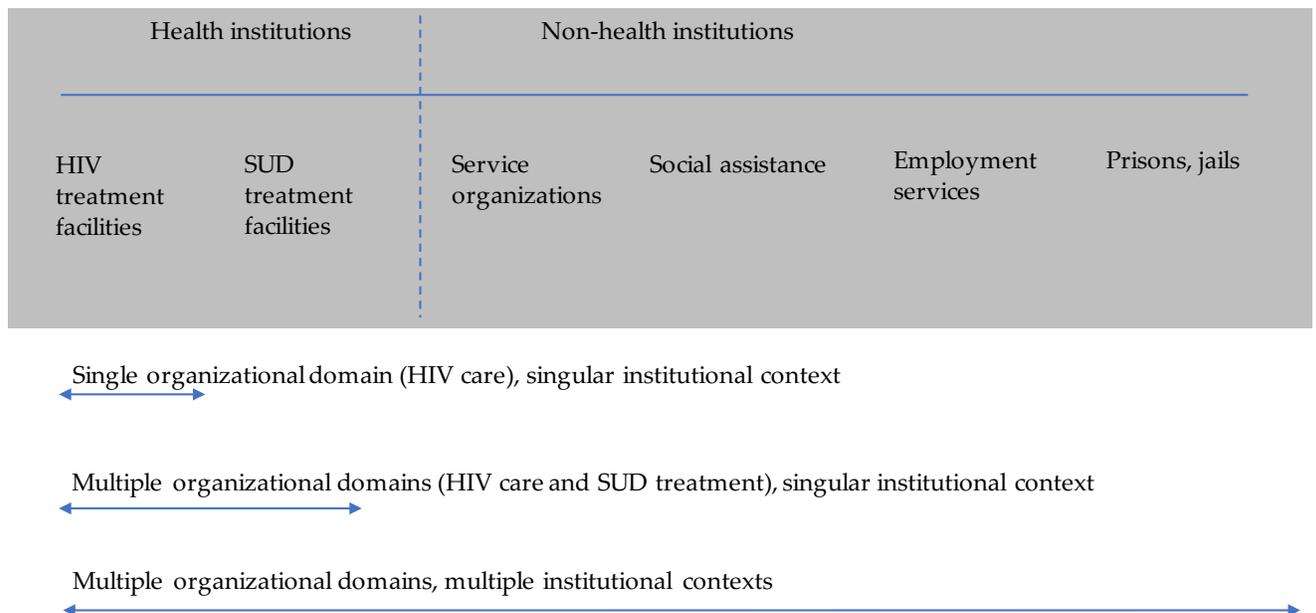
The fourth quadrant (Q4) demonstrates low organizational/institutional congruence, but high individual-organizational interaction levels. Although PWUD may have high levels of interactions with organizations (e.g. better access to a specific organization), the lack of congruence between organizational/institutional domains may not be sufficient in supporting PWUD. In this case, an organization with which a PWUD interact may act independently. Thus, this configuration may produce an “negative impact” on HIV care outcomes, in which the needs of a PWUD, as an individual, are inadequately addressed.

1.2.6 Research Objectives and Hypotheses

This dissertation aims to examine HIV care outcomes among PWUD living with HIV through the lens of individual engagement with institutions relevant to HIV care outcomes. Drawing on institutional perspectives, organizational structures that may or may not be in alignment in terms of the rules, norms and cultural-cognitive beliefs that originate at the institutional-level are assessed. In empirical analyses, this dissertation examines a singular institutional context (in the domain of HIV care),

within institution cross-organizational congruence (HIV care and SUD treatment), as well as between-institutional congruence (health and non-health institutions), as depicted in Figure 1.2. Together, these studies seek to inform a larger research question: How are the institutionalized values, norms and cultural-cognitive beliefs in organizations both internal and external to health institutions related to HIV care outcomes among HIV-positive PWUD? Additionally, how do these relationships inform PCC care among populations with complex comorbid conditions?

Figure 1.2 Institutional environments: different organizational/institutional domains with potential roles in determining the overall well-being of a HIV-positive PWUD



1.2.6.1 Chapter 2: Systematic review

The systematic review described in Chapter 2 specifically assesses the components of MMT service delivery that lead to improvements in HIV care cascade outcomes among HIV-positive PWUD. Although there is an extensive amount of research demonstrating the effectiveness of MMT in ART initiation and adherence [134, 135], the extent to which MMT-related services enhance HIV care cascade outcomes has yet to be assessed. To date, there are numerous platforms in which MMT is delivered in health care and non-health care settings. In some settings, MMT programs are enhanced with clinical or social support that would be essential to assist PWUD who are also HIV-positive. To understand the effectiveness of MMT service delivery within and across institutions on a global level, the objective in this review proposes to systematically assess components of MMT service delivery that are associated with UNAIDS 90-90-90 targets: 1) uptake of HIV testing; 2) exposure to ART; and 3) viral load suppression. The classification of MMT service delivery draws upon four general components of models of care: 1) standard MMT care; 2) standard MMT care and an additional medical component(s); 3) standard MMT care and social support; and 4) standard MMT care, an additional medical component(s) and social support. The dimensions of social support delivered by service providers are further delineated to include instrumental and informational support [136, 137]. In relation to

the proposed framework, this review focuses on the HIV care impacts resulting from congruency within health institutions, specifically by exploring medical components in the domain of SUD treatment and HIV care. Further, it aims to highlight congruency between institutions by exploring social support that potentially supplements health services.

1.2.6.2 Chapter 3: Analyzing empirical evidence within a single institutional domain

Chapter 3 is concerned with practices within the domain of HIV care in relation to medication-related factors. Specifically, the chapter considers the effects of simplified ART regimens as a component of PCC approach. For members of populations with multiple barriers to medication adherence, simplified pill regimens may hold potential to improve healthcare engagement. Qualitative studies involving people using injection and non-injection drugs have reported that they experienced difficulties accommodating an ART regimen into their schedules, particularly when prescribed thrice-a-day dosing [138]. Treatment adherence is further complicated if a physician failed to consider the implications of an individual's social and structural environment, such as living in unstable housing, low socio-economic status and exposure to the criminal justice system [11-22], when prescribing complex regimens

[47]. Despite many studies investigating the impact of pill burden on ART adherence among PLWH in general, the extent to which practices of prescribing complex medication regimens by HIV care providers affect the ability of HIV-positive PWUD to achieve optimal adherence to ART has yet to be longitudinally assessed.

The objective of the study in Chapter 3 is to investigate the association between daily pill burden and adherence to ART using data from a comprehensive source of ART dispensation records in British Columbia, a setting of universal no-cost medical care, inclusive of all HIV care and medication. It is hypothesized that a greater number of pills was associated with higher risk of non-adherence among HIV-positive PWUD.

1.2.6.3 Chapter 4: Analyzing empirical evidence in multiple organizational domains, within a singular institutional context

Chapter 4 is directed at cross-organizational alignment within a healthcare institutional context. Specifically, it examines how the relationship between HIV and SUD treatment is interconnected, using the example of medication co-dispensing practices. Given the benefits of OAT, as a form of essential medication to assist individuals with opioid use disorder, in improving access and adherence to ART, an integrated approach for OAT and HIV care has been strongly recommended by WHO [119]. However, analyses of integration between the two types of services in the

literature has largely focused on cross training of specialists, integrating care under the same management team, establishing cross-referral mechanisms and the role of directly-administered ART with daily methadone doses [139-142]. To our best of knowledge, there are no studies that have investigated the longitudinal effect of co-dispensation of MMT and ART at the same facility on adherence to ART among PWUD, as a specific type of integration.

In Vancouver, all persons living with HIV have access to no-cost ART through the province's universal healthcare system. ART medication is delivered through community pharmacies, physicians' offices or other health care facilities, authorized by general hospitals and medical centres treating PLWH. Similarly, MMT, prescribed by licenced primary care physicians under the provincial healthcare program, is also commonly, but not universally dispensed at these various locations [135]. Understanding the relationship between specific institutional linkages is important to guide efforts around how to best provide comprehensive care for this key affected population. Thus, using longitudinal data, the objective of this chapter is to assess the potential impact of ART-MMT co-dispensation on adherence to ART among HIV-positive PWUD in Vancouver. It is hypothesized that MMT-ART co-dispensation at the same facility improves ART adherence levels among HIV-positive PWUD.

1.2.6.4 Chapter 5: Analyzing empirical evidence in multiple organizational domains, within multiple institutional contexts

Chapter 5 focuses on patients' experience beyond the realm of health institutions, specifically their experience in securing basic material needs such as housing, food and social services in addition to health services. Research has consistently shown that the different exposures common to people living in poverty, including low income levels, low education attainment, housing, a lack of occupational skills, and reduced opportunities for labour market engagement can lead to suboptimal treatment engagement among PLWH [55, 56]. The common exposure of PWUD to poor socioeconomic conditions have placed them at a more vulnerable position by limiting their access to treatment and further increasing risk for HIV mortality and morbidity [143, 144]. However, most studies measuring poverty rely on income as a proxy for poverty or measurements of substandard living conditions that are typically dichotomized, such as homelessness. Unfortunately, there has been limited research using more nuanced quantitative measurement of the material conditions of socioeconomically marginalized individuals and how these material conditions may impact treatment outcomes among HIV-positive PWUD. Although the impact of institutional factors, including incarceration and engagement in substance use treatment, on health outcomes among PWUD has been well

documented, very few studies have tested the relationship between these institutional environments and material security in this population. Further, we are unaware of any longitudinal analysis that has evaluated the impact of material deprivation on adherence to ART among PWUD with access to universal, free HIV care.

Thus, the objective of this study is to examine the degree to which material security is impacted by different individual-institutional interactions (e.g. incarceration, social service access, substance use treatment), and the relationships between material security and adherence to HIV treatment. It is hypothesized that individual's interaction with correctional institutions, such as prison and jail, as well as unmet health and social needs are negatively associated with material security. Further, consistent with research that demonstrates poorer clinical outcomes among people who are socioeconomically marginalized [57], it is hypothesized that lower material security among HIV-positive PWUD is associated with decreased likelihood of optimal adherence to HIV treatment.

1.2.7 Overview of study designs and methods

1.2.7.1 Study setting

The data in empirical studies conducted in chapters 3 to 5 was drawn from a long-running cohort study, the AIDS Care Cohort to evaluate Exposure to Survival

Services (ACCESS), established in 2005. Participants are recruited using referrals, community-based sampling methods and street outreach [145], particularly in the Downtown Eastside (DTES). The DTES is characterized by high rates of poverty, injection and non-injection drug use and HIV infection [146-148]. Further, in the setting of British Columbia, all PLWH, including PWUD and all ACCESS participants, are supported by the provincial universal healthcare system that provides HIV care for free, including diagnosis, ART medications and monitoring through the Drug Treatment Program (DTP), by the British Columbia Centre for Excellence in HIV/AIDS.

Since the availability of highly active ART in 1996, there has been a substantial progress in health and support services in DTES over the years, including syringe distribution, OAT and supervised injecting facilities [149]. The maximally assisted therapy, for instance, is a prominent health program, aiming to deliver a set of services that meet clinical and social needs of PWUD [150]. Dispensation of ART and OAT is conducted amidst a wide range of support, including counselling on ART side effect management, services to address transportation needs in accessing medical care and housing assistance, as well as referrals to mental health care. Additionally, the delivery of medication is enhanced through outreach work in the community for patients who are unable to attend the clinic, extending the coverage of medication

dispensation locations. Beyond conventional health settings, HIV service organizations serving key populations offer a conducive environment which encapsulates actions to address social barriers [149].

1.2.7.2 Data collection and key outcome variable

Eligibility criteria for the ACCESS study include being HIV-positive as demonstrated through serologic testing, at least 18 years of age, reporting illicit drug use other than or in addition to cannabis in the previous month and providing written informed consent. At the baseline interview and each bi-annual interview thereafter, participants answer an interviewer-administered questionnaire eliciting information on sociodemographic factors, drug use patterns and exposure to a wide range of social institutions (e.g., HIV/AIDS service organizations, correctional settings, supervised injection facilities, social services and income assistance). During each visit, participants are examined by a study nurse and provide blood for serologic analyses. Information collected at each interview is augmented with data on HIV treatment and clinical monitoring available from the DTP. Data from this province-wide centralized ART monitoring program provides comprehensive information on all ART dispensation, including antiretroviral agent dispensed, dose and date dispensed to all participants throughout the study period, with CD4 cell counts, and plasma HIV-1

RNA viral loads. This information is confidentially linked to participants by their personal health number, a unique and persistent identifier issued for medical billing and tracking purposes to all residents of British Columbia [151]. The ACCESS study has been approved by the University of British Columbia / Providence Health Care Research Ethics Board (certificate H05-50233).

Studies in Chapters 3 to 5 were assessed using data that are drawn from the ACCESS study. These studies share a common outcome variable: adherence to ART. Consistent with previous analyses [21, 152], adherence was calculated as the number of days for which ART was dispensed in the last 180 days, as shown from pharmacy records, over the number of days since the participant had started ART, to a maximum of 180 days, dichotomized at 95%. Further analytical details are described in each individual chapter.

1.2.8 Summary

To summarize, this dissertation is organized into six main chapters. Chapter One provides an overview of the HIV pandemic among PLWH who use illicit drugs, gaps in the HIV continuum of care in British Columbia, social and structural barriers that are associated with suboptimal adherence to ART encompassing the institutional environment, the values of a PCC approach in meeting the needs of PWUD, the

theoretical and conceptual framework employed in this dissertation, as well as an overview of each specific study. Chapter 2 presents a systematic review on components of MMT services and HIV care cascade outcomes, with a focus on linkages within and across institutional contexts. Chapters 3 - 5 present findings from empirical studies that were developed using quantitative methods from a longitudinal cohort study in Vancouver, Canada. Specifically, Chapter 3 evaluates the association between daily pill burden and adherence to ART among PWUD that offers insights on practices within the HIV care domain; Chapter 4 tests the association between MMT-ART co-dispensing practices and adherence to ART that provides understanding on the relationship between two domains relevant to PWUD clinical needs; and Chapter 5 evaluates factors associated with material insecurity among PWUD, including a set of institutional-related variables, and the association between material insecurity and adherence to ART, that illustrates the significant roles of organizations across institutions. Chapter 6 summarizes key findings of each study, and the theoretical, methodological and substantive contributions of the dissertation. This final chapter offers insights on the relevance of institutional theories in the context of HIV treatment for PWUD, limitations and implications for future research and key actions to improve HIV care outcomes for members of this key affected population.

Chapter 2: A systematic review of methadone maintenance therapy (MMT) service components linked to improvements in HIV care cascade outcomes

2.1 Introduction

The HIV continuum of care (or “care cascade”) is a common conceptual frame used to depict the spectrum of engagement in HIV care [2]. The continuum of care denotes key steps in the progression of HIV treatment, including HIV testing and diagnosis, engagement and retention in clinical monitoring, prescription of antiretroviral therapy (ART), achievement of optimal ART adherence and undetectable HIV-1 RNA plasma viral load (VL) [2, 153, 154]. Assessing retention along the different stages of the HIV care cascade identifies clinical progress made by people living with HIV (PLWH) and allows programmatic or population-level monitoring of barriers to progression along the cascade [6]. In 2014, the Joint United Nations Programme on HIV/AIDS (UNAIDS) announced three sequentially linked targets in relation to the HIV continuum of care to accelerate the end the AIDS epidemic by 2030. The goals, known as the 90-90-90 targets, aim to have 90% of all people living with HIV to know their HIV status, to treat 90% of all people with

diagnosed HIV infection with ART and to achieve virologic suppression in 90% of all people receiving the treatment by 2020 [1].

In many settings, the general population of PLWH are progressing toward achieving these goals [155]. Unfortunately, many HIV-positive people who use illicit drugs (PWUD) continue to experience suboptimal HIV care cascade engagement [3, 9, 156]. Past research has shown that attrition at each step of the cascade is shaped not only by individual behaviours and social-structural exposures, such as socioeconomic marginalization, but also by the health system environment that hosts the delivery of health services and programs [57, 157]. There is a growing recognition of the importance of integrating health services, such as substance use disorder (SUD) treatment, with HIV care to form a comprehensive care program for HIV-positive PWUD [158]. Methadone maintenance treatment (MMT), a common treatment modality for individuals with opioid use disorder, is in many settings the first-line pharmacotherapy, and one of the World Health Organizations (WHO) essential medicines [159]. The benefits of MMT are not limited to reductions in the frequency of illicit opioid use and high-risk injection practices [160], but also extend to supporting the engagement of PWUD in HIV care by improving rates of ART initiation, lowering the risk of non-adherence to ART and, as a result, helping stall HIV disease progression and onward viral transmission [161-163].

Across global health systems, MMT programs are delivered by a broad range of service providers. Treatment initiation, titration and dose stabilization is generally conducted by addiction specialists, psychiatrists or specially-trained physicians in primary health care settings, SUD treatment centers or mental health treatment facilities [164, 165]. Expanded access to MMT through the dispensation of medication in tertiary health facilities or pharmacies in the community promotes better accessibility to treatment [166]. While the incorporation of substance use into HIV care may take place in HIV-focused facilities, the incorporation of HIV care into SUD treatment contexts has also received increased attention, with services ranging from HIV screening and referrals to on-site treatment [167]. Given the numerous platforms in which MMT is delivered, guidelines and program components vary considerably, with some restricted to clinical care while others incorporate social services seeking to support optimal health outcomes.

This systematic review aimed to identify components of MMT service delivery that are associated with improved HIV-related outcomes among PWUD. These three main outcomes correspond to the 90-90-90 targets: 1) receipt of HIV testing, 2) exposure to ART and 3) HIV VL suppression [1]. In recent years, systematic reviews on HIV outcomes among PWUD have focused on quantifying the impact of OST on adherence to ART and viral load suppression [168], behavioural, psychosocial and

medication-assisted interventions to promote ART adherence [169], and SUD treatment and HIV integrated models [167]. This systematic review shares the common goal of assessing the outcomes of integrated care for PWUD. However, it expands the scope of previous reviews to focus on the components of service delivery in the context of MMT across a wider set of HIV treatment outcomes. This review aims to provide a global summary of the scientific evidence of best practices with regards to MMT service delivery and HIV care and holds the potential to assisting government officials, policy makers and service providers to make decisions on designing the provision of MMT among HIV-positive PWUD.

2.2 Methods

2.2.1 Definition of service delivery

Based on the WHO recommendations for multidisciplinary approaches to address PWUD's needs for concurrent clinical and social services [170], a classification heuristic of MMT services that encompassed four general categories of model of care was developed: 1) standard MMT care, 2) standard MMT care and an additional medical component(s), 3) standard MMT care and instrumental or informational social support and 4) Standard MMT care, an additional medical component(s) as well as instrumental or informational social support. The proposition underlying the

classification of the four models of care is the emergence of global attention to provide integrated services for HIV-positive PWUD given the complex social and structural barriers that impede effective HIV care outcomes [158, 171]. We further delineated the dimensions of social support delivered by service providers to include instrumental and informational support [136, 137]. Instrumental support is conceptualized as the various types of tangible aid and services such as provision of transportation, meals, money or housing or residence assistance [172]. Informational support provides individuals with advice, ideas, suggestions, guidance and information on topics including life skills training and educational programs not exclusive to health.

2.2.2 Inclusion/exclusion criteria

To be eligible for inclusion, studies must have assessed a population or sub-population of PWUD engaged in MMT care. Illicit drug use was defined as using substances including illicit opioids (e.g., heroin), cocaine/crack cocaine, or amphetamines through injection or non-injection use. While the focus on MMT service delivery would lend itself to a specific focus on people who use opioids, because polysubstance use is highly prevalent among this population, studies that incorporated non-opioid substance use were included as well [173]. The eligibility of different psychoactive drugs was motivated by a focus on substances documented to

be associated with substantial morbidity and mortality [173], including among PLWH. Studies assessing individuals using cannabis only were excluded.

To be included, studies must have assessed the association of MMT services with (all of, some of, any of) the following outcomes: (1) HIV testing, including a) the proportion of participants who accepted HIV testing and received results, or b) the proportion of participants who were newly diagnosed as HIV positive, (2) Exposure to ART, including a) time to ART initiation, b) the proportion of participants who initiated or received ART, c) the proportion of participants who achieved optimal ART adherence, d) increased ART adherence rates, and (3) HIV RNA-1 plasma VL suppression; the proportion of participants who achieved VL suppression. Only peer-reviewed studies that were randomized controlled trials, clinical trials, cross-sectional, case-control or cohort studies published between 1 January 2006 until 31 December 2017 and written in English were included.

2.2.3 Search strategy and data extraction

This systematic review, registered in PROSPERO (Registration Number: CRD42018096727), was conducted following PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) group guidelines [174]. An electronic search protocol to systematically identify potentially relevant studies was carried out on

MEDLINE, EMBASE, CINAHL, EBM reviews, PsychInfo and Web of Science. Multiple search terms using both MeSH terms and keywords (Appendix A) were deployed to reflect the key population of interest, each cascade stage, enrollment in MMT, provision of medical or social support; (1) drug use (*"heroin", "cocaine", "crack cocaine", "amphetamines" or "substance abuse", "intravenous"*) and HIV (*"HIV", "HIV infections", "AIDS serodiagnosis" or "HIV seropositivity"*), (2) HIV testing (*"HIV testing", "HIV screening", "rapid test", "voluntary counselling and testing"*), (3) exposure to ART (*"antiretroviral therapy", "highly active", "initiation", "uptake", "receive", "adherence" or "compliance"*), (4) viral load suppression (*"viral load", "virologic response", "immunologic success", "undetectable", or "suppression"*), (5) methadone treatment (*"methadone", "opioid replacement" or "opioid substitution"*), 6) provision of medical support (*"comprehensive health care" or "delivery of health care" or "health services accessibility"*) and (7) social support (*"community-based", "non-profit", "non-government", "educational program", "housing assistance", "life-skill training", "peer education" or "peer support"*).

Relevant articles were extracted from data sources. EndNote software was used as a citation management tool. All articles retrieved were managed and checked for duplicates. Titles and abstracts of these articles were screened by two reviewers, independently. Next, the full text of short-listed articles was reviewed based on the screening criteria. Disagreements about study eligibility were resolved by discussing

with senior team members until consensus was reached. Additionally, study authors were contacted when eligibility could not be determined or to confirm which service components were assessed. During the data extraction process, a standardized data collection form was used to extract the following information: first author's name, publication year, cascade stage(s) examined, country, study design, study setting and recruitment, types of drugs use, outcomes assessed, and MMT service delivery components associated with outcomes of interest.

2.2.4 Risk of bias assessment

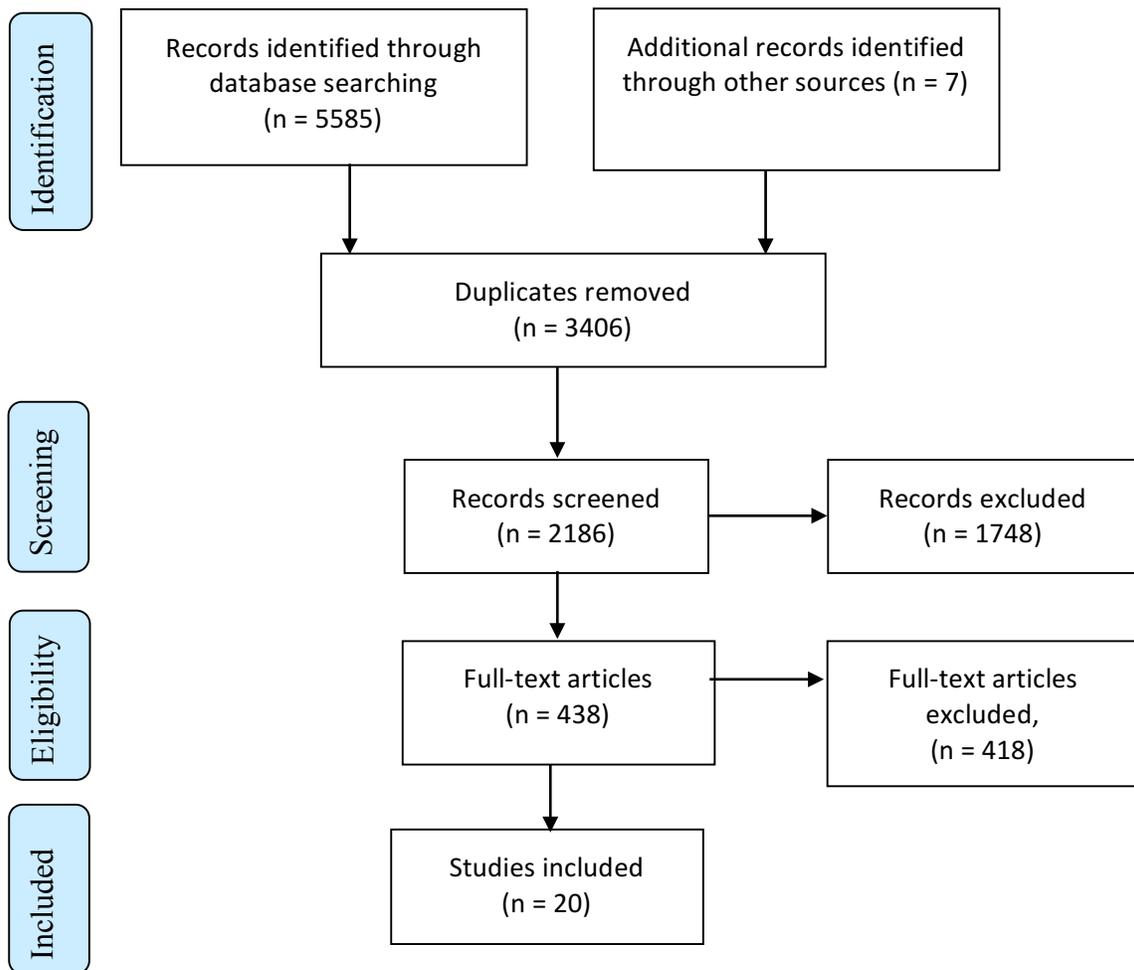
Risk of bias was assessed using the Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) for selected non-randomised studies [175], and the Cochrane Collaboration's tool for randomised trials [157].

2.3 Results

The initial database search yielded 5585 records (Figure 2.1) with 2186 records retained after duplicates were removed. Manuscripts were screened by title and abstract, removing 1748 records and yielding 438 records which were retrieved as full text. From the assessment of these texts, 418 records were excluded for reasons defined through the study criteria such as no inclusion and analysis of a drug-using

population, no exposure to MMT services, or failure to assess outcomes of defined interest in this systematic review. Conference abstracts and short reports were excluded when there was insufficient information to determine the eligibility of those studies. Following full manuscript screening, 20 studies were included for full data extraction in the final set of manuscripts.

Figure 2.1 PRISMA flow diagram for process of selecting included studies



2.3.1 Study characteristics

Characteristics of the 20 selected studies are summarized in Table 2.1. Of these, twelve studies were conducted in North America (nine in United States and three in Canada), three studies in Europe (one study each from Spain, the Netherlands and Ukraine) and five in Asia (two studies each from Vietnam and China, and one from Indonesia). In most studies, data on MMT services were drawn from clinical settings, such as specialized MMT clinics and hospitals. A number of studies drew data from participants recruited in community-based settings. There were eight cohort studies; seven cross-sectional studies; four randomized controlled trials (RCT) and one study with a pre-post design. Study-specific risk of bias scores are presented in Appendix B. Overall, the risk of bias in non-randomized studies was assessed as moderate whereas the quality of randomized controlled studies was assessed as good.

Table 2.1 Characteristics of 20 studies on MMT service delivery and improvements in HIV care cascade outcomes

Study (Year)	Country	Design (Period)	Treatment Setting	Sample Population (%)	Report on types of drugs or drug use route (%)	Female (%)	Ethnicity	Exposure to MMT services (%)
Lappalainen <i>et al.</i> (2015) [176]	Canada	Longitudinal cohort (2005 – 2013)	Following PWUD with access to HIV and addiction care	PWUD, 297 (100.0)	Crack smoking, 297 (100.0); <daily cocaine injection 263 (88.6);	116 (39.1)	Caucasian, 175 (58.9)	297 (100.0)
Pang <i>et al.</i> (2007)[177]	China	Repeated cross-sectional surveys (2004 – 2005)	8 MMT clinics	PWUD: 3,546 (100.0)	Heroin use, 3,546 (100.0)	134 (22.9) ^a	Han, 515 (88.0) ^a	585 (100.0) ^a
Tran <i>et al.</i> (2016)[178]	Vietnam	Cross-sectional (2013)	4 health centers incorporating MMT	PWUD: 1,016 (100.0)	Injection drug use 746 (73.4)	Not reported	Not reported	1016 (100.0)
Seewald <i>et al.</i> (2013) [179]	USA	Cross-sectional (2007 – 2009); two-year period	Hospital-based MMT clinic	PWUD: Phase 1; 7,875 (100.0), Phase 2; 7,870 (100.0).	Opioid-dependence	4,418 (28.1)	Black, 4,496 (28.6) Hispanic, 7,732 (49.1) White, 3,992 (2.4)	15,745 (100.0)
Xia <i>et al.</i> (2013)[180]	China	Cross-sectional (2008)	45 MMT clinics	PWUD: 13,270 (100.0);	Heroin (99.6)	807 (6.1)	Not reported	13,270 (100.0)

Study (Year)	Country	Design (Period)	Treatment Setting	Sample Population (%)	Report on types of drugs or drug use route (%)	Female (%)	Ethnicity	Exposure to MMT services (%)
Achmad <i>et al.</i> (2009) [181]	Indonesia	Cohort study (2006 -2009)	Hospital-based MMT clinic	PWUD: 223 (100.0)	Opioid-dependence	14 (6.3)	Not reported	223 (100.0)
Hung <i>et al.</i> (2016)[182]	Ho Chi Minh City, Viet Nam	Pre-post study design (2013 – 2014)	Community-based centers with HIV care and MMT	PWUD: Pre-Integration: 3,618 (100.0), Post-Integration: 3,903 (100.0) ^b	Heroin Amphetamine Morphine Benzodiazine	Not reported	Not reported	3,903 (100.0) ^b
Sanchez <i>et al.</i> (2012) [183]	Spain	Cohort (2005 – 2009)	Outpatient SUD treatment facility	PWUD: 71 (100.0)	Heroin (87.3); Cocaine (12.7);	30 (42.3)	White, 69 (97.2)	71 (100.0)
Berg <i>et al.</i> (2012) [94]	USA	24- week RCT (2004 – 2007)	12 MMT clinics	PWUD: 77 (100%)	Opioid, 24 (31.0), Cocaine, 42 (55.0)	36 (46.7)	Hispanic, 35 (45.0)	77 (100.0)
Lucas <i>et al.</i> (2006) [184]	USA	18-month observational study (2006)	3 MMT clinics	PWUD: 401 (45.0) Non-PWUD: 490 (55.0)	Injection drug use, 401 (45.0)	310 (34.8)	African-American, 702 (78.8)	157 (17.6)
Safren <i>et al.</i> (2013) [185]	USA	RCT (2005 – 2008)	MMT and HIV clinics	PWUD, 89 (100.0) with depression	Cocaine, 20 (22.5); Opiate, 11(12.7)	35 (39.3)	African-American, 26 (33.0)	89 (100.0)

Study (Year)	Country	Design (Period)	Treatment Setting	Sample Population (%)	Report on types of drugs or drug use route (%)	Female (%)	Ethnicity	Exposure to MMT services (%)
Lambers <i>et al.</i> (2011) [186]	The Netherlands	Longitudinal cohort	Following PWUD with access to HIV and addiction care	PWUD, 102 (100.0), with 733 number of visits	Heroin, cocaine or a mix of both (92.2);	31 (30.4)	Not reported	91 (89.2)
Rothman <i>et al.</i> (2007) [187]	USA	Cohort (1990 – 2002)	12 substance use treatment facilities (7 MMT facilities)	PWID 2,271 (23.0) ^c	Injection drug use	3,572 (36.2) ^c	Black, 3263 (33.0); Hispanic, 4072 (41.2) ^c	>527 (55.7) ^c
Bachireddy <i>et al.</i> (2014) [188]	Ukraine	Cross-sectional (2010)	Integrated and fully, co-located (ICL); non-co-located (NCL); and harm reduction and outreach (HRO) sites	PWUD: 296 (100.0); Unemployed : (46.0)	Opioids	292 (34.0)	Not reported	201 (67.9)
Cooperman <i>et al.</i> (2012) [189]	USA	RCT	12 MMT clinics with on-site HIV care	PWUD: 60 (100.0); Unemployed (97.0);	Opioid-dependence	30 (50.0)	White, 7 (12.0)	60 (100.0)

Study (Year)	Country	Design (Period)	Treatment Setting	Sample Population (%)	Report on types of drugs or drug use route (%)	Female (%)	Ethnicity	Exposure to MMT services (%)
Parashar <i>et al.</i> (2011) [190]	Canada	Cross sectional study (2007 – 2010)	Community health clinic	PLWH 644 (100.0), Unstably housed 212 (32.9)	Current illicit drug use 162 (76.4) ^d	68 (32.1) ^d	Aboriginal, 87 (41.0) ^d	42 (19.8) ^d
Sorensen <i>et al.</i> (2007) [191]	USA	RCT (2001 – 2004)	2 MMT clinics	PWUD, 66 (100.0); Employed (9.0);	Opiates, 25 (38.0); Cocaine, 34 (52.0)	27 (41.0)	Caucasian, 24 (36.4);	66 (100.0)
Simeone <i>et al.</i> (2017)[192]	USA	Cross-sectional	3 different clinics; MMT, HIV and community clinic	PWUD: 65 (100.0)	Opioid-dependence	24 (36.9)	African-American, 27 (41.5); Caucasian, 26 (40.0)	57 (87.7)
Fingerhood <i>et al.</i> (2006) [193]	USA	Retrospective cohort study	Primary care setting in a hospital	PWUD: 175 (100.0); Employed (17.0); Homeless (15.0)	Heroin (94.0); Cocaine (91.0)	85 (48.6)	African-American, 131 (74.9); White/Other, 44 (25.1)	63 (36.0)
Ti <i>et al.</i> (2017) [194]	Canada	Longitudinal cohort study	HIV/AIDS non-governmental, service organization	PWUD: 746 (100.0); Homeless, 222 (29.8)	Heroin, 109 (14.6); Cocaine, 61 (8.2); Crack, 258 (34.6)	246 (33.0)	Indigenous, 302 (40.5)	269 (36.1%)

Study (Year)	Country	Design (Period)	Treatment Setting	Sample Population (%)	Report on types of drugs or drug use route (%)	Female (%)	Ethnicity	Exposure to MMT services (%)
<p>a Study characteristics were drawn at baseline (the first wave of survey, n = 585), year 2004</p> <p>b Reporting study sample from facilities providing 3-services (HIV testing and counseling, MMT and HIV outpatient care) only, do not account for the whole study participants</p> <p>c Proportions of people who inject drugs (PWID) was reported in this sample of people with SUD. Study characteristics were drawn during the year 2002 and do not account for the whole study participants between study period 1990 – 2002.</p> <p>d Among those who were unstably housed</p>								

2.3.2 Study outcomes

Each study documented service components in conjunction with MMT provision, which are associated with one or more HIV care cascade outcomes. Among all 20 selected studies, three studies reported more than one HIV care cascade outcomes. Seven studies reported HIV testing outcomes; eleven studies reported exposure to HIV treatment, including seven studies which examined adherence to ART and four other studies which evaluated initiation and receipt of ART. Seven studies reported on HIV VL suppression. ART adherence levels in the included studies were predominantly assessed using pill count and/or medication event monitoring systems (MEMS), an electronic adherence monitoring system placed on medication bottles that record a presumptive dose each time the cap is opened [195]. One study adopted measurement of adherence self-reports from participants in addition to MEMS caps and pill count but found an overestimation of adherence levels in self-reports compared to other methods.

2.3.3 MMT service delivery components associated with HIV cascade of care outcomes

Each study documented MMT-associated health and social services as well as the results of statistical analyses assessing whether service delivery components were associated with one or more of the HIV care cascade outcomes outlined above. Models of

care that were described in these studies were: 1) standard MMT care, 2) standard MMT care and an additional medical component(s), 3) standard MMT care, an additional medical component(s) as well as instrumental or informational social support. None of the studies reported on services that consisted of MMT care and social support only. All components were delivered in the context of MMT in facility-based settings, either in a HIV facility where HIV and SUD treatment services were combined, or in SUD treatment centers where HIV care was incorporated. A summary of results assessing components of MMT and attendant services and their relationship with cascade outcomes are summarized in Table 2.2.

Table 2.2 Components of MMT service delivery associated with HIV testing, exposure to ART and VL suppression

Study (Year)	MMT service delivery	HIV care cascade outcomes			Other relevant analyses
		Number of participants tested for HIV (%)	Number of participants who initiate, receive, or achieve ART adherence, (%), and/or adherence rates (%)	Number of participants with VL suppression (%)	
1) Standard MMT care					
Lappalainen <i>et al.</i> (2015) [176]	Optimal methadone dose \geq 100mg/day		More than 50% participants receiving methadone dose \geq 150mg/day achieved optimal \geq 95% ART adherence		Dose of \geq 100mg/day positively associated with optimal ART adherence (AOR =1.38; 95% CI=1.08–1.77)
2) Standard MMT care and additional medical component(s)					
Pang <i>et al.</i> (2007) [177]	Provision of voluntary HIV Testing and Counseling (HTC) one month after entry into the MMT program	3069 (86.5)			
Tran <i>et al.</i> (2016) [178]	Integration of voluntary, HTC service in MMT clinics	957 (94.2)			MMT service model (with HTC vs without HTC) associated with improved HIV testing ($r = 0.6$, p -value <0.05 95% CI: 0.1 – 1.1)

Study (Year)	MMT service delivery	HIV care cascade outcomes			Other relevant analyses
		Number of participants tested for HIV (%)	Number of participants who initiate, receive, or achieve ART adherence, (%), and/or adherence rates (%)	Number of participants with VL suppression (%)	
Xia <i>et al.</i> (2013) [180]	Implementation of voluntary HIV and Hepatitis C (HCV) testing	10,046 (75.7)			A significant correlation between HIV test uptake and HCV test uptake (correlation coefficient = 0.64, p -value < 0.001)
Seewald <i>et al.</i> (2013) [179]	A routine, HIV rapid testing was offered on admission to MMT during medical care or at the mandatory annual physical examinations, as opposed to targeted testing in which patients identified by substance abuse counselors as being high risk were offered HIV pre- and post-test counseling and testing, as well as incentives	7870 (34.3)			More patients were tested for HIV in routine testing compared with targeted testing (p -value < 0.0001, OR: 3.2; 95% CI: 2.9–3.4)
Hung <i>et al.</i> (2016) [182]	Services counselling for all three HTC, ART and MMT by the same counsellor who underwent cross-training, under the same administrative structure	Pre-Integration: 3,614 (99.9), Post-Integration: 3,896 (99.8)	266 (68.9%) initiated ART after service integration, as compared 311 (44.4%) before service integration, p -value < 0.05.		

Study (Year)	MMT service delivery	HIV care cascade outcomes			Other relevant analyses
		Number of participants tested for HIV (%)	Number of participants who initiate, receive, or achieve ART adherence, (%), and/or adherence rates (%)	Number of participants with VL suppression (%)	
Bachiredy <i>et al.</i> (2014) [188]	In integrated and co-located (ICL) services, on-site daily observed OAT, free screening and treatment services for HIV and TB, psychosocial counseling were provided, (n = 97), as opposed to comparison groups: 1) non-co-located (NCL) services with only OST and psychosocial counseling (n = 104), and 2) harm reduction only (HRO) with needle-syringe exchange (NSEP but no OAT), case management, referral to ancillary services (including HIV and TB), and psychosocial counseling, (n=95)		48 (49.5%) participants in the ICL group received ART, as compared to 20 (19.2%) participants in the NCL group and 25 (26.3%) participants in the HRO group, <i>p</i> -value <0.001		
Safren <i>et al.</i> (2013) [185]	Cognitive Behavioral Therapy (CBT) for treatment of depression, medication adherence counselling and adherence tools (n= 44), as opposed to comparison group with medication adherence counseling and adherence tools, but no CBT		Increase in adherence rate, measured using MEMS-caps was significantly greater over time among those who received CBT (γ -slope = 0.8873, <i>p</i> -value= 0.02)		

Study (Year)	MMT service delivery	HIV care cascade outcomes			Other relevant analyses
		Number of participants tested for HIV (%)	Number of participants who initiate, receive, or achieve ART adherence, (%), and/or adherence rates (%)	Number of participants with VL suppression (%)	
Lambers <i>et al.</i> (2011) [186]	Complete use of harm reduction (HR), defined as injecting drugs, high MMT dosage (≥ 80 mg/day) and full NSEP; or not injecting drugs and high MMT dosage (number of visits: 452, 61.7%), as opposed to participants with no/incomplete dependence on HR (number of visits: 81, 11.1%)		51 (7.5%) number of visits reporting non-adherence among participants with complete use of HR, as compared to 6 (11.4%) with no/incomplete dependence		
Sanchez <i>et al.</i> (2012) [183]	Infectious disease specialist monitored ART, TB and HCV, with monthly provision of ART; nurses dispensed MMT and identify drug interaction and adherence problems; provide education on adherence; perform directly administered treatment to homeless participants; psychiatrists evaluated mental health and prescribed psychotropic medications such as antidepressants.			62 (87.3%) achieved VL suppression (50 copies/ml), in comparison to a comparator arm consisted of a control group of sexually transmitted HIV-infected participants in which 42 (87.5%) achieved VL suppression	

Study (Year)	MMT service delivery	HIV care cascade outcomes			Other relevant analyses
		Number of participants tested for HIV (%)	Number of participants who initiate, receive, or achieve ART adherence, (%), and/or adherence rates (%)	Number of participants with VL suppression (%)	
Fingerhood <i>et al.</i> (2006) [193]	Multidisciplinary team consisting of general internists, a nurse practitioner and a nurse case manager/educator. Provision of short-term counseling and treatment of depression and a weekly HIV patient support group.		80 (45.7%) received ART	52 (61.0) who received ART achieved undetectable VL, after 5 years from initial visit	
Berg <i>et al.</i> (2012) [94]	Directly administered antiretroviral therapy (DAART) with methadone doses and counselling (n = 39), as opposed to comparison group, treatment as usual (TAU) with self-administered medication		Adherence rate, measured using pill count or MEMS-caps, was 86% in the DAART group, as compared to 56% in the TAU, <i>p</i> -value < 0.0001	54 (70%) in DAART achieved undetectable VL (<75 copies/ml), as compared to 32 (42%) in TAU groups	At week 24, the odds of having undetectable VL were 3-fold greater for DAART than TAU participants (<i>p</i> -value < 0.02, 95% CI: 1.1–5.4)

Study (Year)	MMT service delivery	HIV care cascade outcomes			Other relevant analyses
		Number of participants tested for HIV (%)	Number of participants who initiate, receive, or achieve ART adherence, (%), and/or adherence rates (%)	Number of participants with VL suppression (%)	
Lucas <i>et al.</i> (2006) [184]	DAART with methadone doses (n = 82); as opposed to self-administered ART in comparison groups: 1) PWID-MMT (n = 75), 2) PWID-Non-MMT (n = 244) and 3) Non-PIUD (n = 490).			46 (56%) DAART participants achieved VL suppression (<400 copies/ml), as compared to 24 (32%) PWID-MMT, 81 (33%) PWID-Non-MMT and 216 (44%) non-PWID groups	In adjusted analyses, DAART participants were significantly more likely to achieve VL suppression than participants in each of the 3 cohort comparison groups
Achmad <i>et al.</i> (2009) [181]	HTC offered consistently throughout enrollment in MMT, in addition to on-site HIV care, CD4 cell measurement; weekly provision of ART	95 (42.6)	16 (72.8%) out of 22 HIV-positive individuals with indication for ART (CD4 count less than 200 cell/mm ³) initiated ART	34 (97.1%) patients out of 35 HIV-positive individuals who received ART at the clinic achieved VL suppression (< 400 copies/mL)	

Study (Year)	MMT service delivery	HIV care cascade outcomes			Other relevant analyses
		Number of participants tested for HIV (%)	Number of participants who initiate, receive, or achieve ART adherence, (%), and/or adherence rates (%)	Number of participants with VL suppression (%)	
3) Standard MMT care, an additional medical component(s) as well as instrumental or informational social support					
Rothman <i>et al.</i> (2007) [187]	Co-location of HIV prevention services in substance use treatment program. Service components include HTC, risk reduction education, group and individual supportive counseling, and linkage with hospitals for subspecialty services, community-based organizations for social services and local government agencies responsible for health insurance and welfare programs	Among individuals with SUD, 52,562 (31.2%) tests were conducted on PWIDs out of 168,340 HIV tests, between 1990 – 2002			In 2002, 527/946 (55.7%) HIV-positive PWUD were from MMT treatment settings.
Cooperman <i>et al.</i> (2012) [189]	DAART with 15-month period adherence counselling to identify unaddressed mental health, substance abuse, financial, vocational, and housing issues (n =22), as opposed to comparison group, DAART with no counseling (n=38)		Adherence rate, measured using MEMS-caps and pill count, was 61% in participants with adherence counselling, as compared to 78% in participants with no counselling, <i>p</i> -value < 0.05		Among participants who received adherence counselling, each additional hour of counselling was associated with a 20% increase in adherence rate

Study (Year)	MMT service delivery	HIV care cascade outcomes			Other relevant analyses
		Number of participants tested for HIV (%)	Number of participants who initiate, receive, or achieve ART adherence, (%), and/or adherence rates (%)	Number of participants with VL suppression (%)	
Parashar <i>et al.</i> (2011) [190]	Enrolment in maximally assisted therapy (MAT) program which included provision of daily meals, arrangement of transportation to specialist visits, assistance in securing stable housing, medication delivery by outreach workers		Among unstably housed participants (n = 212), 42 (19.8%) enrolled in MAT and of these, 32 (76.2%) participants enrolled in MAT achieved optimal \geq 95% ART adherence		Unstably housed participants enrolled in MAT were significantly associated with optimal \geq 95% ART adherence than those who did not (AOR = 4.76, 95% CI 1.72–13.13)
Sorensen <i>et al.</i> (2007) [191]	Adherence coaching and voucher reinforcement for opening electronic medication (MEMS) caps on time, as opposed to comparison group with adherence coaching only. Participants could earn up to \$1172.40 in vouchers if all medication doses are taken as scheduled through the 12-week period.		Adherence rate, measured using MEMS-caps, was 77.6% among participants who received vouchers and 55.5% in the comparison group, <i>p</i> -value < 0.0001		Adherence rate, measured by pill count, in voucher and comparison groups was 85.9% vs. 75.4%. Adherence rate, measured by self-reports, in voucher and comparison groups was 87.3% vs. 68.7%

Study (Year)	MMT service delivery	HIV care cascade outcomes			Other relevant analyses
		Number of participants tested for HIV (%)	Number of participants who initiate, receive, or achieve ART adherence, (%), and/or adherence rates (%)	Number of participants with VL suppression (%)	
Simeone <i>et al.</i> (2017) [192]	On-site opt-out HIV screening, DAART, integrated HIV primary care and psychiatric services, social HIV case management at a MMT clinic (n = 15, 23.1%), as opposed to comparison groups, 1) HIV specialty clinic (n = 42, 64.6%) and 2) community clinic (n = 8, 12.3%)			14 (93.3%) participants from MMT clinic achieved VL suppression (<40 copies/ml), as compared to 33 (78.6%) in HIV specialty clinic and 5 (62.5%) in community clinic, <i>p</i> -value: 0.164	
Ti <i>et al.</i> (2017) [194]	Enrolment in a HIV/AIDS non-government service organization which provides support including nursing care residence, enhanced supported housing program, therapeutic and harm reduction service, counseling and food.			At baseline, 83 (51.6%) participants who were enrolled in a HIV/AIDS service organization achieved VL suppression (<50 copies/mL), compared to 206 (35.2%) who were not enrolled	The odds of VL suppression in those who were enrolled in a HIV/AIDS service organization was higher compared to those who did not (AOR = 1.51; 95% CI=1.13–2.02)

2.3.3.1 Standard MMT care

Standard MMT care was reported in one study included in the review, documenting the potential role of MMT care with adequate dosing in improving HIV care cascade outcome among participants who were recruited from the community [176]. In British Columbia, Canada, Lappalainen *et al.* found that more than 50% of participants receiving daily methadone doses of more than 150 mg achieved optimal ART adherence in a longitudinal study. Adherence was assessed using a validated measure based on pharmacy refill records and defined as achieving $\geq 95\%$ adherence in the previous six months. They also observed a positive association between provision of higher daily methadone doses (i.e., more than 100mg) with achieving $\geq 95\%$ adherence, with a dose-dependent relationship between higher methadone doses and likelihood of optimal ART adherence [176].

2.3.3.2 Standard MMT care and an additional medical component(s)

Four studies documented MMT provision with routinized HIV testing, including the implementation of voluntary HIV testing and counseling (HTC) as standard upon MMT initiation and throughout enrollment period [177-180]. As noted by Pang *et al.*, in response to the high rate of HIV transmission among PWUD in China, the establishment of MMT clinics in southwest China incorporated HIV testing

in which voluntary HTC was offered after one month enrollment in the MMT program [177]. This led to 3069 (86.5%) PWUD being tested for HIV, with a resulting seroprevalance rate of 11.4% [177]. Similarly, Tran *et al.* found that MMT care models integrating voluntary HTC services in Vietnam were associated with improved HIV testing uptake compared to care models that did not integrate the same service, with 957 (94.2) PWUD undergoing HIV testing [178]. In a different province in China, Xia *et al.* reported on the potential role of an MMT program offering free, voluntary, routine HIV testing bundled with hepatitis C (HCV) screening in which 10,046 (75.7) participants were tested for HIV [180]. They additionally found that there was a significant correlation between HIV and HCV test uptake, indicating the advantage of testing for multiple morbidities within MMT settings [180]. Further, a study in MMT clinics in New York by Seewald *et al.* found a 20% increase in the proportion of participants tested for HIV in routine universal testing upon admission in a MMT program or at the mandatory annual physical examinations for MMT patients. compared to a previous approach of targeted HIV rapid testing whereby counsellors identified individuals at high risk for HIV transmission [179].

In two studies, additional medical components in MMT care were associated with ART initiation [182, 196]. In Vietnam, Hung *et al.* evaluated the effect of integrated services in a community-based center which incorporated counselling for

MMT and HTC and HIV by staff who were cross-trained, in comparison to a period when such services were provided within separate administrative structures [182]. It was found that there was a 24.5% increase in the proportion of ART-eligible participants who initiated ART after service integration was implemented. The provision of standard MMT care and additional medical components has been associated with ART initiation in only one study. In Ukraine, Bachireddy *et al.* demonstrated that higher proportions of participants received ART in a single location where multiple services were delivered concurrently—including on-site daily observed OST (i.e., methadone and buprenorphine), screening and treatment services for HIV and tuberculosis (TB), and psychosocial counseling—compared to two other locations providing addiction or needle-syringe exchange programs but no on-site HIV care [196].

Further, two studies found better adherence to ART linked to additional medical components in conjunction with MMT. Safren *et al.* evaluated the use of cognitive behavioral therapy to assist with depression and self-care in addition to a single-session intervention on ART adherence among participants with depression [185]. They found that participants who received cognitive behavioral therapy had significantly higher ART adherence rates, compared to participants receiving only the single session intervention. One study by Lambers *et al.* explored the potential impacts

of exposure to a comprehensive harm reduction strategy in Amsterdam to improve medical conditions associated with problematic drug use by promoting MMT uptake as well as use of a needle and syringe exchange program (NSEP) [186]. This longitudinal cohort study highlighted the potential role of comprehensive harm reduction utilization, consisting of participation in NSEP and MMT with daily dosage of more than 80mg on self-reported ART adherence among a group of PWUD with recent injection and non-injection use [186]. Participants who received comprehensive harm reduction care (i.e., both NSEP and MMT with doses more than 80mg) had lower ART non-adherence rates, compared to those who did not use comprehensive harm reduction care.

Additional medical components associated with VL suppression was reported in two studies [183, 193]. In Spain, Sanchez *et al.* demonstrated multidisciplinary care in a SUD treatment facility, including monitoring of co-morbidities [HIV, HCV, TB and mental health care], prescription of psychotropic medications, monthly on-site ART provision as well as directly administered treatment to homeless participants [183]. Study results showed that VL suppression (i.e., <50 copies/mL plasma) was achieved in 62 (87.3%) PWUD attending this facility, in comparison to a control group of sexually transmitted HIV-infected participants in which 42 (87.5%) achieved VL suppression (p -value = 0.1779). In Baltimore, USA, Fingerhood *et al.* have reported the

five-year outcomes of participants receiving HIV care in a primary care setting that included a multidisciplinary team that provided clinical services including short term counselling and treatment of depression follow-up [193]. In this study, undetectable VL was achieved in 52 (61%) of the participants who received ART [193].

Notably, additional medical components were associated with more than one care cascade outcomes in three studies [94, 181, 184]. For example, the implementation of a directly administered ART (DAART) approach in conjunction with MMT services improved ART adherence and VL suppression several studies [94, 184]. In an RCT, Berg *et al.* reported an adherence rate of 86% among participants who received DAART along with their daily methadone doses, compared to a 56% rate among participants who self-administered ART, by week 24 of the intervention [94]. Adherence was measured by calculating pills remaining in the pill tray on a weekly basis for all time points during the assessment period (i.e., weeks 4, 8, 16 and 24) [94]. Additionally, in this study, the percentage of participants who achieved VL suppression was approximately 28 percentage points higher in the DAART group than in the comparison group, with the odds to achieve undetectable levels (<75 copies/mL) three times greater among those who received DAART [94]. In an observational study, Lucas *et al.* observed a higher proportion of DAART participants who achieved low VL (i.e., <400 copies/ml), compared to participants who self-

administered ART in three different subgroups; PWUD enrolled in MMT, PWUD not enrolled in MMT and non-PWUD [184]. Only one study described the potential role of additional medical components that are not exclusive to MMT associated with all cascade outcomes: uptake of HIV testing, initiation of ART and VL suppression [181]. In Indonesia, Achmad *et al.* reported 95 (42.6%) participants tested for HIV at a hospital-based MMT clinic, in which HTC was provided with repeated counseling throughout participants' enrollment in the MMT program, with 72 (75.8%) were positive [181]. In addition to HTC, on-site HIV care, including regular CD4 cell measurement to examine ART eligibility for those who were diagnosed positive for HIV, as well as initiation and provision of ART medications was provided [181]. Following this, among 22 individuals who presented low CD4 cell counts (i.e., <200 cell/mm³), 16 (72.8%) initiated ART, with 34 (97.1%) patients out of 35 HIV-positive individuals who received ART at the MMT clinic achieved low VL (i.e., < 400 copies/mL) [181].

2.3.3.3 Standard MMT care, an additional medical component(s) as well as instrumental or informational social support

The integration of social support as an additional component of care to supplement MMT and other forms of medical services to address social and structural barriers has been observed. In a 12-year study by Rothman *et al.*, the co-location of

HIV care in substance use treatment centers, including seven MMT facilities, was linked to improvements in HIV testing uptake among PWUD in New York [187]. Medical services described in the study consisted of provision of HTC, education to reduce risk for HIV acquisition, on-site primary HIV care with the delivery of ART medication. Social support components included referrals to community-based organizations that offer social support as well as government agencies that offer welfare assistance [187]. Between 1990 and 2002, 168,340 HIV tests were conducted, with 52,562 (31.2%) tests were done in participants identified as engaging in higher risk injection drug use [187].

The provision of all three services (i.e., standard MMT care, additional medical components, as well as informational and/or instrumental support services) was linked to higher ART adherence levels in three studies [189-191]. The use of counseling to improve adherence levels among PWUD who receive MMT was also investigated. Extending Berg *et al.*'s study on a DAART approach [94], Cooperman *et al.* reported the potential role of adherence counsellors through counselling sessions that identified unaddressed adherence barriers including mental health, SUD, financial, vocational and housing issues, for DAART participants who were enrolled in a MMT program [189]. They found that there was 20 percentage point increase in ART adherence rate for each additional hour of counseling among those who received

this intervention. Although the mean adherence rate was 61% in DAART participants who received counseling, 17 percentage points lower than those who did not receive the intervention, it is worth noting that in this small sample size, only a small proportions of participants received longer periods of counselling [189]. In British Columbia, Canada, Parashar *et al.* reported that enrollment in a maximally-assisted therapy (MAT) program was associated with higher ART adherence levels among participants with unstable housing compared to participants with stable housing [190]. This MAT program consisted of medication support, including provision of MMT and HIV medications, adherence support, as well as assistance for transportation needs to access medical care, securing stable housing and referrals to mental health and addiction counseling. A study by Sorenson *et al.* in the United States reported on the effectiveness of incentives to promote ART adherence in a setting where MMT patients received ART on-site [191]. In this RCT, the mean adherence rate was 78% among participants who received a voucher that were exchangeable for goods and services each time a medication cap was opened. This rate was 22 percentage points higher than those who did not receive incentives.

Two studies included in this review demonstrated associations between the provision of standard MMT care, additional medical components and social support, and VL suppression [194]. Simeon and colleagues reported that 93% of participants

achieved VL suppression (i.e., <50 copies/mL) in an urban MMT clinic in San Francisco, California, that offers on-site opt-out HIV screening, integrated HIV primary care including a DAART approach and psychiatric services, as well as informational support through social HIV case management. This is in comparison to the 79% of participants who achieved VL suppression at an HIV specialty clinic with on-site MMT and ART but no provision of case management, and 62 % of participants who achieved VL suppression at a community clinic, (p -value = 0.164) [192]. In one study conducted in British Columbia, *Ti et al.* found that participants enrolled in a non-governmental AIDS service organization had greater odds of achieving VL suppression compared to those who were not enrolled [194]. The authors noted that these positive results could potentially be attributed to the provision of multidisciplinary services covering a wide range of social and clinical needs to PWUD accessing the organization, including nursing care, enhanced supportive housing, counseling and food.

2.3.4 Discussion

In this systematic review, we identified 20 studies assessing the impacts of components of MMT services on HIV cascade of care-related outcomes among PWUD engaged in MMT care. Taken together, these studies provide evidence that health and

social service delivery components were associated with better likelihood of optimal HIV treatment-related outcomes. Overall, the studies included in this review improve understandings of how organizational units providing MMT can combine their services with additional clinical and social support to address barriers experienced by PWUD to achieve better clinical outcomes along the HIV care cascade. Specific components include on-site HIV testing, clinical management of comorbidities, medication dispensing including directly administered ART and delivery of ART medication into the community. Social support includes psychosocial services and ART adherence counselling to address social barriers to effective engagement in HIV care, linkage and referrals to relevant support services as well as meal programs, housing and transportation assistance.

Voluntary HTC was implemented in MMT programs, following the guidelines set by national health agencies that conduct health promotion [177, 179]. In line with WHO recommendations for more widespread screening, the expansion of HIV testing venues to include settings where high-risk populations receive treatment for SUD is a strategic approach to identify PWUD living with HIV. In many contexts, voluntary HTC was offered upon admission to and throughout enrollment in MMT treatment as a standard procedure with a view to increase rates of PWUD tested for HIV. Although these studies did not present a comparison group to determine whether

HIV testing uptake was improved from routine testing, the high proportions of PWUD being tested demonstrates progressive efforts towards UNAIDS call for 90% of PLWH to know their HIV status. Additionally, the routine offering of HTC rather than a targeted, mandatory or coercive approach as practiced in many drug treatment settings is an important feature of service delivery as it may represent a strategy to reduce stigma and discrimination associated with HIV and illicit drug use in primary care settings [197].

The studies in this review clearly indicate that on-site HIV care alongside MMT is linked to better HIV care outcomes among PWUD [94, 181, 183, 184, 186, 193, 196, 198]. In countries where there are challenges in following WHO guidelines to initiate ART regardless of disease stage (i.e., CD4 cell count), provision of CD4 cell count monitoring in MMT settings is a promising step to ensure HIV-positive PWUD receive timely treatment in resource-limited settings [181]. Further, on-site medication dispensing through approaches such as DAART has been designed as a convenient support strategy to dispense ART medication in MMT settings, as it can be delivered concurrently with daily methadone doses under the supervision of service providers. Although studies in this review have demonstrated the effectiveness of DAART alongside MMT in improving adherence rates and reducing VL among participants who received DAART [94, 184], it is worth noting that the same effects were not

sustained after DAART was discontinued [199]. While this would support calls for the long-term implementation of DAART within MMT settings, it is also important to consider the potential role of a broader range of more sustainable supplementary services to support PWUD in committing to life-long medication adherence, such as the delivery of ART in the community where it is easily accessible. One study in this review suggests that this may be the case, particularly where informational social support through counselling sessions that identified social barriers is available in conjunction with DAART [189].

Notably, this review describes evidence for the integrated management of comorbidities in settings where ART is offered alongside MMT to enhance clinical HIV outcomes [192, 200]. The presence of HIV-associated comorbidities, such as viral hepatitis, TB and mental illness, among PWUD has an impact on health outcomes, including a heightened risk of HIV disease progression [201]. On-site management of these illnesses helps to reduce barriers to optimal HIV treatment through multidisciplinary teams to support PWUD with co-occurring disorders and successful movement along the continuum of care [192, 202]. Previous studies have reported that co-located SUD treatment and HIV services may improve accessibility among service users by assessing multiple services at a single location and reducing travel time [203], whereas for service providers, there is an opportunity to treat multiple comorbidities

at the same time and improve monitoring of medication interaction by the same clinical team [139]. While primary care settings may be more structured to provide an exhaustive list of medical services compared to settings that focus primarily on MMT provision, studies in the review have shown that the incorporation of multiple services to manage comorbidities in MMT settings seems practical [183, 192]. Nevertheless, given the lack of understanding on the conclusive impact of multidisciplinary health services within SUD treatment settings on HIV care cascade outcome among PWUD, future research should explore the feasibility of such services, especially in MMT platforms.

A key contribution of this review is the consideration of the potential role of informational and instrumental social services in supporting clinical substance use and HIV treatment outcomes. These services may reduce the impact of socio-economic marginalization on HIV treatment engagement and retention, especially in contexts where inadequate social services may contribute to health inequities among marginalized subgroups living with HIV [204-206]. For instance, previous studies have shown that unmet subsistence needs, such as housing, transportation and financial assistance, were reported by PWUD [206], and were linked to lower levels of engagement in HIV care among vulnerable sub-groups of PLWH including PWUD [205]. While MMT programs may be well positioned to enable access to such support,

in the past decade, there is a dearth of information that provides understanding on the provision or use of these services in conjunction with MMT and subsequent HIV cascade care outcomes. Although none of the studies in this current systematic review described a model of care that encompassed MMT care and social support without additional medical services, this review did identify a limited number of studies that report services that integrate all three MMT care, additional medical services and social support [187, 189, 192, 194, 196].

Among these studies, a small number of studies have outlined the potential role of informational support in facilitating PWUD along the HIV care cascade through counselling services to address adherence barriers such as housing or financial issues [189] and social HIV case management [192]. Although psychosocial counselling indicated in the study by Bachireddy *et al.* did not specify the contents of the counselling provided [196], the use of psychosocial counselling has been recognized as a useful informational social support not only to address mental and emotional well-being [207], but also in providing information on resources for housing, legal aid and meal program for PWUD in non-MMT platforms [172, 208]. In the current literature, informational support has not been commonly described in MMT platforms. However, provision of such services may potentially improve access to instrumental support, as such it links PWUD to specific agencies such as social

assistance departments through referral services, as demonstrated in one study by Rothman *et al.* [187]. Thus, informational support is crucial for PWUD to be able to access relevant instrumental social support, such as income assistance, supported or subsidized housing or vocational training to support employment uptake and retention opportunities [28, 29, 97], all of which have been widely linked to improved progress along the HIV care cascade among the general population of PLWH. Additionally, studies in this review have pointed out the relevance of instrumental social support in MMT platforms [190, 194]. Specifically, monetary incentives, meals provision, housing assistance or residential services and key actions to reduce distance barriers including transportation assistance indicated in these studies were components of the broader instrumental social support provided alongside other MMT care and additional medical services [190, 194]. Importantly, this review suggests that informational and instrumental support within MMT platforms alongside HIV care may potentially address concerns around social and structural-level barriers to engagement in HIV care among PWUD. Given the paucity of data in this area, further research is strongly needed to confirm the role of integrated services in MMT platforms and explore how different forms of support could reinforce each other in delivering a comprehensive, support service for this population.

Despite the potential of community-based organizations to improve program acceptability among PWUD, the evaluation of HIV care cascade outcomes in community-based facilities that integrate MMT and HIV care, as well as social support, is limited. In this review, only one study evaluated the associations between HIV clinical outcomes and enrollment in a HIV/AIDS non-government service organization which supports health and basic life needs including on-site ART and MMT dispensation, provision of meals, and housing assistance [194]. Further, no gender-specific services were assessed in the review although there have been consistent reports on gender-related inequities in service access among PWUD, particularly within SUD and HIV treatment environments [209, 210]. The lack of strategies to address needs specific to women, such as reproductive health, childcare or domestic violence for women who use illicit drugs and who are involved in SUD treatment, may represent barriers to adequately engaged in HIV care [211]. Similarly, none of the studies reported enhanced MMT services for incarcerated PWUD despite the role of OAT in incarceration settings to improve HIV clinical outcomes [212], particularly support services that facilitate OAT and ART continuity in the community upon release such as housing assistance.

This review has several limitations to note. First, since the aim was to systematically describe evidence on health and non-health service delivery that

enhance HIV care cascade outcomes in the context of MMT provision, we have not reviewed qualitative studies and gray literature, such as policy reports, which may contain descriptions of services delivered in MMT platforms as part of standard operating procedures. Although these studies offer additional understanding on how specific service delivery models can hamper or facilitate efforts to improve treatment outcomes, such data is limited by the low number of RCTs in this review to infer effectiveness as it is difficult to infer causal pathways between different care models and HIV clinical outcomes. Further, qualitative studies and gray literature may be less informative in terms of documenting progress towards the 90-90-90 targets. Second, although an increase in ART adherence rates was observed, a strong majority of studies demonstrated adherence levels that were below the 95% cut-off value of optimal adherence to achieve VL suppression [94, 189, 191]. These findings are consistent with existing literature in non-MMT environments which describes low uptake of ART and suboptimal adherence to treatment among this key population [9]. Thus, it is difficult to conclude the potential role of associated services in improving optimal adherence to ART among PWUD using what is becoming the international standard of optimal adherence. Third, despite using multiple database platforms to search for eligible studies, most studies were from higher income countries. There are very limited studies from non-Western settings with a substantial number of PWUD,

such as in East and South Asia, Russia and Iran. Therefore, studies in this review may over-represent findings from countries with more resources. Finally, many studies explored provision of social support in general, for instance, the use of adherence counselling or case management to address social needs that would impede treatment success. However, a more standardized understanding and reporting of well-defined and separately measured informational and instrumental social services would better advance scientific understandings in this area.

2.3.5 Conclusion

Evidence in this review has identified the potential role of multi-modal strategies to manage health and social comorbidities in supporting optimized HIV clinical outcomes among PWUD across the HIV care cascade. However, a paucity of data evaluating different complementary MMT service models may hinder the implementation of person-centered approaches which seek to address the complex needs of members of this key population. While such approaches are key to ending the HIV pandemic, evidence-based practices that promote models of care that optimize treatment for opioid use are currently underdeveloped. Nonetheless, studies included in this review indicate that there is a growing empirical basis for integrated models to improve HIV care cascade outcomes among PWUD. This systematic review

underscores a clear need for further research to continue to assess the effectiveness of integrated services. Further, there is a need to determine ways to improve conceptualization of informational and instrumental support services to help refine the specific components of these models in improving the well-being of PWUD living with HIV as a key affected population in the international pandemic.

Chapter 3: A Longitudinal Analysis of Daily Pill Burden and Likelihood of Optimal Adherence to Antiretroviral Therapy (ART) among HIV-positive People Who Use Drugs

3.1 Introduction

The widespread scale-up of access to antiretroviral therapy (ART) has resulted in substantial declines in rates of morbidity and mortality among people living with HIV (PLWH) [213]. However, treatment success is largely determined by the level of adherence to ART achieved by individuals, which in turn strongly predicts virologic and immunologic responses. Fortunately, optimal adherence to ART typically leads to suppression of plasma HIV-1 RNA viral load (VL), eliminating the risk of onward viral transmission [214] and stalling progression to AIDS [215].

Incomplete adherence to ART among people who use illicit drugs (PWUD) is common and continues to pose a serious challenge to achieving optimal clinical outcomes [216]. Studies have identified several risk factors for non-adherence to ART among members of this key population, largely focused around factors associated with illicit drug use, including inability to access addiction treatment [217], as well as other social and structural factors. For example, socioeconomic obstacles, such as low income [218, 219], and living in unstable housing or being homeless, have been shown to limit engagement in HIV care [220]. Further, criminalization and incarceration of

PWUD has been associated with interruption of ART in many settings [21], and the social stigmatization faced by PWUD and PLWH creates additional barriers to uptake and maintenance of ongoing care [221].

In contrast to these behavioral, social and structural factors, less well detailed is the extent to which the complexity of medication regimens affects the ability of PWUD to achieve optimal adherence to ART [222]. Among non-drug using people living with HIV, observational studies of pill burden have identified the role of simplified antiretroviral regimens on improved adherence [223-225]. Two meta-analysis identified an advantage of once-daily dosing using studies that assessed adherence through methods including pill counts and medication event monitoring systems [226, 227]. Additionally, single pill fixed-dose regimens have been associated with improved adherence [228]. In contrast, several studies relying on self-reported adherence have not found an association between pill burden and adherence [229, 230].

Although studies among non-drug-using groups of individuals on ART have revealed the importance of medication-related factors on adherence [231, 232], very few studies have investigated the effect of factors such as daily pill burden and dosing frequency on adherence among PWUD [163]. Such studies are needed to inform treatment guidelines and guide efforts to improve HIV care among members of this

key affected population. Further, studies examining pill burden and dosing frequency among non-drug using people living with HIV have predominantly used cross-sectional designs and relied on self-reported measures of adherence. Thus, we sought to assess the potential impact of daily pill burden on adherence to ART in British Columbia, Canada, where all persons living with HIV have access to free ART using data gathered via a long-running community-recruited longitudinal cohort of PLWH who use drugs with complete pharmacy dispensation data.

3.2 Methods

3.2.1 Study design

In this study, we used data from the AIDS Care Cohort to Evaluate Exposure to Survival Services (ACCESS), an ongoing prospective observational cohort of HIV-seropositive PWUD in Vancouver, Canada. As described in detail elsewhere [21, 148], study recruitment began in 2005 centered on the Downtown Eastside neighbourhood, an area characterized by an open drug market with high prevalence of injection and non-injection drug use, HIV infection and poverty [233]. Eligibility criteria include being HIV seropositive, aged >18 years, use of illicit drugs (other than or in addition to cannabis) in the month prior to enrollment, and the provision of written informed consent. At the baseline interview and each semi-annual interview thereafter,

participants answer an interview-administered questionnaire, are examined by a study nurse, and provide blood for serologic analyses. The ACCESS study has been approved by the University of British Columbia / Providence Health Care Research Ethics Board.

Information on sociodemographic characteristics, substance use patterns and other key activities and exposures collected at each interview is augmented with data on HIV treatment and clinical monitoring available from the British Columbia Centre for Excellence in HIV/AIDS. As described in detail elsewhere [145], data from this province-wide centralized ART pharmacy provides comprehensive information on all ART dispensation, including antiretroviral agent dispensed, dose and date dispensed to all participants throughout the study period, including clinical and community settings and during periods of incarceration. This information is confidentially linked to participants by using their personal health number, a unique and persistent identifier issued for medical billing and tracking purposes to all residents of British Columbia. The Centre's HIV/AIDS monitoring lab also provides a complete retrospective and prospective clinical profile for each participant. Of note, all medical care including HIV medications is provided at no cost to residents of British Columbia, allowing us to examine determinants of medication adherence independent of the influence of cost.

3.2.2 Study sample

The present analysis included all those participants who were ART-exposed at the time of recruitment or who initiated ART following study recruitment. In addition, participants were included if they completed ≥ 1 study interview following ART initiation and had ≥ 1 CD4 observation within 180 days of the earliest eligible interview. For all participants meeting these criteria, all observations following ART initiation were included.

3.2.3 Variable selection

In these analyses, the outcome of interest was adherence to ART in the 180-day period prior to each study interview. Consistent with previous analyses [21, 152], at each study interview date, adherence was calculated as the number of days for which ART was dispensed and collected in the previous 180 days from pharmacy records over the number of days since the participant had started ART, to a maximum of 180 days, dichotomized at 95%. We have previously shown that optimal adherence using pharmacy refill data is strongly associated with both virologic suppression and survival [234, 235].

Our primary explanatory variable of interest was pill burden, or the daily number of pills prescribed to be ingested per day, expressed as a continuous measure.

Using the pharmacy dispensation data, we ascertained the pill burden on the date of the interview. If the individual was not dispensed ART for that day, we used the pill burden on the most recent dispensation. In a sub-analysis, we repeated analyses using a dichotomized measure of being on a single-tablet regimen (STR; i.e., 1 pill vs. > 1 pill per day). Further, in another sub-analysis, to account for reverse causality, in which poorer adherence can potentially create treatment resistance and result in the prescription of complex regimens in second or third line treatment options, we restricted the sample to individuals who initiated ART after being recruited into the ACCESS study.

We considered a range of explanatory variables that could confound the relationship between pill burden and adherence including: age (per year older); gender (male vs. non-male); ancestry (white vs. non-white); unstable housing (yes vs. no); participation in addiction treatment (yes vs. no); illicit income generation (yes vs. no); formal employment (yes vs. no); injection drug use (yes vs. no); alcohol use (< 4 drinks/day vs. \geq 4 drinks/day); binge drug use, defined as any period of uncontrolled or higher than usual frequency of drug use (yes vs. no); and incarceration (yes vs. no). A clinical variable, CD4+ cell count (per 100 cells/mL) was included in the analysis to account for HIV disease progression. As in previous analyses, we used the mean of all CD4 cell count observations conducted within the previous 180 days at each

interview or, if none were available, the most recent observation. All non-fixed variables were time-updated and referred to the period starting 180 days prior to the interview.

3.2.4 Statistical analysis

As a first step, we determined the distribution of explanatory characteristics at the earliest study interview, in addition to recent adherence (≥ 95 vs. $<95\%$), stratified by daily pill burden (dichotomized at the median of all observations, or >4 vs. ≤ 4 pills/day). Next, we estimated bivariate statistics for the relationships between adherence and all explanatory variables over the study period using generalized linear mixed-effects modelling (GLMM). This method accounts for the correlation inherent in serial measures from the same individual and across individuals at the same time point, and can estimate the independent effect of the explanatory variable of interest on adherence. To prepare a multivariable model, we used an a priori-defined modelling procedure. First, we fit a full model including all explanatory variables. Using a manual backward approach, we constructed reduced models, eliminating one variable from the full set of explanatory variables one at a time. The coefficient values from the full model and each of the reduced models were compared. We continued this process until the maximum change from the full model exceeded

5%. This procedure retains secondary covariates with greater relative influence on the relationship between the outcome and the primary explanatory variable. The same technique has been used in previous analyses to successfully estimate the relationship between the outcome of interest and primary explanatory variable [21].

3.3 Results

Between December 2005 and May 2014, 845 eligible individuals were identified, of whom 770 (91%) were ART-exposed prior to their final study interview, had complete baseline CD4 and VL data and were included in these analyses. Study participants included 257 (34%) women, with a median age of 43 years (inter-quartile range: 37–48), and contributed 5810 interviews over the course of the study period, equal to 2905 person-years of observations. Of these, 3465 (59.6%) interviews were characterized by $\geq 95\%$ adherence in the previous 180 days.

Selected sociodemographic and clinical characteristics, stratified by median daily pill burden (i.e., > 4 vs. ≤ 4 pills / day) for this analytic sample are presented in Table 3.1. Of note, at baseline, participants who were prescribed 4 pills per day or less showed higher levels of optimal adherence to ART (62%) compared to those prescribed greater than 4 pills per day (47%), reflecting an odds ratio [OR] of 0.54 (95% confidence interval [95% CI]: 0.40–0.72.)

Table 3.1 Baseline characteristics of 770 HIV-positive PWUD in Vancouver, Canada, stratified by daily pill burden (> 4 pills/day vs. ≤ 4), between December 2005 and May 2014

Characteristic	Pill burden ≤ 4 n = 389, 46 (%)	Pill burden > 4 n = 456, 54 (%)	Odds Ratio (95% CI)	p-value
ART adherence				
< 95%	185 (37.7)	148 (53.0)	1.00	
≥ 95%	306 (62.3)	131 (47.0)	0.54 (0.40–0.72)	< 0.001
Age				
Per year older	44.0 (37.5–48.5)	43.6 (37.7–48.7)	0.99 (0.98–1.02)	0.959
Gender				
Male	326 (66.4)	187 (67.0)	1.00	
Non-male	165 (33.6)	92 (33.0)	0.97 (0.71–1.33)	0.873
Ancestry				
Non-white	206 (42.0)	121 (43.3)	1.00	
White	285 (58.0)	158 (56.7)	0.94 (0.70–1.27)	0.705
Unstable housing ^a				
No	155 (31.6)	105 (37.6)	1.00	
Yes	336 (68.4)	174 (62.3)	0.76 (0.56–1.04)	0.096
Addiction treatment ^a				
No	228 (46.4)	127 (45.5)	1.00	
Yes	263 (53.6)	152 (54.5)	1.04 (0.77–1.39)	0.821
Illicit income				
Generation ^a				
Yes	343 (69.9)	179 (64.2)	1.00	
No	148 (30.1)	100 (35.8)	1.29 (0.95–1.77)	0.109
Employment ^a				
No	408 (83.1)	234 (83.9)	1.00	
Yes	83 (16.9)	45 (16.1)	0.95 (0.64–1.41)	0.840
Injection heroin ^a				
< Daily	430 (87.8)	245 (88.1)	1.00	
≥ Daily	60 (12.2)	33 (11.9)	0.97 (0.61–1.52)	0.909
Injection cocaine ^a				
< Daily	454 (92.7)	258 (92.8)	1.00	
≥ Daily	36 (7.3)	20 (7.2)	0.98 (0.55–1.72)	0.999
Crack smoking ^a				
< Daily	326 (66.4)	196 (70.3)	1.00	
≥ Daily	165 (33.6)	83 (29.7)	0.84 (0.61–1.15)	0.297
Cannabis use ^a				
< Daily	375 (76.4)	216 (77.4)	1.00	
≥ Daily	116 (23.6)	63 (22.6)	0.94 (0.66–1.34)	0.790

Characteristic	Pill burden ≤ 4 n = 389, 46 (%)	Pill burden > 4 n = 456, 54 (%)	Odds Ratio (95% CI)	p-value
Alcohol use ^a				
< 4 drinks/day	370 (75.4)	215 (77.1)	1.00	
≥ 4 drinks/day	121 (24.6)	64 (22.9)	0.91 (0.64–1.29)	0.661
Binge drug use ^a				
No	271 (55.2)	166 (59.5)	1.00	
Yes	220 (44.8)	113 (40.5)	0.84 (0.62–1.13)	0.257
Incarceration ^a				
No	434 (88.4)	253 (90.7)	1.00	
Yes	57 (11.6)	26 (9.3)	0.78 (0.48–1.28)	0.397
CD4 cell count				
Per 100 cells/mL	3.3 (2.1–4.6)	2.8 (1.5–4.2)	0.63 (0.47–0.85)	0.002
Year of observation				
Per year later	2009 (2007–2011)	2007 (2006–2009)	0.62 (0.57–0.67)	< 0.001

^a Variables that are time-updated referring to the last 6 months from the last interview

Note: Some columns may not add up to 100%, as participants may not respond to sensitive questions.

Crude and adjusted longitudinal estimates of the odds of optimal adherence for the primary variable (daily dosage of pills) and other secondary variables are presented in Table 3.2. In bivariable analyses, a greater daily dosage of pills was negatively associated with achieving $\geq 95\%$ adherence (Odds Ratio [OR] = 0.85 per additional pill, 95% CI: 0.81 – 0.88.) In a multivariable model, a greater daily dosage of pills remained negatively associated with achieving $\geq 95\%$ adherence (AOR = 0.87 per pill, 95% CI: 0.84–0.91), after adjusting for confounders including age, ancestry, being engaged in addiction treatment, \geq daily heroin injection, year of observation, and alcohol use (R-squared = 0.44).

Table 3.2 Longitudinal GLMM analysis of daily dosage of pills associated with adherence to ART among 770 HIV-positive PWUD in Vancouver, Canada

Characteristic	Unadjusted		Adjusted	
	OR (95% CI)	<i>p</i> -value	OR (95% CI)	<i>p</i> -value
Pill burden				
Per pill	0.85 (0.81 – 0.88)	< 0.001	0.87 (0.84–0.91)	< 0.001
Age				
Per year	1.07 (1.05 – 1.08)	< 0.001	1.05 (1.04–1.07)	< 0.001
Gender				
(Non-male vs. male)	0.65 (0.49 – 0.86)	0.002		
Ancestry				
(white vs. non-white)	1.61 (1.23 – 2.11)	0.001	1.39 (1.06–1.81)	0.015
Unstable housing^a				
(yes vs. no)	0.89 (0.75 – 1.05)	0.175		
Addiction treatment^a				
(yes vs. no)	1.55 (1.29 – 1.86)	< 0.001	1.50 (1.25–1.80)	< 0.001
Illicit income^a				
(yes vs. no)	0.62 (0.51 – 0.74)	< 0.001		
Employment^a				
(yes vs. no)	0.98 (0.80 – 1.19)	0.817		
Injection heroin use^a				
(<Daily vs ≥Daily)	0.47 (0.36–0.62)	< 0.001	0.52 (0.40–0.68)	< 0.001
Crack smoking^a				
(<Daily vs. ≥Daily)	0.52 (0.43–0.62)	< 0.001		
Cocaine injection^a				
(<Daily vs. ≥Daily)	0.68 (0.51–0.90)	0.007		
Cannabis use^a				
(<Daily vs. ≥Daily)	0.94 (0.76–1.15)	0.549		
Alcohol use^a				
(yes vs. no)	0.75 (0.63 – 0.90)	0.002	0.81 (0.67–0.97)	0.026
Binge drug use^a				
(yes vs. no)	0.71 (0.62 – 0.82)	< 0.001		
Incarceration^a				
(yes vs. no)	0.70 (0.52 – 0.92)	0.013		
CD4 cell count				
per 100 cells	1.30 (1.24 – 1.36)	< 0.001		
Year of observation				
Per year later	1.13 (1.12–1.13)	< 0.001	1.03 (1.03–1.03)	< 0.001

^a Variables that are time-updated referring to the last 6 months from the last interview; OR: Odds Ratio; CI: Confidence Interval

Table 3.3 presents crude and adjusted longitudinal estimates for the secondary analysis of the odds of optimal adherence for once-a-day STR versus regimens with more pills per day. In an adjusted model, individuals prescribed once-a-day STR regimens were 39% more likely to achieve optimal adherence than individual on non-STR once-a-day regimens (AOR = 1.39, 95% CI: 1.07 – 1.80), after adjustment for \geq daily heroin injection, alcohol use and CD4 cell count.

Table 3.3 Longitudinal GLMM analysis of pill burden (once vs. \geq once/day) associated with adherence to ART among 770 HIV-positive PWUD in Vancouver, Canada

Characteristic	Unadjusted		Adjusted	
	OR (95% CI)	<i>p</i> -value	OR (95% CI)	<i>p</i> -value
Pill burden				
Once vs. \geq once/day	1.43 (1.10 – 1.85)	0.007	1.39 (1.07–1.80)	0.013
Age				
Per year	1.07 (1.05 – 1.08)	<0.001		
Gender				
(non-male vs. male)	0.65 (0.49 – 0.86)	0.002		
Ancestry				
(white vs. non-white)	1.61 (1.23 – 2.11)	0.001		
Unstable housing^a				
(yes vs. no)	0.89 (0.75 – 1.05)	0.175		
Addiction treatment^a				
(yes vs. no)	1.55 (1.29 – 1.86)	<0.001		
Illicit income generation^a				
(yes vs. no)	0.62 (0.51 – 0.74)	<0.001		
Employment^a				
(yes vs. no)	0.98 (0.80 – 1.19)	0.817		
Heroin injection^a				
(\geq Daily vs. <daily)	0.47 (0.36–0.62)	< 0.001	0.49 (0.38–0.65)	< 0.001
Crack smoking^a				
(\geq Daily vs. <daily)	0.52 (0.43–0.62)	< 0.001		
Cocaine injection^a				
(\geq Daily vs. <daily)	0.68 (0.51–0.90)	< 0.001		
Cannabis use^a				
(\geq Daily vs. <daily)	0.94 (0.76–1.15)	0.549		
Alcohol use^a				
(yes vs. no)	0.75 (0.63 – 0.90)	0.002	0.77 (0.64–0.92)	0.004
Binge drug use^a				
(yes vs. no)	0.71 (0.62 – 0.82)	<0.001		
Incarceration^a				
(yes vs. no)	0.70 (0.52 – 0.92)	0.013		
CD4 cell count				
per 100 cells	1.30 (1.24 – 1.36)	<0.001	1.29 (1.23–1.35)	< 0.001
Year of observation				
Per year	1.13 (1.12–1.13)	< 0.001		

^a Variables that are time-updated referring to the last 6 months from the last interview; OR: Odds Ratio; CI: Confidence Interval

Finally, in a sub-analysis to address the possibility of reverse causation (i.e., that left-censored poorer adherence caused treatment failure leading to the prescription of regimens with greater pill burden), we repeated the main analysis restricted to 118 individuals who first initiated ART after being recruited into the cohort. In this sub-analysis, a greater daily dosage of pills was significantly associated with suboptimal adherence in crude analysis (Odds Ratio [OR] = 0.83 per additional pill, 95% CI: 0.77 – 0.89). In a multivariable model, a greater daily dosage of pills remained significantly associated with suboptimal adherence (Adjusted Odds Ratio [AOR] = 0.89 per additional pill, 95% CI: 0.82 – 0.96), after adjusting for age, ancestry, being engaged in addiction treatment, \geq daily heroin injection, year of observation, and alcohol use.

3.4 Discussion

In this longitudinal study investigating the relationship between daily pill burden and adherence to ART among PLWH who use drugs in Vancouver, Canada, the results demonstrate that a greater number of pills prescribed per day was independently associated with a lower likelihood of achieving optimal adherence to ART. In a secondary multivariable analysis, use of once-a-day single-tablet regimens was associated with higher rates of optimal adherence to ART. Additionally, a greater

number of pills was associated with lower likelihood of achieving optimal adherence to ART in participants who newly initiated treatment. Therefore, daily pill burden was significantly associated with suboptimal adherence to HIV treatment among HIV-positive PWUD who were both treatment-naïve and treatment-experience in this study.

Previous studies that have examined the role of pill burden on adherence levels among individuals receiving ART have reported inconclusive results [223-230]. For example, in contrast to our findings, a 7-year retrospective study in Spain has found that a greater daily pills was not significantly associated with adherence to ART, potentially due to the high quality of care received in which adherence support was provided to patients accessing care, as noted by study authors [229]. Additionally, a meta analyses has demonstrated that adherence levels differed between groups receiving once who were treatment-naïve and treatment-experience, as such that adherence rates were lower in the latter group [226]. While inconsistencies are potentially explained by the different methods used to assess adherence, previous studies may have been limited by the lack of consideration of substance use and PWUD in analyses. Given potentially important considerations for PWUD in relation to achieving ART adherence [217], including significant social and structural barriers

to accessing and sustaining optimal HIV care, previous studies may therefore not be generalized to PWUD.

Despite the current availability of STR to promote adherence when taking medication [236], remarkably little work has been done to assess the potential importance of medication-related factors among diverse key affected populations. PWUD are a population that could particularly benefit from advances in ART medication, and the current study provides evidence to inform treatment guidelines and efforts to scale up ART among PWUD to support optimal outcomes among this population. The findings point to the possibility of improving ART adherence using simplified or single-tablet ART regimens. In the secondary analyses, we observed that the effect of STR regimens on optimal adherence was independent of patterns of both binge drug use and alcohol use, suggesting that scaling up access to once-a-day regimens could mitigate the well-described negative impact of substance use on suboptimal HIV treatment outcomes [216]. The findings support the evaluation of STR-based interventions to promote ART adherence among PWUD facing multiple barriers to optimal adherence.

Few studies have examined adherence to ART and dosing requirements in the context of substance use. In one qualitative study involving people using injection and non-injection drugs, participants reported that irregular lifestyles caused difficulty

accommodating their ART regimen into their schedules, particularly when prescribed thrice-a-day dosing [138]. Treatment adherence is further complicated by the lack of consideration by physicians of an individual's behavioral and social conditions by prescribing complex regimens [47]. A prospective cohort study evaluating ART adherence among HIV-infected individuals with alcohol and other substance use issues showed that use of drugs or alcohol in the previous 30 days was associated with poorer adherence [217]. As essential as it is to promote treatment for substance use disorders among HIV-infected individuals with persistent drug and alcohol use, it is also important for ART regimen decisions to be tailored to patients' daily activities and exposures by reducing regimen complexity as much as possible.

The problem of pill burden in the management of HIV treatment for PWUD is heightened in the presence of other co-morbidities including viral hepatitis, tuberculosis and mental illness [202]. Among those who inject drugs, co-infection of HIV and hepatitis C (HCV) global prevalence is estimated at 82.4%, which accounts for more than half of the 2.3 million people who are HIV-HCV infected worldwide [237]. The risk of disease progression into advanced stages is even higher among individuals with HIV-HCV co-infections, making the coordination of HCV treatment as important as HIV management [238]. PWUD are also at high risk of contracting tuberculosis due to increased risk for incarceration where such settings are prone to

poor ventilation and overcrowding [239]. Failure to adhere to ART is also associated with interrupted treatment for depression; a condition that is common among individuals with substance use problems [240]. In summary, co-treatment of HIV, viral hepatitis, tuberculosis and mental illness contribute to the overall pill burden of HIV-positive PWUD, lending further weight to the need to evaluate the use of simplified, single-tablet, or innovative ART forms to improve treatment adherence.

A range of studies have investigated the potential impact of adherence interventions on adherence to ART among HIV-positive PWUD [169]. For example, the implementation of directly administered ART (DAART) through observed ingestion of ART medication at clinical settings has been shown to improve adherence among PWUD, however, the same effects were not sustained once DAART was discontinued [94]. Overall, such intervention does not only result in short term outcomes but can also be costly for countries with limited resources [241]. In view of this evidence, the benefits of medication simplification in improving treatment outcomes among PWUD deserve closer attention in addition to existing adherence interventions.

This research has several limitations to note. First, while the cohort was recruited using community-based methods, we cannot conclude it is necessarily representative of PLWH who use drugs in this setting or others. Second, several

explanatory variables such as injection and binge drug use, alcohol consumption and incarceration were derived from participant self-report. Social desirability bias might generate under-reporting of these stigmatized exposures. However, this outcome of interest was ascertained through administrative data and we do not believe individuals differentially self-reported explanatory variables based on adherence or pill burden. Finally, adherence measurement based on dispensation data from the pharmacy does not necessarily ensure consumption of the medications. Nevertheless, we emphasize that this method of measuring adherence has been shown to predict virologic response and mortality [234, 235].

3.5 Conclusion

In conclusion, these results showed that a greater number of ART pills per day was negatively associated with the likelihood of achieving optimal medication adherence and that use of once-a-day STR was associated with higher rates of optimal adherence to ART among PWUD living with HIV in a setting of universal no-cost healthcare. These results suggest that evaluating efforts to minimize pill burden and promote the use of simpler regimens to improve ART adherence should be prioritized within the context of HIV care for PWUD. Although complex regimens are often required for patients with long treatment histories and extensive comorbidities, the

findings from this study also suggests that patients with more demanding regimens (in terms of pill burden or dosing frequency) require additional support to achieve optimal adherence. Given the challenges that many HIV-positive PWUD face in adhering to their medication in many settings worldwide, novel strategies based on medication simplification could contribute to ongoing efforts to scale-up ART to eliminate HIV-associated morbidity, mortality and viral transmission.

Chapter 4: Co-dispensation of low-barrier methadone maintenance therapy (MMT) and antiretroviral therapy (ART) linked to improved ART adherence among HIV-positive people who use illicit drugs in a Canadian setting

4.1 Introduction

The use of antiretroviral therapy (ART) is a central part of global efforts to control the HIV pandemic by reducing viral transmission rates and HIV-related morbidity and mortality among people living with HIV (PLWH) [242]. On the individual level, the effectiveness of the seek, test, treat and retain approach relies on high levels of adherence to ART to ensure durable plasma HIV-1 RNA viral load (VL) suppression [243]. Among people who use drugs (PWUD), there are longstanding concerns that this group may be less likely to achieve optimal adherence to ART [3], as a result of both behavioural and social-structural factors such as untreated substance use disorders, poor healthcare utilization and socio-economic marginalization, including unmet subsistence needs [31, 57, 244].

Due to its beneficial effects on the health and well-being of people with opioid use disorder, methadone maintenance therapy (MMT) is a vital component of a comprehensive HIV care package for HIV-positive PWUD with opioid use disorder

[95]. The use of this long-acting synthetic opioid as opioid agonist treatment (OAT) has been clearly linked to reductions in illicit opioid use and high-risk injection practices as well as improved engagement in addiction care [245]. Further, low-threshold MMT, where reducing barriers to MMT is supported through the dispensation of MMT in community settings or the provision of take-away dosing, has been associated with achieving optimal ART adherence, which in turn is strongly linked to positive immunologic and virologic outcomes [246, 247]. Beyond its stabilizing effect on opioid use patterns [248], the positive association between MMT use and outcomes from ART can be partly explained by the role of MMT as an important point of contact which facilitates entry into HIV care through HIV testing and referral services [184, 249]. Effective service delivery that meets the needs of PWUD may similarly involve strong collaboration between HIV and addiction specialists.

In current health systems, many care models for HIV-positive PWUD have emphasized the integration of HIV care and treatment for substance use disorder (SUD) to ensure that the clinical management of HIV enhances health outcomes among this population [140, 141, 158, 250]. Previously described elements of integration include screening for SUD or HIV at either facility, combining screening with an established referral mechanism, cross training of specialists, integrating care

under the same management team, as well as integrating care into community or residential settings [94, 139, 190, 194, 196]. Overall, these coordination processes are significant steps towards achieving a fully comprehensive integrated healthcare model for PWUD living with HIV.

Despite high-profile calls for an integrated approach for treatment of SUD and concurrent HIV infection [158], existing studies on co-dispensation of treatment medications has mainly focused on integrated care at a single location and the use of MMT with directly administered antiretroviral therapy (DAART) [93, 94, 251], a strategy to promote ART uptake and adherence in which a health worker dispenses and observes a patient taking daily doses of ART. Notably, there has been a gap in understanding the longitudinal effect of co-dispensation of ART and MMT on ART adherence among PWUD using data from real-world settings such as those with multiple low-barrier dispensation outlets in the community as a part of regular clinical care, distinct from DAART strategies. In the current study, we therefore sought to assess the potential impact of ART-MMT co-dispensation at the same facility across low-threshold dispensation outlets on adherence to ART among HIV-positive PWUD in Vancouver, Canada, where all persons living with HIV are entitled to access free ART as a part of a universal no-cost healthcare system. We hypothesized that co-

dispensation of MMT and ART at the same facility would be associated with greater odds of achieving $\geq 95\%$ adherence among HIV-positive PWUD.

4.2 Methods

4.2.1 Study design

In this study, we used data from the AIDS Care Cohort to evaluate Exposure to Survival Services (ACCESS), a prospective observational cohort of HIV-seropositive PWUD in Vancouver, Canada, linked to the Drug Treatment Program (DTP), a provincial registry operated by the British Columbia Centre for Excellence in HIV/AIDS. For a full description of the ACCESS study and DTP program, please refer to section 3.2.1 of this dissertation.

4.2.2 Study sample

The analytic sample of the current study was restricted to ART-exposed individuals (i.e., all interview periods from participants with at least one day of ART dispensation in the previous six months). Also, to ensure a sample possessing characteristics relevant to the central research question of the relationship between MMT and ART co-dispensation, characterized by the receipt of both ART and MMT at the same facility across multiple low-threshold dispensation outlets, we further

restricted to all individuals who ever reported engagement with MMT during the study period. Participants who reported being in the maximally assisted therapy (MAT), a low-barrier program which promotes ART adherence by implementing support strategies such as housing assistance and ART management, were excluded.

4.2.3 Variable selection

The primary outcome of interest was adherence to ART in the 180-day period prior to each study interview. Adherence was calculated as the number of days for which ART was dispensed in the last 180 days from pharmacy records, divided by the number of days since the participant had initiated ART, to a maximum of 180 days. Consistent with previous analyses [21, 176], this measure was dichotomized at 95%. Notably, in previous studies, we have shown that optimal adherence using pharmacy refill data is strongly associated with both HIV VL suppression and survival [235]. The main explanatory variable of interest in these analyses was MMT and ART co-dispensation (yes vs. no) in the last six months. Information on MMT dispensation locations was based on the interview question: “Which pharmacy administers your methadone?” a new questionnaire item added to the ACCESS study instrument in 2012. In Vancouver, Canada, HIV-positive PWUD have access to low-barrier community-based MMT and universal no-cost ART. Authorized pharmacies such as

general hospitals and medical centers treating HIV-positive individuals may deliver ART medication to community pharmacies, physicians' offices or other health care facilities for further dispensation. MMT, prescribed by licensed primary care physicians under the provincial healthcare program, can also be dispensed at these locations [135]. For the specific purposes of this study, responses from interviews were newly coded and matched with data on ART dispensing locations elicited from the DTP using the DTP data entry closest to the date of follow up interview date.

To estimate the independent effect of MMT-ART co-dispensation on ART adherence, we also selected several potential confounders for inclusion in multivariate models based on findings from previous research [54, 252], including: age (per year older); gender (male vs. non-male); ancestry (white vs. non-white); unstable housing (yes vs. no); education (\geq high school diploma vs. $<$ high school diploma); recent incarceration (yes vs. no); regular, temporary or self-employment (yes vs. no); informal and prohibited income generation, including sex work, illegal income generation such as theft, drug dealing, as well as informal street-based income sources such as car window washing or informal recycling (yes vs. no); heroin injection or non-injection use (\geq daily vs. $<$ daily); cocaine injection or non-injection use (\geq daily vs. $<$ daily); crack smoking (\geq daily vs. $<$ daily); cannabis use (\geq daily vs. $<$ daily); heavy alcohol use, defined as more than 4 drinks a day (yes vs. no); hepatitis

C virus antibody (positive vs. negative). To account for HIV disease progression, we included CD4+ cell count (per 100 cells/mL), calculated as the mean of all observations collected within the six-month follow-up period or, if none, the most recent observation. All non-fixed variables were time-updated and referred to the six-month period prior to the follow-up interview, with the exception of age, gender, ancestry and education.

4.2.4 Statistical analyses

First, we examined the distribution of all explanatory variables at baseline, in addition to recent ART adherence (≥ 95 vs. $<95\%$), stratified by MMT-ART without co-dispensation and MMT-ART co-dispensation, using Pearson's χ -square for categorical variables and Wilcoxon rank-sum for continuous variables. We also quantified the magnitude of multicollinearity using the variance inflation factor. Subsequently, we produced multivariable models using an a priori-defined modelling procedure. To build each multivariable model, we first examined bivariate relationship between each variable and the outcome of interest, using a generalized linear mixed model (GLMM). We then fit a full model including the primary explanatory variable and all secondary explanatory variables that were associated with $\geq 95\%$ adherence in bivariate analyses at p -value < 0.10 . Next, we constructed

reduced models by using a backward approach, eliminating explanatory variables that produced the smallest relative change in the MMT-ART co-dispensation coefficient. We continued this process until the minimum change in the coefficient of the primary independent variable of interest from the full model exceeded 5%. As in previous analyses, we produced a final model that retains explanatory variables with the greatest relative influence on the relationship between the main explanatory variable and outcome of interest [21] (Full analysis is demonstrated in Appendix C).

A sub-analysis was performed to account for the non-randomized nature of observational data. We constructed a marginal structural model weighted using the inverse probability of treatment (IPTW) method by measuring the causal effect of a time-dependent exposure [253, 254]. Based on a randomization assumption, marginal structural models assume that among individuals who are identical with respect to measured covariates, the observed adherence of individuals who are exposed to the primary explanatory variable is representative of the counterfactual adherence [254]. This model adjusts confounders for the effect of ART-MMT co-dispensation and selection bias, with each observation weighted by the inverse of the probability of the observed exposure level given the observed value of the confounders [255]. In this analysis, we reported stabilized weights as this approach increases statistical efficiency by attaining lower variance in estimators [255]. To find stabilized weights,

we defined the numerator as time-fixed covariates including age, gender, ancestry and education, and denominator as both time-fixed and the observed time-varying covariates. Finally, we used GLMM to estimate the effect of MMT-ART co-dispensation on adherence levels, adjusting for the stabilized weights. The same technique has been used in previous analyses in this setting to successfully estimate the relationship between the outcome of interest and primary explanatory variable using a marginal structural model [256]. All statistical analyses were conducted using R version 1.0.143.

4.3 Results

Between June, 2012 and December, 2017, 345 eligible individuals were identified, of whom 190 (55.1%) had achieved $\geq 95\%$ adherence at baseline. Study participants included 145 (42.0) non-males, with a median age of 45.8 years (inter-quartile range: 39.8 – 51.9 years), and contributed 1690 observations over the course of the study period. Baseline sociodemographic and clinical characteristics as well as levels of ART adherence, stratified by MMT-ART without co-dispensation and MMT-ART co-dispensation for this analytic sample are presented in Table 4.1.

Table 4.1 Baseline characteristics of 345 HIV-positive PWUD in Vancouver, Canada, stratified by MMT-ART dispensation, between June 2012 and December 2017

Characteristic	Total N = 345	MMT-ART Non-Co- Dispensation n = 224 (64.9%)	MMT-ART Co-Dispensation n = 121 (35.1%)	<i>p</i> - value
ART adherence				
< 95%	136 (39.4)	95 (42.4)	41 (33.9)	0.037
≥ 95%	190 (55.1)	110 (49.1)	80 (66.1)	
Age				
median (IQR)	45.8 (39.8 –	46.7 (39.9 – 51.9)	44.7 (39.6 – 51.8)	0.381
Gender				
Male	198 (57.4)	135 (60.3)	63 (52.1)	0.147
Non-male	145 (42.0)	87 (38.8)	58 (47.9)	
Ancestry				
White	186 (53.9)	121 (54.0)	65 (55.9)	0.999
Non-white	159 (46.1)	103 (46.0)	56 (44.1)	
Unstable housing ^a				
Yes	240 (69.6)	144 (64.3)	96 (79.3)	0.003
No	101 (29.3)	78 (34.8)	23 (19.0)	
Education ^a				
≥ High School	154 (44.6)	100 (44.6)	54 (44.6)	0.999
< High School	181 (52.5)	117 (52.2)	64 (52.9)	
Recent incarceration ^a				
Yes	23 (6.7)	20 (8.9)	3 (2.5)	0.041
No	321 (93.0)	204 (91.1)	117 (96.7)	
Employment ^a				
Yes	59 (17.1)	39 (17.9)	20 (15.7)	0.704
No	285 (82.6)	178 (81.7)	107 (84.3)	
Prohibited income ^a				
Yes	148 (42.9)	95 (42.4)	53 (43.8)	0.893
No	197 (57.1)	129 (57.6)	68 (56.2)	
Heavy alcohol use ^a				
Yes	25 (7.2)	16 (7.1)	9 (7.4)	0.999
No	320 (92.8)	208 (92.9)	112 (92.6)	
Heroin use ^a				
≥ Daily	54 (46.4)	41 (18.3)	13 (10.7)	0.088
< Daily	290 (53.4)	182 (81.3)	108 (89.3)	

Characteristic	Total N = 345	MMT-ART Non-Co- Dispensation n = 224 (64.9%)	MMT-ART Co-Dispensation n = 121 (35.1%)	p - value
Cocaine use ^a				
≥ Daily	27 (7.1)	16 (26.1)	11 (9.1)	0.682
< Daily	316 (92.0)	206 (73.5)	110 (90.9)	
Crack use ^a				
≥ Daily	67 (19.4)	46 (20.5)	21 (17.4)	0.556
< Daily	277 (80.3)	177 (79.0)	100 (82.6)	
Cannabis use ^a				
≥ Daily	70 (20.3)	50 (22.3)	20 (16.5)	0.256
< Daily	275 (79.7)	174 (77.7)	101 (83.5)	
Hepatitis C^a				
Yes	320 (92.8)	207 (92.4)	113 (93.4)	0.907
No	25 (7.2)	17 (7.6)	8 (6.6)	
CD4 count				
median (IQR)	380 (245 – 589)	380 (250 – 580)	370 (230 – 600)	0.808

^a Variables that are time-updated referring to the last 6 months from the last interview

Note: Some columns may not add up to 100%, as participants may not respond to sensitive questions.

Unadjusted and adjusted longitudinal estimates of the odds of optimal ART adherence for the primary explanatory variable (MMT-ART co-dispensation, yes vs. no) and other secondary variables in a multivariable GLMM are presented in Table 4.2. In bivariable analyses, MMT-ART co-dispensation was positively associated with achieving $\geq 95\%$ adherence (Odds Ratio [OR] = 1.52, 95% Confidence Interval [95% CI]: 1.23 – 1.90). In the final multivariable model, MMT-ART co-dispensation remained positively associated with achieving $\geq 95\%$ adherence (Adjusted Odds Ratio [AOR] = 1.56, 95% CI: 1.26 – 1.96) after adjusting for gender.

Table 4.2 Longitudinal GLMM analysis of MMT-ART co-dispensation associated with ART adherence among 345 HIV-positive PWUD in Vancouver, Canada

Characteristics	Unadjusted		Adjusted	
	OR (95% CI)	<i>p</i> -value	Odds Ratio (95% CI)	<i>p</i> -value
MMT-ART				
Co- Dispensation ^a				
(yes vs. no)	1.52 (1.23 – 1.90)	<0.001	1.56 (1.26 – 1.96)	<0.001
Age ^b				
Per year	1.02 (1.01 – 1.04)	<0.001		
Gender ^b				
(male vs. non-male)	1.31 (1.05 – 1.62)	0.016	1.36 (1.10 – 1.70)	0.005
Ancestry ^b				
(white vs. non-white)	1.27 (1.03 – 1.58)	0.026		
Unstable housing ^a				
(yes vs. no)	1.02 (0.81 – 1.29)	0.845		
Education ^b				
(higher vs. <high school)	1.14 (0.92 – 1.41)	0.238		
Recent incarceration ^a				
(yes vs. no)	0.75 (0.44 – 1.29)	0.288		
Employment ^a				
(yes vs. no)	1.07 (0.81 – 1.41)	0.648		
Prohibited income ^a				
(yes vs. no)	0.68 (0.55 – 0.84)	<0.001		
Heavy alcohol use ^a				
(yes vs. no)	0.54 (0.37 – 0.78)	0.001		
Daily heroin use ^a				
(≥ daily vs. < daily)	0.61 (0.46 – 0.82)	<0.001		
Daily cocaine use ^a				
(≥ daily vs. < daily)	1.34 (0.90 – 2.02)	0.160		
Daily crack use ^a				
(≥ daily vs. < daily)	0.57 (0.43 – 0.75)	<0.001		
Daily cannabis use ^a				
(≥ daily vs. < daily)	1.36 (1.03 – 1.81)	0.034		
Hepatitis C ^a				
(yes vs. no)	0.90 (0.52 – 1.50)	0.689		
CD4 ^a				
per 100 cells	1.07 (1.03 – 1.12)	<0.001		

^a Variables that are time-updated referring to the last 6 months from the last interview; OR: Odds Ratio; CI: Confidence Interval

Table 4.3 presents comparisons of results from unweighted and weighted estimates of the effect of MMT-ART co-dispensation on $\geq 95\%$ adherence. The marginal structural model using IPTW to adjust for stabilized weights has demonstrated that participants with MMT-ART co-dispensation were 1.48 (95% CI: 1.15 – 1.80) times more likely to achieve $\geq 95\%$ adherence to ART than those whose MMT-ART was not co-dispensed.

Table 4.3 Regression analyses on the association between MMT-ART co-dispensation and ART adherence among 345 HIV-positive PWUD in Vancouver, Canada

Model Specification	Measure of effect [OR (95% CI)]	<i>p</i> -value
<i>Unweighted estimates</i>		
Unadjusted, generalized linear model	1.52 (1.23 – 1.90)	<0.001
Adjusted, generalized linear model*	1.56 (1.26 – 1.96)	<0.001
<i>Weighted estimates</i>		
Marginal structural model with inverse probability of treatment weights (IPTW)	1.48 (1.15 – 1.80)	0.001

OR: Odds Ratio; CI: Confidence Interval

4.4 Discussion

In the current longitudinal study investigating the relationship between MMT-ART co-dispensation on adherence to ART among HIV-positive PWUD in a setting with low-barrier MMT dispensation and no-cost ART, we found that dispensation of

MMT-ART within the same facility was independently associated with a higher likelihood of achieving optimal adherence to ART. The positive association between MMT-ART co-dispensation and optimal adherence to ART was observed in both multivariable statistical approaches that were applied.

These results are consistent with findings from other studies that highlight the advantages of MMT delivery in conjunction with ART. One such advantage is the fact that daily ingestion of MMT provides an opportunity for DAART in MMT settings. A clinical trial has demonstrated that the decrease in adherence levels associated with opioid use was eliminated among participants randomized to DAART receiving one dose of ART concurrent with their daily MMT [251]. Nevertheless, the benefits of DAART may not represent the larger population of HIV-positive PWUD, particularly for individuals who are not participating in a DAART program or stabilized MMT patients who receive take-home doses. Additionally, despite the benefits of DAART on ART adherence for PWUD receiving MMT, effects were not sustained once the trial was finished [199], and concerns have been raised about the costs, convenience and practicality of DAART programs for both patients and healthcare providers [257]. While these studies highlight the benefits of DAART in an MMT-ART co-administration approach, the study has the advantage of using longitudinal

observational data assessing routine access to both MMT and ART among PWUD in community-based settings, which are less resource intensive than DAART programs.

Several studies have documented the benefits of integrated healthcare that incorporates SUD treatment and HIV care for PWUD. In Ukraine, participants enrolled in a fully co-located integrated model that included on-site provision of OAT and HIV screening and treatment were more likely to receive ART, with higher health-related quality of life scores [196]. Additionally, in one cross-sectional study in the United States, the coordination of multiple services, including provision of referrals to substance use and assistance to address social needs, further increased accessibility to ART [140]. Further, adherence counselling sessions using motivational interviewing and cognitive-behavioral therapy offered to patients in a MMT clinic with on-site provision of ART through a DAART program were positively associated with adherence to ART [189]. Overall, these studies reflect the stabilizing effect of OAT that facilitates the implementation of comprehensive care to ensure HIV-positive PWUD receive adequate support to adhere to treatment [163]. Despite the emphasis on the co-location of health and non-health services, to my knowledge little work has assessed the possible causal relationship between co-dispensation of OAT and HIV medication on ART adherence levels among PWUD. Whereas other studies have emphasized integrated services at a single location, accompanied by adherence

interventions [189, 190], the study considered medication dispensation as an essential element of service delivery. This points to the possibility of increasing accessibility to ART by filling out medication prescriptions at facilities other than main medical centres where treatment is initiated.

Focus group discussions in several qualitative studies have elicited useful information from the perspectives of PWUD and healthcare providers on structural barriers to access to ART and OAT medication relevant to the findings [250]. For example, PWUD reported the inconvenience of travelling to different places to fill prescriptions and long waiting times for medication due to increased workloads among healthcare providers in settings with comprehensive HIV and OAT care [258, 259]. Additionally, MMT providers reported that administering HIV care in their clinics—including ART initiation, regimen and dosage selection, as well as side-effect management—can be a challenge due to the lack of expertise [258]. Notably, the current study offers insights on the possibility of a simpler integrated approach through MMT-ART co-dispensation to promote accessibility among patients and reduce the burden on healthcare systems. Decentralizing HIV and OAT treatment delivery could include community-based distribution settings and the potential engagement of peer workers to mitigate the effects of stigma and discrimination often experienced by PWUD [194, 260]. Nevertheless, it is important to note that in some

countries, the procurement of ART can only be done through official bodies such as HIV treatment centers and may not be widely distributed to less centralized facilities [261]. Although co-dispensation remains a significant challenge, it is worthwhile to consider its function in effectively integrating care in light of existing concerns of the complexities in managing both HIV and SUD, as demonstrated in this study.

This study has several limitations to note. First, these findings may not be generalized to HIV-positive PWUD in this or other settings since the ACCESS cohort was recruited using community-based methods and not random sampling. Second, several explanatory variables, such as methadone dispensation, illicit drug use practices, alcohol intake and recent incarceration, were derived from participant self-report, potentially introducing recall or social desirability bias into the data. However, the outcome of interest was ascertained using administrative data and there is no reason to believe that participants differentially self-reported explanatory variables based on ART adherence levels. Finally, since the exact date of MMT dispensation is not available, it could not be determined if co-dispensation of MMT and ART took place on the same day. However, there was an attempt to address this by selecting ART dispensation location information closest to the interview date.

4.5 Conclusion

Our results demonstrate that MMT-ART co-dispensation was positively associated with the likelihood of achieving optimal adherence to ART among PWUD living with HIV in a setting of universal no-cost healthcare and low-barrier to MMT. These results shed light on the value of co-dispensation of HIV and substance use treatment in integrated care models designed for members of a key affected population that experiences multiple challenges to adhere to medication. Efforts to implement co-dispensation in treatment plans could contribute towards a more patient-centered care system, such that the services across sectors are aligned around the needs of PWUD. Co-dispensation of MMT and ART should be considered as an essential component of HIV care among individuals with HIV infection and concurrent opioid addiction to reduce morbidity and mortality rates, contribute to efforts to curb viral transmission and support seek, test, treat and retain focused programs for key affected populations.

Chapter 5: Material insecurity and adherence to antiretroviral therapy (ART) among HIV-positive people who use illicit drugs in Vancouver, Canada: Role of institutions

5.1 Introduction

There is compelling evidence that poverty disproportionately affects health, with significant evidence documenting poorer health outcomes among populations living in poverty in both resource-limited and developed settings [262]. People living with HIV (PLWH) and people who use illicit drugs (PWUD) are two overlapping populations who commonly face the challenges of poverty and its adverse effect on health [143]. In the case of HIV infection, although treatment with combination antiretroviral therapy (ART) has been shown to effectively suppress plasma HIV-1 RNA viral loads in PLWH and stall disease progression, HIV-positive PWUD continue to experience poor HIV care outcomes, resulting in lower rates of optimal exposure to ART [3, 42]. In conditions of socioeconomic marginalization, whereby traditional economic opportunities are limited, PWUD may engage in illegal and prohibited income generation activities, including sex work and drug dealing [263]. Involvement in these types of income generating activities may limit engagement in HIV care, further exacerbating health inequities in HIV treatment outcomes [57].

Analyses of poverty and health are commonly dominated by income-based measures despite well-known limitations in this approach, including variations in living expenses across cities [264]. Further, income has a complex association with illicit drug use as higher income among PWUD has been found to be associated with more frequent drug use and greater risk of drug-related harms [265]. This suggests that income alone may not sufficiently capture conditions of socioeconomic marginalization and material hardship that people living in poverty who use illicit drugs can face [266]. Despite its potential to provide a more nuanced understanding of resource scarcity, to our knowledge, material security—a concept encompassing access to individual necessities, including housing, food and economic resources—has not been used to assess the relationship between poverty and HIV treatment outcomes among HIV-positive PWUD. Further, we are unaware of any analysis among PWUD that has assessed the longitudinal relationship between material security and the likelihood of achieving optimal adherence to ART.

How individuals engage with different types of institutions and the resulting impact on material security is key consideration in understanding the poverty – material security – HIV treatment outcome nexus. For example, institutions that provide social supports, such as food subsidies, housing assistance or healthcare, may mitigate the material impacts of poverty [267]. Although the impacts of varying

institutional exposures, such as incarceration and engagement in substance use treatment facilities, on health outcomes among PWUD have been well documented [31], to our knowledge very few studies have examined the role of institutional environments on material security in this population. While previous research among PWUD found an association between inadequate material resources and different income sources, including employment, public assistance and illegal activity [268], this research pointed to a need to expand analyses of the role of these and other institutional factors.

Poverty rates in British Columbia, Canada are consistently among the highest in the country, with over 13% of individuals in the province living below the poverty line [269]. The Downtown Eastside in Vancouver, British Columbia is an urban neighborhood with high levels of illicit drug use, HIV infection and HIV-related mortality [270]. Poverty rates in this geographic area are high, with additionally heightened risk of poor living conditions and homelessness [271]. In the current study, using data from a long-running prospective cohort study of PWUD in a setting with free access to HIV care, we sought to extend research on material security among PWUD to examine factors associated with material security in this population, including a range of institution-specific variables of theorized relevance to material security. We additionally sought to assess the relationship between material security

and adherence to ART, taking into consideration individual engagement with institutions with high theoretical relevance to both material security and associated outcomes. We hypothesized that, (1) high levels of material insecurity associated with correctional facilities and poor engagement with social support systems as well as healthcare institutions are present in a population of HIV-positive PWUD; and (2) material insecurity is associated with lower likelihood of achieving optimal adherence to ART among HIV-positive PWUD. The implications of material insecurity for HIV care among PWUD may be implicated in efforts to identify public health strategies that could mitigate disparities in adherence to ART.

5.2 Methods

5.2.1 Study design

In this study, we used data from the AIDS Care Cohort to evaluate Exposure to Survival Services (ACCESS), a prospective observational cohort of HIV-seropositive PWUD in Vancouver, Canada, linked to the Drug Treatment Program (DTP), a provincial registry operated by the British Columbia Centre for Excellence in HIV/AIDS. For a full description of the ACCESS study and DTP program, please refer to section 3.2.1 of this dissertation.

5.2.2 Study sample

For this study, we restricted the analytic sample to ART-exposed periods, or all interviews following an individual's earliest dispensation of ART prior to the study period end date. Questions on material security were added to the ACCESS study instrument in June 2014, and we therefore additionally restricted the sample to ART-exposed participants who were followed up between June 2014 and December 2017, treating the first study visit after June 1, 2014 as the study baseline.

5.2.3 Variable selection and statistical analysis

5.2.3.1 Analysis of factors associated with material security

We conducted two groups of analyses: the first examining material security in the study population and the second to identify potential associations between material security and HIV treatment outcomes. Critical to this analysis is self-reported material security, determined by a 18-item scale, modified from the 30-item Family Resource Scale [268, 272, 273] for suitability in the current study population. The modified 18-item version has been validated among PWUD in New York [268]. At each study interview, participants were asked whether they had adequate access to a series of material resources in the last six months (i.e., since the time of the last study interview), including having food, adequate shelter, sufficient money for various

expenditures and access to a range of services (Appendix D1). Responses were based on a 5-point Likert scale with higher scores indicating better access to resources; scored as 1) never, 2) occasionally, 3) sometimes, 4) usually and 5) always having access. An overall material security score was generated by taking the mean of all 16 questions, with higher scores indicate better levels of material security. In previous analyses, an exploratory factor analysis was conducted which identified a three-factor structure to the scale [274]. This three factors structure, employed in the current analyses, were Factor 1 involving basic needs (food, clothes, medical/dental care, transport); Factor 2 encompassing housing-related variables (house/apartment, heat, water and furniture); and Factor 3 including economic resources (obtaining a job and having money for necessities, entertainment and savings).

For the first set of analyses, we examined factors associated with material security. We considered a range of explanatory variables, including sociodemographic characteristics: age (per 10 years older); ancestry (white vs. non-white); gender (male vs. non-male); education (\geq high school vs. $<$ high school); employment, including regular job, temporary job, or self-employed (yes vs. no); social income assistance (yes vs. no); illegal income generation, including theft, robbing, stealing, selling drugs or other criminal activity (yes vs. no); street-based income, including recycling, squeegeeing, or panhandling (yes vs. no); sex work (yes

vs. no) and total income (per \$1000). A list of illicit drug use-related variables was selected, including at least daily cocaine use; at least daily heroin injection; at least daily crack smoking; at least daily cannabis use; heavy alcohol use (defined as >14 drinks per week or >4 drinks on one occasion for male, and >7 drinks per week or >3 drinks on one occasion for female vs. no); and overdose (yes vs. no).

We also considered a range of variables that described institutional engagement: incarceration (yes vs. no); access to general health facilities, including a doctor, clinic, specialist, emergency department, hospital or dental care (yes vs. no); access to substance use treatment, including detox programs, residential treatment centers, counselling or suboxone or methadone/methadose (yes vs. no); and access to support services, including food bank, HIV service organizations, women's organization, employment services or drop-in centers (yes vs. no). Variables that indicate participants' inability to obtain health and social services at times when they needed them were also considered. These variables were defined as unmet health needs, including drug treatment facility, supervised injecting facility, hospital, dentist, optometrist and needle distribution (yes vs. no); and unmet social service needs, including housing, peer group/support group, social worker, welfare worker, income assistance worker, income assistance or food services (yes vs. no). Health-related variables considered were CD4 cell count at baseline (per 100 cells); hepatitis

C diagnosis (yes vs. no) and mental illness diagnosis (yes vs. no). Time-updated variables referred to the six-month period prior to the follow-up interview. The CD4 cell count data was accessed from the DTP and included readings from blood drawn either through the study or through regular clinical care. We also quantified the magnitude of multicollinearity using a standard correlation matrix. There was a low degree of correlation between variables and the effects of removing the collinear variables on the estimates for material security score were low, with little or no change in estimates. Therefore, collinear variables were retained in final analyses.

In statistical analyses, we first examined the mean material security scores for each factor within the scale across different characteristics of the study sample at the baseline interview. Next, using a generalized linear mixed model (GLMM), we constructed multivariate models of factors associated with material security scores. We used an a priori-defined modelling procedure. In the first step of this procedure, we fit a full model including all potential explanatory variables with p -values <0.1 in bivariate analyses. After noting the value of the Akaike Information Criterion (AIC) values for the full model, we constructed reduced models by using a backward selection approach, eliminating the explanatory variable that was associated with the largest p -value. We continued this process until there were no co-variables other than the explanatory variable of interest left in the model. Comparing the AIC values for

all full and reduced models, we selected the final model with the lowest AIC value. The same technique has been used in previous analyses to estimate the relationship between an outcome of interest and primary explanatory variable [275]. (Full analysis is included in Appendix D2).

5.2.3.2 Associations between material security and adherence to ART

In the second set of analyses examining the association between material security and adherence to ART, the primary outcome of interest was adherence to ART in the 180-day period prior to the study interview. Adherence was calculated as the number of days for which ART was dispensed in the last 180 days from pharmacy records, divided by the number of days since the participant had started ART (to a maximum of 180 days.) Consistent with previous analyses examining optimal ART adherence [21, 152], this measure was dichotomized at 95%. Notably, in previous studies, we have shown that this measure of adherence using pharmacy refill data is strongly associated with both virologic suppression and survival [235].

The main explanatory variable of interest was mean material security score. Multivariable logistic regression models using GLMM were produced to estimate associations between overall mean material score, as well as mean score for each of the three factors within the scale and the outcome of interest adjusting for the same

confounders used in the previous analysis. To produce the models, we again used an a priori-defined modelling procedure. First, we fit a full model including all explanatory variables. Next, we constructed reduced models by using backward selection, eliminating explanatory variables that produced the smallest relative change in the material security score coefficient. We continued this process until the minimum change from the full model exceeded 5%. As in previous analyses, we produced a final model that retains explanatory variables with the greatest relative influence on the relationship between the main explanatory variable and outcome of interest [21].

5.3 Results

Between June, 2014 and December, 2017, 623 individuals completed ≥ 1 study interview and were eligible for the current study. They contributed 2476 observations during the study period, equal to 1238 person-years of observation. Table 5.1 presents the demographic characteristics of the study sample. Among these individuals, the median age was 49 years (interquartile range [IQR] 42–54 years), 334 (53.6%) were of White ancestry, and 217 (34.8%) were non-male.

Table 5.1: Baseline characteristics of 623 PLWH who use illicit drugs in Vancouver, stratified by ART adherence ($\geq 95\%$ and $<95\%$) between June, 2014 and December, 2017.

Characteristics	Total (%) (N=623)	$\geq 95\%$ ART adherence (n = 367)	$< 95\%$ ART Adherence (n = 232)	<i>p</i> -value
Socio-demographic				
Non-white ancestry	334 (53.6)	206 (56.1)	121 (89.0)	0.351
Non-male	217 (34.8)	122 (33.2)	85 (36.6)	0.307
Education \geq high school	297 (47.7)	174 (47.4)	112 (48.3)	0.916
Age (median, IQR)	49 (42 – 54)	49 (43 – 55)	49 (42 – 54)	0.500
Income-related variables				
Employment ^a	131 (21.0)	75 (20.4)	51 (22.0)	0.651
Income assistance ^a	612 (98.2)	360 (98.1)	230 (99.1)	0.420
Illegal income generation ^a	104 (16.7)	55 (15.0)	45 (19.4)	0.159
Street-based income ^a	125 (20.1)	65 (17.7)	56 (24.1)	0.056
Sex work ^a	60 (9.6)	30 (8.2)	30 (12.9)	0.060
Total income in \$ (median, IQR)	1600 (1100 – 4800)	1500 (1100 – 4800)	1800 (1100 – 5000)	0.500
Substance-related variables				
Daily cocaine use ^a	31 (5.0)	19 (5.2)	11 (4.7)	0.812
Daily heroin injection ^a	81 (13.0)	33 (9.0)	41 (17.7)	0.002
Daily crack non-injection ^a	72 (11.6)	33 (9.0)	35 (15.1)	0.022
Daily cannabis use ^a	156 (25.0)	99 (27.0)	52 (22.4)	0.210
Heavy alcohol use ^a	88 (14.1)	44 (12.0)	41 (17.7)	0.052
Overdose ^a	38 (6.1)	22 (6.0)	16 (6.9)	0.659
Institutional factors				
Recent Incarceration ^a	29 (4.7)	15 (4.1)	13 (5.6)	0.385
Unmet health needs ^a	39 (6.3)	28 (7.6)	11 (4.7)	0.167
Unmet social needs ^a	45 (7.2)	26 (7.1)	17 (7.3)	0.899
Access to general health facilities ^a	610 (97.9)	363 (98.9)	225 (97.0)	0.073
Access to substance use treatment facilities ^a	346 (55.5)	208 (56.7)	129 (55.6)	0.797
Access to social services ^a	550 (88.3)	326 (88.8)	205 (88.4)	0.975
Health-related variables				
CD4 cell counts (per 100 cells)				
Hepatitis C (HCV) ^a	520 (83.5)	305 (83.1)	193 (83.2)	0.979
Mental illness ^a	426 (68.4)	254 (69.2)	156 (67.2)	0.514

^a Variables that are time-updated referring to the last 6 months from the last interview, IQR: Interquartile Range

Baseline mean material security scores for Factor 1 (basic needs such as food, clothing and transport), Factor 2 (housing-related variables) and Factor 3 (economic resources) across sociodemographic-, substance use-, institutional- and health-related variables for this analytic sample are presented in Table 5.2. Two variables did not fit into any of the three factors: having a phone or access to a phone and access to social assistance, and were dropped from the analysis. Among HIV-positive PWUD in this setting, mean material security was lowest for economic resources (Factor 3), compared to basic needs (Factor 1) and housing (Factor 2)-components. Participants reporting unmet social needs presented the lowest mean material security score in all three factors of the material security scale (Factor 1 mean = 3.89, standard deviation [SD] = 0.75); Factor 2 mean = 3.51, SD = 1.39; and Factor 3 mean = 2.52, SD = 0.82). Of the institutional-related variables, lowest score in unmet social needs was followed by recent incarceration in terms of having the lowest scores across the three factors (Factor 1 mean= 4.07, SD = 0.61; Factor 2 mean = 3.59, SD = 1.44; and Factor 3 mean = 2.57, SD = 0.87). Conversely, higher mean material security scores were observed among participants who reported having had recent access to general health facilities (Factor 1 mean = 4.33, SD = 0.64; Factor 2 mean = 4.60, SD = 0.82; and Factor 3 mean = 2.90, SD = 0.897).

Table 5.2: Baseline mean material resource scale scores stratified by basic needs (Factor 1), housing variables (Factor 2) and economic resources (Factor 3), among 623 HIV-positive PWUD in Vancouver, Canada, between June 2014 – December 2017.

Characteristics	Factor 1		Factor 2		Factor 3	
	Mean(SD)	<i>p</i> -value	Mean(SD)	<i>p</i> -value	Mean(SD)	<i>p</i> -value
Socio-demographic						
Non-white ancestry	4.32(0.63)	0.846	4.61(0.80)	0.576	2.99(1.02)	0.028
Non-male	4.28(0.63)	0.226	4.49(0.93)	0.023	2.83(0.98)	0.215
Education ≥ high school	4.32(0.67)	0.828	4.57(0.83)	0.606	2.92(1.02)	0.799
Income-related variables						
Employment ^a	4.45(0.59)	0.014	4.76(0.55)	0.011	3.51(0.94)	<0.001
Income assistance ^a	4.33(0.64)	0.084	4.6(0.83)	0.348	2.90(1.01)	0.825
Illegal income generation ^a	4.06(0.66)	<0.001	4.24(1.17)	<0.001	2.81(0.99)	0.344
Street-based income ^a	4.19(0.63)	0.008	4.53(0.91)	0.335	2.77(0.94)	0.102
Sex work ^a	4.04(0.70)	<0.001	4.26(1.01)	0.001	2.63(0.96)	0.030
Substance-related variables						
Daily cocaine use ^a	4.29(0.62)	0.715	4.77(0.46)	0.218	2.87(0.99)	0.878
Daily heroin injection ^a	4.12(0.69)	0.002	4.22(1.18)	<0.001	2.88(1.03)	0.883
Daily crack non-injection ^a	4.14(0.75)	0.009	4.42(1.14)	0.065	2.89(1.14)	0.935
Daily cannabis use ^a	4.32(0.68)	0.834	4.64(0.76)	0.388	2.94(1.02)	0.574
Heavy alcohol use ^a	4.26(0.69)	0.319	4.51(0.95)	0.282	2.78(0.97)	0.254
Overdose ^a	4.13(0.79)	0.052	4.32(1.06)	0.038	2.84(0.88)	0.725
Institutional factors						
Recent Incarceration ^a	4.07(0.61)	0.027	3.91(1.44)	<0.001	2.57(0.87)	0.075
Unmet health needs ^a	4.03(0.59)	0.002	4.46(0.88)	0.282	2.53(0.92)	0.018
Unmet social needs ^a	3.89(0.75)	<0.001	3.51(1.39)	<0.001	2.52(0.82)	0.009
Access to general health facilities ^a	4.33(0.64)	0.274	4.60(0.82)	0.589	2.90(1.01)	0.897
Access to substance use treatment facilities ^a	4.25(0.66)	<0.001	4.52(0.89)	0.008	2.85(0.99)	0.169
Access to social services ^a	4.30(0.65)	0.010	4.58(0.85)	0.182	2.85(0.98)	<0.001
Health-related variables						
Hepatitis C (HCV)	4.35(0.64)	0.090	4.62(0.81)	0.100	2.94(1.02)	0.012
Mental illness	4.32(0.62)	0.493	4.60(0.84)	0.828	2.84(0.98)	0.026

^a Variables that are time-updated referring to the last 6 months from the last interview; SD: Standard Deviation

Results from the first set of analyses including unadjusted bivariate and adjusted multivariate associations with material security are presented in Table 5.3. In the adjusted model, institutional engagement-related variables including recent incarceration [β -coefficient (β) = -0.18, 95% Confidence Interval [95% CI]: -0.29, -0.063), unmet health service needs (β = -0.11, 95% CI: -0.18, -0.042), unmet social service needs (β = -0.26, 95% CI: -0.34, -0.19), and having had access to social services (β = -0.10, 95% CI: -0.16, -0.046) were significantly and negatively associated with material security. Further, non-institutional engagement-related variables, including street-based income generation (β = -0.081, 95% CI: -0.13, -0.03), engaged in sex work (β = -0.076, 95% CI: -0.16, 0.006) daily heroin injection (β = -0.077, 95% CI: -0.14, -0.014) and mental illness (β = -0.064, 95% CI: -0.13, 0.006), were also significantly and negatively associated with material security. Additionally, factors that were significantly and positively associated with higher material security scores were older age (β = 0.046, 95% CI: 0.007, 0.085), regular employment (β = 0.16, 95% CI: 0.11, 0.20), total income per \$1000 (β = 0.004, 95% CI: 0.003, 0.006) and having had access to general health facilities (β = 0.15, 95% CI: 0.015, 0.29). Pearson's chi-squared test (χ^2) was 0.10.

Table 5.3: Longitudinal GLMM analysis of factors associated with material security among 623 HIV-positive PWUD in Vancouver, Canada

Characteristic	Unadjusted		Adjusted	
	β -coefficient (95% CI)	<i>p</i> -value	β -coefficient (95% CI)	<i>p</i> -value
Age (per 10 years)	0.095 (0.055, 0.14)	<0.001	0.046 (0.007, 0.085)	0.022
Ancestry	-0.036 (-0.11, 0.036)	0.334		
Gender	0.041 (-0.035, 0.12)	0.291		
Education	-0.007 (-0.08, 0.07)	0.863		
Employment ^a	0.160 (0.12, 0.21)	<0.001	0.16 (0.11, 0.20)	<0.001
Social income assistance ^a	0.061 (-0.11, 0.23)	0.487		
Illicit income generation ^a	-0.059 (-0.11, -0.003)	0.038		
Street-based income ^a	-0.092 (-0.14, -0.04)	<0.001	-0.081 (-0.13, -0.03)	0.002
Sex work ^a	-0.099 (-0.18, -0.02)	0.015	-0.076 (-0.16, 0.006)	0.07
Total income (per \$1000) ^a	0.003 (0.002, 0.01)	<0.001	0.004 (0.003, 0.006)	<0.001
Daily cocaine use ^a	0.046 (-0.05, 0.14)	0.349		
Daily heroin injection ^a	-0.085 (-0.15, -0.02)	0.008	-0.077 (-0.14, -0.014)	0.018
Daily crack non-injection ^a	-0.054 (-0.12, 0.02)	0.131		
Daily cannabis use ^a	-0.015 (-0.07, 0.04)	0.593		
Heavy alcohol use ^a	0.036 (-0.03, 0.10)	0.287		
Overdose ^a	-0.013 (-0.08, 0.05)	0.703		
Incarceration ^a	-0.22 (-0.33, -0.10)	<0.001	-0.18 (-0.29, -0.063)	0.002
Unmet health needs ^a	-0.12 (-0.19, -0.05)	<0.001	-0.11 (-0.18, -0.042)	0.002
Unmet social needs ^a	-0.27 (-0.34, -0.20)	<0.001	-0.26 (-0.34, -0.19)	<0.001
Access to general health facilities ^a	0.13 (-0.02, 0.27)	0.084	0.15 (0.015, 0.29)	0.03
Access to substance use treatment ^a	-0.049 (-0.10, -0.0002)	0.049		
Access to social services facilities ^a	-0.13 (-0.18, -0.07)	<0.001	-0.10 (-0.16, 0.046)	<0.001
CD4 cell count (per 100 cells)	0.001 (0.06, 0.14)	0.865		
HCV	0.089 (0.001, 0.18)	0.047		
Mental illness	-0.091 (-0.17, -0.015)	0.019	-0.064 (-0.13, 0.006)	0.073

^a Variables that are time-updated referring to the last 6 months from the last interview; 95% Confidence Interval (CI)

Table 5.4 presents results of analyses examining associations between material security score and $\geq 95\%$ adherence to ART, for overall mean material security score and each factor individually. Since there were no significant associations between material security and adherence for overall score and each of the factors in bivariable analyses, multivariate models were built instead of confounding models. In multivariable models, overall mean material security score was not significantly associated with $\geq 95\%$ adherence to ART (Model 1: Adjusted odds ratio [AOR] = 1.15, 95% CI: 0.89 – 1.48). Similarly, there was no significant association between $\geq 95\%$ adherence and mean scores in Factor 1 (Model 2: AOR = 1.14, 95% CI: 0.91 – 1.43); Factor 2 (Model 3: AOR = 1.13, 95% CI: 0.93 – 1.36) and Factor 3 (Model 4: AOR = 0.97, 95% CI: 0.85 – 1.11).

Table 5.4: Longitudinal GLMM analysis of mean material score associated with ART adherence ($\geq 95\%$ vs. $<95\%$) among 623 HIV-positive PWUD in Vancouver, Canada

Characteristics	Bivariate	Multivariate [OR (95% CI)]			
	OR (95% CI)	Model (Overall)	Model 2 (Factor 1)	Model 3 (Factor 2)	Model 4 (Factor 3)
Mean material score ^a					
Overall	1.15 (0.90 – 1.49)	1.15 (0.89 – 1.48)			
Factor 1	1.14 (0.91 – 1.42)		1.14 (0.91 – 1.43)		
Factor 2	1.16 (0.97 – 1.40)			1.13 (0.93 – 1.36)	
Factor 3	0.95 (0.83 – 1.09)				0.97 (0.85 – 1.11)
Age (per 10 years)	1.26 (1.02 – 1.55)	1.19 (0.96 – 1.48)	1.19 (0.96 – 1.48)	1.20 (0.96 – 1.49)	1.22 (0.99 – 1.52)
Ancestry	1.60 (1.12 – 2.30)	1.24 (0.86 – 1.80)	1.25 (0.87 – 1.81)	1.26 (0.87 – 1.82)	1.21 (0.84 – 1.74)
Gender	1.42 (0.98 – 2.07)	1.31 (0.89 – 1.93)	1.30 (0.88 – 1.91)	1.25 (0.85 – 1.84)	1.27 (0.86 – 1.87)
Education	1.20 (0.84 – 1.73)				
Employment ^a	1.22 (0.90 – 1.67)				
Social income assistance ^a	2.10 (0.70 – 6.32)				
Illicit income generation ^a	0.75 (0.52 – 1.07)				
Street-based income ^a	0.83 (0.60 – 1.16)				
Sex work ^a	0.68 (0.42 – 1.11)				
Total income ^a	0.96 (0.92 – 1.00)				
Daily cocaine use ^a	1.47 (0.77 – 2.78)				

Characteristics	Unadjusted	Adjusted [OR (95% CI)]			
	OR (95% CI)	Model 1 (Overall)	Model 2 (Factor 1)	Model 3 (Factor 2)	Model 4 (Factor 3)
Daily heroin injection ^a	0.62 (0.42 – 0.92)	0.64 (0.43 – 0.94)	0.64 (0.43 – 0.95)	0.62 (0.42 – 0.92)	0.62 (0.42 – 0.92)
Daily crack non-injection ^a	0.70 (0.45 – 1.10)				
Daily cannabis use ^a	1.16 (0.83 – 1.62)				
Heavy alcohol use ^a	0.67 (0.45 – 1.01)	0.71 (0.47 – 1.07)	0.71 (0.47 – 1.06)	0.71 (0.48 – 1.07)	0.67 (0.45 – 1.01)
Overdose ^a	0.90 (0.56 – 1.43)				
Incarceration ^a	1.19 (0.57 – 2.51)				
Unmet health needs ^a	0.95 (0.60 – 1.49)				
Unmet social needs ^a	0.80 (0.50 – 1.28)				
Access to general health facilities ^a	0.94 (0.35 – 2.54)				
Access to substance use treatment facilities ^a	1.39 (1.03 – 1.86)	1.43 (1.06 – 1.94)	1.39 (1.03 – 1.89)	1.41 (1.04 - 1.91)	1.39 (1.02– 1.88)
Access to social service facilities ^a	1.39 (0.94 – 2.05)	1.36 (0.92 – 2.01)	1.37 (0.93 – 2.02)	1.38 (0.94 – 2.03)	1.35 (0.92 – 1.99)
CD4 cell count (per 100 cells)	1.16 (1.09 – 1.24)		1.10 (1.03 – 1.18)	1.10 (1.03 – 1.18)	1.10 (1.02 – 1.18)
HCV	1.26 (0.78 – 2.03)				
Mental illness	1.25 (0.85 – 1.84)				

^a Variables that are time-updated referring to the last 6 months from the last interview; significant associations of $p < 0.05$ are bolded

5.4 Discussion

In this study, we assessed poverty and its association with HIV care outcomes using an innovative material security scale among HIV-positive PWUD in Vancouver, Canada. We found that indicators of participants' engagement or non-engagement with different types of institutions, including the criminal justice system, social support systems and healthcare institutions, were significantly associated with material security. However, unexpectedly, when estimating the relationship between material security and the likelihood of achieving optimal adherence to ART, we found no significant associations between overall material resource scale and ART adherence, using the whole scale or each of the three previously identified factors within the scale. The implications of these findings are twofold. First, institutions are clearly implicated in material hardship among PWUD living with HIV. Second, the association of poverty and suboptimal HIV care outcomes are less relevant in a context of universal no-cost access to HIV treatment and care.

These analyses link institutional-related processes to material insecurity—including exposure to correctional environments, and having unmet health and social service needs—independently of income. That recent incarceration was linked to material insecurity in these analyses aligns with previous research demonstrating the association between incarceration and poverty [276-279]. The effect of incarceration

on material security could flow through multiple pathways, including reduced employment opportunities, financial hardship upon release, housing instability and relapse into illicit drug use, all of which may contribute to the entrenchment of poverty, socioeconomic and health inequities among incarcerated individuals [276, 277]. Similarly, individuals living in poverty may be more likely to be incarcerated because of structural pressures to engage in non-legal activity to meet their basic needs [279]. Despite existing calls for recovery and re-entry strategies for people living custody, including vocational training and substance use disorder treatment to reduce recidivism rates, provision and uptake of these services remains low for HIV-positive PWUD; such programs are rarely institutionalized within incarceration settings [277, 280]. Further, in many settings, health inequities are further perpetuated by the loss of eligibility for public benefits available to non-incarcerated individuals, such as housing and income assistance, as a collateral consequence of being incarcerated [281, 282]. These findings confirm the negative association of incarceration on the well-being of PWUD through an innovative measure of material security, highlighting the critical need of programs that could mitigate the socioeconomic cost of incarceration that have affected HIV-positive PWUD.

In this present study, unmet social services, including income and housing assistance as well as food provision, were associated with material insecurity. We

observed that lower levels of material security were also significantly associated with recent access to social services, including food banks, HIV service organizations, women's organization and employment services. These findings could indicate that PWUD who engaged with these facilities were among those who were materially deprived and require support services. The extent to which engagement improves material security levels in this population should be investigated further to fully understand the role of social support services in mitigating the negative impacts of material insecurity. In the current literature, social assistance has been the focus of social protection to reduce social and economic vulnerabilities through public and private practices [283]. For example, in British Columbia, programs and policies have been structured to facilitate PLWH with their income needs, including social assistance programs and disability benefits [284]. However, the complexity of the programs regulations and policy, as well as barriers for PLWH in accessing relevant social assistance information from government agencies may present significant barriers for PLWH to achieving material security and income stability [284]. These findings reinforce the need to explore the role of social supports, such as HIV service organizations, in reducing levels of material insecurity, specifically through efforts to coordinate actions around meeting the social needs of HIV-positive PWUD.

Similarly, we found that unmet health needs, including need for care at a hospital, drug treatment and supervised injecting facilities, were significantly associated with material insecurity. In the current literature, several studies have outlined the association between unmet health needs among PLWH and economic factors in both developed and resource-limited settings [285-290]. For example, healthcare costs, lack of health insurance and having lower income have collectively enacted barriers in obtaining health services [286, 288]. Other markers of poverty, including transportation barriers experienced by PLWH in rural areas [289] and competing demands with other necessities such as food and housing [18, 290], have also contributed towards unmet health needs among the general population of PLWH. Notably, we found a significant association between higher levels of material security and recent access to general health facilities, including hospital, clinic and the emergency department. This finding could indicate that PWUD with better levels of material security are more likely to access general health facilities compared to those having fewer material resources.

This present study demonstrated an association between fewer material resources and non-institutional-related variables, including frequent heroin injection and diagnosed mental illness. As extensively described in literature, the link between poverty and illicit drug use has been linked to low socioeconomic status, limited

employment opportunities and living in or relocating to deprived areas that may perpetuate vulnerability to illicit drug use [263, 291]. Additionally, the significant relationship between mental illness and material insecurity echoes previous findings that demonstrated the links between mental health and poverty through potential channels including stressful life experiences, lack of access to mental health treatment for marginalized populations and other unmet health or social needs [206, 292, 293]. These findings reiterate the importance of mental health and opioid use disorder treatment for HIV-positive PWUD, particularly as these services seek to support the material security of this population given the results of the current study.

Notably, a number of the variables associated with material insecurity have been previously associated with suboptimal HIV care outcomes, highlighting the role of various institutional domains in facilitating engagement in HIV care. First, previous findings in this setting and many others have described the link between illicit drug use on poorer adherence to ART [14]. However, widespread evidence, including that synthesized in Chapter 2, highlights the benefits of engaging in methadone maintenance therapy for ART outcomes among individuals living with HIV who experience opioid-use disorder [152]. Second, repeated cycles of incarceration among PWUD were associated with poor adherence to ART [21], a result of factors including the lack of support for transition into the community upon release [22]. Third, several

existing studies suggest that unmet clinical and support services impede effective engagement in HIV care among the general population of PLWH, manifested in poorer adherence to ART [205, 294-296]. For instance, a study of members of marginalized populations, including PWUD, in an urban area in the United States, identified unmet housing, transportation and financial assistance to be associated with lower levels of HIV care outcomes [205]. Thus, in determining potential areas to support health interventions, future research is needed to examine the indirect relations between material insecurity and adherence to ART through pathways involving illicit heroin use, incarceration and unmet clinical and support services.

We would anticipate that because of the implication of these factors in material insecurity found in the current study, combined with the strong evidence that they have been related to ART treatment outcomes in previous research, that material security would also be negatively associated with suboptimal ART outcomes. Failure to detect an association between material insecurity and ART adherence was therefore highly surprising, particularly given the consistently documented association between poverty and suboptimal HIV treatment patterns among vulnerable populations [297]. Specifically, in the United States, factors including food insufficiency, poverty-related stress, financial difficulties, neighbourhood deprivation and housing insecurity have been associated with non-adherence to ART in HIV

positive PWUD [17, 298, 299]. However, these studies were conducted in settings where the cost of HIV care may present a considerable socioeconomic burden to accessing care, especially for those who may be only partially insured [300]. This is in direct contrast to the current study context, where the direct financial costs of accessing HIV treatment and care, such as medications, laboratory tests, and appointments with healthcare providers, are removed in British Columbia's universal, no-cost HIV treatment context. Thus, the provision of universal HIV care to all PLHIV in the province represents an important potential explanation for the lack of association between material insecurity and ART adherence among the socioeconomically disadvantaged population observed in the current study.

While material insecurity was significantly associated with access to general health care facilities, including emergency departments and hospitals, findings in this study have shown that it was not significantly associated with adherence to ART among HIV-positive PWUD. In British Columbia's universal healthcare system, the expansion of HIV treatment coverage to the general population of PLWH has potentially reduced individual financial barriers to access HIV treatment [214]. Universal access to HIV care is therefore not limited to no-cost HIV medication, but also ensures that ART is being dispensed in the broader community, rather than restricting ART provision in mainstream health facilities. This potentially removes

geographical and transportation barriers for vulnerable populations. Moreover, there are notable health and social service facilities available for HIV-positive PWUD in the Downtown Eastside [149], including HIV/AIDS service organizations providing holistic clinical and social support to PLWH, with evidence on better HIV treatment outcomes among PWUD, including on-site delivery of ART medications [194]. The importance of support services has been demonstrated in other settings as well, wherein the use of case management to coordinate care for vulnerable populations in accessing relevant services was associated with improved adherence to ART [301]. Thus, while these findings represent potentially critical evidence on the capacity of no-cost HIV care services to mitigate the negative impacts of poverty on ART outcomes, further investigation may help discern how the interplay of low-barrier, clinical or social support services in this setting has an impact on HIV-related outcomes.

This study has several limitations to note. First, since the ACCESS cohort was recruited using community-based methods and not random sampling, it may not be representative of HIV-infected PWUD in this or other settings. Second, several explanatory variables, such as illicit drug use practices, alcohol intake and recent incarceration, were derived from participant self-report, potentially introducing recall or social desirability bias into the data. However, ART adherence was ascertained

using administrative data, therefore we have no reason to believe that participants differentially self-reported explanatory variables based on ART adherence levels.

5.5 Conclusion

Poverty among HIV-infected PWUD raise questions about causes and consequences economic and social marginalization, as well as concerns about health equity. In documenting correlates of material security among HIV-infected PWUD, this study adds empirical evidence around how the social, structural and institutional processes through which material security is produced and entrenched among marginalized PWUD living with HIV is an area of potentially important future research. While findings in this study call for further investigation on linkages between social, health and economic institutional strategies that aim to reduce poverty and improve levels of health equity, there is a strong implication for no-cost, universal access to healthcare for HIV care outcomes to potentially alleviate the impacts of socioeconomic disadvantage among members of this key population.

Chapter 6: Discussion, Future Research and Conclusions

6.1 Summary of findings, study strengths and contributions

Applying a set of perspectives from institutional theories, the current dissertation examines individual and institutional interactions linked to HIV care outcomes among HIV-positive people who use illicit drugs (PWUD). Specifically, studies in this dissertation examined a singular institutional context, within institution cross-organizational congruence, as well as between institution congruence. Key findings that emerged from specific studies described in Chapters 2 to 4 are consistent with the larger body of literature which suggests that structural factors play a prominent role in influencing individual HIV care outcomes [302-304]. This dissertation adds value to existing knowledge by applying a theoretical framework that incorporates the idea of congruency within and between organizations and institutions in terms of institutional regulation, normative standing and cultural-cognitive beliefs and linking these interactions to improvements in HIV care outcomes.

As conceptualized in Chapter 1 using the four-quadrant diagram (Figure 1.1), it has been theorized that, first, a marginal positive impact of HIV care outcome is produced when there is high organizational/institutional congruence but low

individual-organizational interaction levels; second, a marginal negative impact of HIV care outcome is produced when there is low organizational/institutional congruence and low individual-organizational interaction levels; third, a significant positive impact of HIV care outcome is produced when there is high organizational/institutional congruence and high individual-organizational interaction levels; and fourth, a negative impact of HIV care outcome is produced when there is low organizational/institutional congruence, but high individual-organizational interaction levels. Findings in this dissertation demonstrated that in conditions where there was lack of organizational/institutional congruence, suboptimal outcomes (i.e., poor adherence to HIV treatment) among PWUD were observed, whereas better outcomes were present in instances where different organizational/institutional domains may be more congruent in addressing the needs of PWUD.

Chapter 2 described the findings of a systematic review on different components of methadone maintenance therapy (MMT) services associated with improved HIV care cascade outcomes among populations or sub-populations of HIV-infected PWUD who were engaged in MMT treatment. The review identified 20 peer-reviewed studies that met the eligibility criteria. In each of these studies, at least one of the three key HIV care outcomes of interest linked to the Joint United Nations

Programme on HIV/AIDS (UNAIDS) 90-90-90 goals were reported: uptake in HIV testing; exposure to antiretroviral therapy (ART), including treatment initiation, receipt or adherence; and HIV-1 RNA viral load (VL) suppression. From the findings, MMT services demonstrated in the selected studies encompassed three models of care. The first model was composed of standard MMT care with adequate doses. The second model included standard MMT care and an additional medical component(s), such as: on-site HIV testing and HIV care; clinical management of other concurrent disorders, including viral hepatitis, mental health and tuberculosis (TB); medication dispensing, including directly administered ART (DAART); and delivery of ART medication into the community. The third model encompassed standard MMT care, an additional medical component(s), as well as informational and instrumental social support, including ART adherence counselling to address social barriers to effective engagement in HIV care; linkage and referrals to relevant support services; meals provision as well as housing and transportation assistance.

The findings of the systematic review support the relevance of institutional structures to HIV care among PWUD. These results not only highlight the interaction between HIV care and substance use disorder (SUD) treatment within healthcare system hospitals and specialized SUD treatment facilities, but also extended to include broader interactions across institutions beyond healthcare organizations, such

as government or non-government housing and income assistance as well as community-based service organizations that facilitate access to social support. Thus, this chapter contributes to the scientific literature by summarizing existing knowledge on institutional structures across health and non-health institutions and highlighting gaps in knowledge in the context of HIV and MMT treatment for PWUD.

The implementation of practices that hold the potential to favourably impact HIV-related outcomes among PWUD may occur through a range of institutionalization processes. For example, several selected studies cited the influence of external organizations, specifically local health authorities, in providing technical expertise and guidelines on the implementation of MMT services in either general health facilities or specialized SUD clinics, which included the formalization of procedures and HIV testing as part of standard MMT care for PWUD [177, 180]. These findings are consistent with earlier studies that demonstrated strong regulative institutionalization processes involving the important role of public health agencies in recommending the integration of HIV testing in opioid treatment programs [127]. Although guidelines generally serve to streamline evidence-based approaches and assist providers in locating specific services, they are typically not mandatory in nature. In practice, the implementation of these health interventions commonly relied on state regulations as authorities that enforce policies and practices consistent with

guidelines proposed by agencies that overseeing the development of public health strategies [127]. Such efforts may require strong congruency among organizations responsible for establishing and enforcing policies and those that deliver the services, in order to prioritize practices that seek to improve person-centered care (PCC) models.

In addition to the role of external organizations in influencing the delivery of MMT services potentially through regulative processes, findings from the systematic review contained meaningful information on the institutionalization of practices across different domains within healthcare. For instance, on-site HIV care that included the management of other co-infections; DAART in MMT clinics [94, 183, 184, 189]; the integration of MMT into general health facilities [190, 193], and the provision of MMT-HIV care in the community [194], have been associated with optimal adherence to ART and increased rates of VL suppression. These findings aggregate findings across studies that highlight the need to strengthen integrated services for HIV-positive PWUD through the presence of multidisciplinary teams [122, 140, 305]. These findings are also consistent with findings from qualitative studies exploring integrated clinical care, which have expounded upon elements of institutional processes that account for variation in practice integration [250], similar to the variation observed in the systematic review. One striking example is the different

treatment approaches and care philosophies across different organizations that treat HIV and opioid use disorders. Different configurations of norms, values and beliefs demonstrate that while some providers may be more oriented towards providing a fully integrated approach through a centralized, “one-stop shopping” model as a selection of service delivery [306], others may opt for decentralized models of care that expand provision of ART into SUD treatment facilities or the community [307], with both approaches being endorsed by World Health Organization (WHO).

The advantages of each model of care may be perceived differently by service providers, depending on the context and cultural background in which these health interventions are embedded. For instance, decentralized models that are brought closer to patients have been shown to benefit populations experiencing access barriers, including geographical factors or transportation costs, particularly in resource-limited settings or in rural areas [308]. Meanwhile, centralized co-located care services have potentially created the capacity to treat multiple comorbidities (e.g., HIV, SUD and mental illness) at the same time and location, reduced logistical barriers and improved monitoring of medication interaction by the same clinical team [139, 309]. Additionally, the implementation of these models of care should theoretically resonate well with values hold by service users. For instance, that these models of care are highly valued by PWUD based on their experiences in navigating through HIV

care and OAT has been well-documented in the literature, with common narratives on treatment accessibility and individual preferences concerning treatment options [307, 310]. The alignment of multiple services should thus pave way towards improving the delivery of PCC-focused care in meeting the clinical needs of PWUD.

A dearth of information on support services that can effectively supplement MMT care for HIV-positive PWUD persists despite extensive research over the past decade on the adverse impact of socioeconomic factors on HIV care outcomes among PWUD [19, 20, 57, 58, 204]. For instance, research has pointed to markers of poverty such as homelessness and unstable housing as well as socioeconomic marginalization and unmet social needs as all negatively associated with HIV care outcomes [57, 58, 204]. Research on models that address these barriers through integrated care models is an underdeveloped area. Nevertheless, studies included in this review revealed that the integration of informational support focused on advice, suggestions and directives to address social barriers, including financial, vocational and housing issues in MMT services, in addition to other forms of medical support including HIV care, have been linked with better care cascade outcomes [187, 189-192]. Notably, the implementation of informational support services in MMT care models may reflect that health organizations exhibit cultural-cognitive beliefs that support the social needs of PWUD.

Given that the systematic review did not locate studies of service models where MMT providers had direct involvement of non-health-related instrumental forms of support (e.g., social assistance departments, housing agencies), more research is needed to evaluate the effectiveness of multidisciplinary teams consisting of social or outreach workers providing instrumental social support within health facilities. Such models, and evaluations assessing their effectiveness, may represent the next phase of care provision and research in supporting members of key affected populations to overcome social and structural barriers that impede HIV care outcomes [190]. Despite there being a strong empirical and theoretical case for breaking down silos and integrating key practices across organizations, the complex institutional landscape that is navigated by HIV-positive PWUD, including programmatic barriers and policy reforms in the social welfare system, may contribute to the marginalization of disadvantaged populations [311]. In sum, the systematic review in Chapter 2, points to a lack of institutional interaction and service provision between health and social protections, and highlights a potentially effective service provision model that to date has not been widely implemented or evaluated.

Chapter 3 evaluates the association between daily pill burden and likelihood of optimal adherence to ART among PWUD enrolled in a longitudinal prospective cohort study. This study was designed to understand the medication-related practices

within single institutional domain (i.e. HIV care) and its links with adherence levels among populations with multiple barriers in attaining optimal HIV care outcomes. The major finding of this chapter revealed that a greater number of pills per day were negatively associated with achieving $\geq 95\%$ adherence. Meanwhile, the use of once-a-day single tablet regimens was positively associated with achieving $\geq 95\%$ adherence.

To our knowledge, this is one of the first studies to assess the relationship between pill burden and the likelihood of optimal adherence levels among PWUD. It used data from a long-running, community-recruited longitudinal cohort in a setting with universal no-cost access to HIV treatment and care, including medications. While the link between greater pill burden and risk of suboptimal adherence have been well established in non-drug using populations living with HIV [223-225], research on pill burden among PWUD remains scarce, with a lack of consideration of potential confounders including the social and structural factors that have been consistently associated with poor adherence in this population [31]. This study thus contributes to the scientific literature by adding valuable insight on the adverse effects of ART prescribing practices within the HIV domain on PLWH, particularly among marginalized groups.

Examining these findings in relation to the theoretical frame for this dissertation, the accumulation of existing work norms, beliefs and perceptions around

managing HIV care for PWUD may explain the association between pill burden and adherence to ART. First, a regulative process may play a role in shaping ART prescribing practices. In British Columbia, physician selection of ART regimens is guided by existing guidelines, with specific consideration placed on tolerability, toxicities, drug interaction with treatments for other co-morbidities and issues of convenience [117, 118]. Physicians' decisions in determining treatment options and regimen selection for PLWH are therefore influenced by the institutionalization of treatment guidelines via guideline endorsement by provincial and international guidelines [118]. Although modern ART is now simpler to take, without the proper consideration of PWUD's social conditions and circumstances, this study shows that the choice of a complex regimen may pose an additional barrier for members of this population to effectively adhere to treatment [228].

Second, ART prescribing practices can also be influenced by physicians' work norms in treating PLWH. As such, the link between ART prescribing practices and adherence to treatment can be established by the quality of interaction between HIV service providers and the HIV-positive individuals whom they treat. For example, greater physician experience has been linked to patients' optimal adherence to treatment [312], and improved rates of VL suppression among PWUD [313]. This is potentially because these physicians have better knowledge with which to treat HIV

and a more positive attitude towards PLWH, as well as they are more likely to prescribe combination regimens to minimize the risk of non-adherence [314, 315]. Unfortunately, adherence to ART is often inaccurately assessed by physicians, with heavy concerns on failure to identify individuals with suboptimal adherence (which is common among PWUD), leading to the prescription of complex regimens [316]. Furthermore, there may be concerns regarding potential challenges for HIV care physicians who are not addiction specialists in expanding their roles to manage individuals with substance use disorders and related co-morbidities [317].

In sum, findings from this study suggest that daily pill burden may pose a barrier to achieving optimal adherence to HIV treatment among HIV-positive PWUD. These findings point not only to the importance of prioritizing a simplified regimen for HIV-positive PWUD, but also to how prescribing practice is linked to the interaction between healthcare professionals and PWUD. This points to potential challenges related to physician beliefs about whether having a substance use disorder may prohibit the achievement of optimal adherence, which in turn lead to decisions made by treating physicians about treatment regimens that could inhibit optimal outcomes. Thus, critical to the findings on the negative association between daily pill burden and adherence to ART is that training for physicians who treat PLWH should explicitly aim to address care considerations for PWUD in addition to specific

guidelines on ART prescribing practices that would assist physicians in deciding appropriate treatment regimens.

Chapter 4 examines the association between MMT-ART co-dispensation— the receipt of both ART and MMT at the same location, including primary care physicians' offices, community pharmacies, or other health care facilities—and the likelihood of optimal adherence to ART among HIV-positive PWUD. Conceptually, this study moves away from the realm of HIV care to include SUD treatment, specifically MMT, to assess empirical evidence situated in two different health domains within a single institution. In a longitudinal multivariable model adjusting for potential confounders, MMT-ART co-dispensation at the same facility was associated with greater odds of achieving $\geq 95\%$ ART adherence, compared to non-co-dispensation. The odds of achieving optimal adherence to ART were 56% higher during periods in which MMT and ART medications were co-dispensed at the same facility. This study reiterates the potential benefits of integrated services that optimize the role of OAT in HIV care, with added knowledge that expands existing assessments that have evaluated directly administered ART with MMT doses and service integration concentrated at a single location. Instead, this longitudinal study examines multiple dispensation outlets, which are dispersed widely in the setting of British Columbia.

In British Columbia, PWUD have access to no-cost, low-threshold OAT if they are in receipt of income assistance or below a certain income threshold [318]. The dispensation of OAT is not constrained within specialized substance use clinics, but is widely accessible through local community pharmacies and physicians' offices [247]. In this model, programmatic barriers that may include long waiting lists or prerequisites to enter program that may overall limit treatment accessibility are sufficiently reduced [318]. Additionally, authorized pharmacies in treatment centers that treat HIV-positive individuals may deliver ART medication to these locations, enabling co-dispensation of OAT and ART at the same facility. This wide coverage of medication dispensation has offered extra convenience for patients who experienced difficulties in accessing mainstream health services [319]. Thus, the delivery of both ART and OAT medications in various locations supports efforts to scale up access to both treatments.

Findings in this study may indicate a strong congruence in the current study context between HIV care and SUD treatment. This is specifically related to how treating individuals with opioid use disorder can also lead to the delivery of ART and MMT medications at the same location given considerable focus on providing this type of integrated service. Such congruence can be reflective of a type of service mandated by policies, guidelines and recommendations that call for the provision of

both medications through a wider community sphere [320], rather than restricting ART and MMT to their respective treatment settings or in highly-regulated contexts [261, 320]. Additionally, the analyses of co-dispensation could serve as a proxy for organizational domains that have shared values that enhance congruence between HIV care and MMT, potentially through care-related norms and conceptual beliefs around co-dispensation. The delivery of ART in MMT settings, or vice-versa, is a practice likely only possible through shared organizational values. The results of the current study point to how this congruency in shared values across care domains is potentially supportive of improved HIV treatment outcomes, with implications for service coordination.

Chapter 5 explores how material security, and the institutional roles that affect material security, may be implicated in HIV care outcomes. Given the lack of widespread use of explicit measures of material insecurity, we first explored factors associated with material insecurity as a marker of poverty and socioeconomic marginalization among HIV-positive PWUD, explicitly including indicators of institutional interactions to discern their potential relationship with material insecurity. Consistent with previous research on the relationship between poverty and HIV care outcomes, we then estimated the association between material insecurity and adherence to ART. Findings have shown that institutional factors,

including recent incarceration and participants' inability to obtain health services (e.g., hospital, dentist, optometrist, drug treatment, needle distribution or supervised injecting services) as well as social services (e.g., housing or income assistance, support groups, food services or, social, welfare or income assistance worker) were significantly associated with material insecurity. In addition to these institutional-related variables, unstable housing, street-based income generation, frequent heroin use and mental illness were significantly associated with material insecurity. Surprisingly, despite high levels of material insecurity in this population and contrary to expectations that this would lead to poor adherence to ART, the relationship between material security and ART adherence was not statistically significant. To the best of my knowledge, this is the first study that operationalizes poverty using a robust material security measure and examines its potential association with adherence to ART among PWUD.

This study expands understandings of the role of institutions in HIV treatment outcomes to include institutions outside the domain of HIV care by assessing the involvement of non-health organizations. Findings of this exploratory research increase understandings of the relationship between institutional engagement and levels of material insecurity, as well as the association between material insecurity and ART adherence. The material security component of this research has reinforced

findings on previous studies of poverty among vulnerable populations of PLWH that institutional circumstances and the broader structural environment are strongly associated with the existence of poverty in the population [276, 287, 295, 321]. Specifically, existing disparities may have been accentuated through unmet housing, transportation financial assistance services [287, 295, 321] and engagement with the criminal justice system [276]. Individual-level barriers in obtaining social needs among PWUD, for instance may stem from having a low income to access these services [321], lower help-seeking behaviours [33], and health-related limitations such as mental illness [206], viral hepatitis or ongoing SUD [202]. These barriers potentially impede the interactions between an individual and support organizations within a complex institutional landscape.

Conceptual beliefs that preeminently account for health and social protection may vary across institutions [322]. Strategies to deliver social services to vulnerable populations can be hampered by policies that have overlooked how health concerns may affect service access, thus increasing the disparities in the provision of services and contributing in the overall health burden in vulnerable populations [323-325]. In policy reform, for example, the elimination of disability benefits on the basis of being diagnosed with a substance use disorder has led to PWUD dropping out of MMT programs due to financial constraints [325], with potentially harmful consequences

on HIV treatment related outcomes. In the context of British Columbia, health and social services are concentrated in the Downtown Eastside neighborhood [149], an area that is marked by high-intensity of illicit drug use [326]. There are notable social service facilities available for HIV-positive PWUD in this area [281], including HIV/AIDS service organizations providing holistic clinical and social support to PLWH, with evidence on better HIV treatment outcomes among PWUD [181]. While the structure of these facilities may suggest that there is a high level of organizational/institutional congruence, the lack of interaction between individuals and service providers can be problematic. Specifically, insufficient linkage between agencies that are relevant to social assistance and a PLWH may substantially reduce access to necessary services [284]. Despite the important links between material security and health, inadequate provision of supports that effectively address socioeconomic marginalization in this population may be a barrier to achieve overall well-being of a PWUD.

A core contribution of Chapter 5 is what it suggests about the potential role of universal care in mitigating the negative impacts of poverty on HIV clinical outcomes among key affected populations. Surprisingly, although poverty has previously been linked to unfavorable HIV-related outcomes [17, 298, 299], this study found no significant relationship between material insecurity and adherence to ART among

HIV-positive PWUD. Understandings of the role of economic scarcity in driving health inequalities are therefore challenged by these findings. These counterintuitive findings raise an important consideration that may help us to understand how wealth and poverty can be associated with risks or protective effects in different settings [327]. It is important to note that this research was conducted in a context of universal no-cost HIV treatment and care. The provision of universal healthcare for all PLWH may account for the lack of association between material insecurity and adherence to ART, contrary to expectations that socio-economically disadvantaged populations may experience challenges in adhering to HIV treatment. Findings in this study are aligned with existing studies that found that broader health coverage has potentially resulted in improved population health, especially among poorer people [328, 329]. Thus, free access to HIV care, including ART medications through a universal healthcare system, can be a protective policy that is uniquely situated to mitigate the cumulative effects of poverty on health.

Universal access to ART is a priority for many countries [330], but scaling up ART in many countries may depend on the coordinated participation of government, health and social institutions, individuals and communities. Thailand offers an extraordinary example of how a developing country has scaled-up ART initiatives, building on shared values of multi-partnered network of groups involved in HIV,

including non-governmental organizations who bring their knowledge on local sensitivities of the disease and experiences of core community activities around HIV care [331]. The supportive role played by these non-state institutions may have been instrumental in facilitating the government's decision to adopt the policy of providing universal access to ART for all PLWH in the country [331]. Meanwhile, in British Columbia, a key contributor to the momentum surrounding support for universal access to HIV care across the province may have been attributed to continuous research activities that have drawn on centralized HIV surveillance data. The British Columbia example highlights the potential role of academic and health institutions collaborating to provide evidence on the effectiveness of ART expansion on reduced morbidity and mortality rates among PLWH [214]. The provision of universal access to free HIV care undoubtedly requires strong political will and a successful implementation process, with evidence to support such practices. Thus, the implementation of public health approaches that seek to protect all subgroups of PLWH, particularly low-income and highly stigmatized populations, could be enhanced by the involvement and institutional alignment of a wide array of organizations, within and beyond health institutions.

In general, the conceptual framework developed and employed for this dissertation that builds on institutional theories has been a useful analytic tool to

assess the different configurations of interaction that occur within institutional environments. Chapters 2 to 5 provide significant contributions to the scientific literature on HIV care outcomes among HIV-positive PWUD by examining the potential role of institutional interaction (or a lack thereof) at different levels in changing the likelihood of a key HIV clinical outcome. Care facilities comprising different domains of health that are relevant to SUD and HIV care; the criminal justice system, including prison or jail settings; governmental departments such as social development agencies; and non-governmental organizations all appear to play a potential role in the overall well-being of HIV-positive PWUD, in terms of both adherence to treatment and material security. Modern perspectives of institutional theories recognize that the institutional environments of different organizational fields can be misaligned and act in silos [35]. A specific contribution of this dissertation is that it expands understanding of the role of service coordination by conceptualizing and theorizing the alignment of regulation, normative standing and cultural-cognitive beliefs between organizations. The results from this dissertation further support calls to focus multi-sectoral efforts on service coordination between different domains of organizations and institutions [332, 333]. Considerations of these institutional elements may provide the conceptual basis to address concerns and challenges related

to service coordination, and in particular why certain health or non-health interventions fail to be adopted, widely accepted or effective in their implementation.

A further strength of this dissertation is that studies in chapters 3 to 5 are based on longitudinal data that was gathered from two robust datasets; one, the long-running, community-recruited ACCESS cohort, provides data on socio-demographics, drug use patterns, health characteristics and institutional-related variables such as exposure to SUD treatment, the criminal justice system and social development agencies; and two, the Drug Treatment Program (DTP) dataset that consists of comprehensive information on ART dispensing data for all PLWH in British Columbia. In contrast to cross-sectional studies evaluating HIV care outcomes at a single point [181, 192, 196], the ACCESS study provides data at multiple points using repeated measures. Social processes, particularly involving institutional process and development, normally take a long time to unfold given the complex dynamics of individual-organizational interaction [334]. Thus, the use of a longitudinal study allows variations in exposure to institutional-related variables to be followed and assessed over time. Further, data for each participant is confidentially linked to the DTP dataset which enables outcome of interest to be ascertained using administrative data. Moreover, as these studies are conducted in a setting where HIV care and treatment are provided for free, it is less likely that the financial burden of HIV

treatment should compound the relationships between explanatory variables and outcome of interest. Indeed, this critical characteristic of the current study context is of specific relevance to unexpected findings of no association between material insecurity and adherence to HIV treatment.

6.2 Study limitations

This dissertation has several limitations specific to the utilization of the institutional framework and methods employed in each study chapter; and, the limitations of each empirical study have been described in their designated chapter (chapters 3 – 5). Therefore, here, the limitations that cut across the suite of studies undertaken for this dissertation are summarized.

Despite employing an institutional framework to assess HIV care outcomes among PWUD in institutional environments, this dissertation did not attempt to evaluate institutionalization processes driven by regulative, normative and cultural-cognitive pressures directly [84]. Specifically, variables that reflect organizational core features, such as managerial values on service delivery and policy-related indicators, as used in previous studies to describe institutionalization processes in the context of HIV care for PWUD [127, 128, 131, 132], were not available. Such considerations would have been more informative in elaborating barriers or facilitators of service

delivery that stem from an organizational internal structure and its immediate institutional environment. For instance, managerial perceptions on the value of harm reduction components for PWUD have been reported in one study that demonstrated that programs whose senior management supported a needle and syringe exchange program (NSEP) were more likely to recognize HIV counselling and testing as part of their program mission, compared to those who did not value NSEP [131]. While the extrapolation of direct measures of these theoretical concepts is useful, the inclusion of these variables is beyond the scope of this dissertation. Instead, this dissertation draws attention to interactions between individuals and organizations whose functions embody a range of the constituent components of institutions within and beyond healthcare. In using this institutional framing, this dissertation elaborates the degree to which institutional interaction configurations can be understood to be in tandem with a PCC approach for HIV-positive PWUD.

The systematic review in Chapter 2 is limited by the exclusive selection of MMT, as opposed to the wider options of OAT treatment including buprenorphine/naloxone and slow release oral morphine. However, there is a considerable amount of evidence describing the benefits of MMT in managing opioid dependence, including superiority in treatment retention for flexible MMT doses compared to buprenorphine [335, 336]. As MMT is the main form of OAT in a larger

global context [307, 337-339], additional research examining a broader scope of OAT-based interventions will be important moving forward as service guidelines and practices evolve. Moreover, as polysubstance use is common among individuals who use illicit opioids [173], a review of MMT services can potentially identify strategies to cope with different types of substance use in conjunction with opioid-use treatment. Similarly, in Chapter 4, the focus of SUD treatment is centered around MMT use, rather than other forms of OAT. That MMT is closely linked to HIV care among HIV positive PWUD has been consistently documented in the context of Vancouver, British Columbia [135, 162, 340], and aligns well with the outcome of interest in empirical studies in this dissertation. Although findings from studies in these two chapters may not be generalized to the drug using population who are not experiencing opioid-use disorder, given evidence that links opioid use to detrimental health and social outcomes [173], it is reasonable to assess MMT within the domain of SUD treatment for PWUD, specifically how this treatment can be optimized.

As with all observational studies, it is not possible to draw causal inferences between exposure and outcome of interest. In contrast with experimental studies, participants are not randomly assigned to the exposure of interest, i.e., the number of ART pills prescribed daily, MMT-ART co-dispensation or material security. Thus, the possible influence of confounding variables on adherence to ART cannot be entirely

eliminated. To minimize confounding effects, multivariable models are built using an *a priori* technique described in each chapter. Further, in chapter 4, in estimating the relationship between MMT-ART co-dispensation and adherence to ART, an inverse probability of treatment technique was additionally applied to produce estimates of causal effects from observational data.

Additionally, a variety of biases may potentially arise from interviews with study participants, including recall and social-desirability bias. This is particularly common especially when dealing with issues involving substance use, given that illicit drug use is criminalized and stigmatized in society. However, several techniques have been deployed during interviews to minimize the risk for recall bias, such as the use of cue cards to assist participants to recall previous events. In addressing social-desirability bias, rapport-building skills, such as asking sensitive questions at the end of the interview process, are key to gaining confidence and trust from participants.

6.3 Recommendations and future research

This dissertation has produced findings that support key actions within the institutional environments and their ability to optimally respond to the HIV pandemic, specifically in improving adherence to ART, among PWUD as a key

affected population. Additionally, it offers new directions for future studies to expand research on institutional processes and structures in the context of HIV treatment for PWUD. For each of the study chapters, recommendations for public health interventions or policy considerations, as well as suggestions for potential research are presented below. These have been developed in consideration of the theoretical and conceptual framework deployed in this dissertation.

In Chapter 2, given the scarcity of data on MMT service delivery linked to improved HIV cascade outcomes especially in areas of social support, while it is insufficient to make recommendations, it is reasonable to explore how the implementation of MMT services through a regulative process. Specifically, in this systematic review, this mechanism highlights the potential role of external organizations, such as public health authorities, in their capacity to set rules and monitor activities within organizations that deliver services to PWUD in improving HIV testing uptake. Such a strategy could potentially be replicated in other areas of care with reasonable expectation that such a process may prove beneficial to improve exposure and adherence to ART, as well as increase VL suppression rates. To date, the evaluation of HIV service delivery implemented in response to regulative processes have largely focused on HIV testing for PWUD enrolled in SUD treatment [127, 177, 180]. Attempts to improve the overall HIV care cascade outcomes among PWUD

could be informed by similar processes to institutionalize the expansion of more comprehensive service delivery and HIV care practices, including the management of comorbid disorders, medication dispensing strategies and the provision of support services. For instance, a mandate to include comprehensive services as routine could be strengthened through health policies. Specifically, the incorporation of multiple services that span relevant organizations and institutions in formal service structures through policy and guideline development may be the first step to improve coordination efforts. However, the literature provides inadequate information on this specific pathway, particularly in the context of HIV treatment for PWUD. Future research should therefore seek to expand the field's understanding of how regulative institutions with active input into cross-institutional policy processes interact with organizations responsible for service delivery.

In Chapter 3, findings on the negative contribution of greater pill burden to the likelihood of optimal adherence to ART among PWUD, within a single domain of healthcare provision. As prescribing practices are deeply rooted in physicians' knowledge in treating PLWH, it is becoming increasingly evident that efforts to strengthen and maintain up-to-date training on delivering effective HIV care for key populations is critical, particularly to those with limited exposure to patients with comorbid substance use disorders. Existing guidelines have recommended that

provision of ART medications is made under the advice of physicians with high levels of experience in HIV care, in addition to the incorporation of patients' insights on treatment options to determine their willingness to commit to complex regimens [117, 341]. However, it is less clear if these considerations are reflected in HIV care practices in the context of HIV treatment for PWUD. Future research should explore the complex interplay of physicians' prescribing norms that may or may not conform to current guidelines and whether these practices ascribe to values that would inform ART prescribing best practices for HIV-positive PWUD. Further, there is a need to identify additional support services that can potentially assist PWUD who are prescribed complex regimens to adhere to their treatment. Therefore, engaging with other forms of care, particularly treatment for SUD and social care, is relevant in mitigating the impact of pill burden on adherence to ART.

In Chapter 4, in addition to addressing individual needs to assess both treatment for HIV infection and opioid use disorder in a convenient approach through MMT-ART co-dispensation [310], this study offers insights on how to reduce the number of organizational challenges associated with the coordination of multiple services [258, 259, 309, 342]. For example, a high workload to treat both comorbidities in the absence of adequate financial resources and an insufficient number of trained medical staff [343], may jeopardize the successful co-delivery of HIV and SUD care

services. This study proposed a simplified approach to integrated care that highlights the potential benefit of MMT-ART co-dispensation. Existing studies OAT and HIV care have demonstrated evidence on integrated approaches, including on-site care management, such as treatment initiation and monitoring in conjunction with MMT provision that can be beneficial in improving HIV care outcomes [181]. This study adds to knowledge by identifying the role of co-dispensing practices as part of an integrated approach to achieve optimal adherence to ART among PWUD. To support expanded coverage of outlets that co-dispense MMT and ART, more research is needed to identify potential pathways in which MMT-ART co-dispensing practices could proliferate in non-health settings, especially, given findings of the systematic review, in community-based organizations that provide social support services.

Finally, in Chapter 5, despite high levels of material insecurity, we observed no association between material insecurity and optimal adherence to ART among PWUD. However, markers of poverty among members of this key population should continue to be researched given other implications for health and well-being among HIV positive PWUD. Given the links between material insecurity and social/structural factors, these findings have direct relevance on public health strategies to mitigate the risk of poverty in vulnerable populations. Additionally, that factors that are shown to be linked with suboptimal treatment outcomes among PWUD, such as poor housing

conditions, incarceration and unmet social needs [21, 58] are positively associated with material insecurity calls attention to the need for future research to explore how these factors are indicators of pathways with specific implications for adherence to ART independently of their impact on material security. Further, strategies that ensure universal no-cost access to HIV prevention and care services—e.g., HIV testing, treatment consultations, lab monitoring and HIV medications—may mitigate the impact of poverty on engagement in HIV care. In view of these findings, there is a justification to advance institutional initiatives that address all dimensions of well-being for HIV positive PWUD. For instance, coordination around employment services, housing and financial assistance when needed, as well as health interventions to treat mental illness and substance use disorder, are a promising way forward [28, 97, 135]. Thus, future research might aim to explore institutional processes that facilitate the alignment of work norms and values, as well as perceptions and conceptual beliefs across institutions in the context of HIV treatment for PWUD. In the current study, this might involve prioritizing the reduction of health inequity for PWUD, but research on multi-sectoral institutionalization processes and optimizing of care delivery could be applied to other domains as well.

Taken together, the studies in this dissertation mark an initial approach to using an institutional framework focused on institutional interaction and alignment

to assess HIV treatment outcomes among PWUD. There has been a recognition on the need to explore the institutionalization of evidence-based interventions in healthcare settings in the field of dissemination and implementation science [114, 344]. As such, the identification of a wider social and structural forces that are external to an organization in addition to internal organizational conditions can be informative in explaining the embeddedness and sustainability of evidence-based practices [114, 344]. This speaks not only to the importance of the policy process that shapes structural reforms within institutions, but also the role of academic institutions as “agents” to influence new institutional forms [35] through the production of scientific evidence. Specifically, academic institutions disseminate research results and increasingly focus on the translation of knowledge, thus potentially changing the institutional landscape in terms of conceptual beliefs [125]. This is particularly important to support the alignment of new evidence-based practices with existing norms and healthcare policies, as well as the context in which these practices are situated [345]. While it is useful to employ longitudinal quantitative data to inform organizational practices and the extent to which individuals interact with certain organizations over time, as conducted in this dissertation, research findings on institutional process should also be assessed through qualitative inquiries that elicit

pragmatic information, particularly around the mechanisms of change vis-à-vis values and conceptual beliefs.

In addition to academic institutions, powerful community organizations that represent key populations may similarly act as “agents” to ensure that the needs of PWUD are reflected in practices endorsed within institutional environments. Although community organizations may enforce internal rules to develop their own practices, these organizations do not often have broader institutional guideline setting functions outside their own jurisdiction. Moreover, challenges to build bridges between institutions often exist due to sociocultural barriers concerning norms, values, attitudes, and beliefs that stem from stigma and discrimination towards illicit drug use and HIV [346]. However, community-based organizations have demonstrated strong cultural competency which increases their potential not only in engaging in advocacy work to express the complex needs of key populations affected by HIV but also to establish links across health and non-health institutions [347]. For instance, treatment advocates in an HIV/AIDS service organization have assisted PLWH in navigating through systems of care through referrals to services for subsistence and health needs, potentially improving HIV care outcomes [348]. Despite their potential roles as “agents”, there is very limited research on the process of how community-based organizations serving HIV-positive PWUD seek to transmit their

values and beliefs across institutions and more importantly to address the existence and harmful impacts of stigma. Hence, a future analysis might find an institutional framework useful to investigate how cultural-cognitive beliefs and values embedded within community organizations support the service interests of HIV positive PWUD, as well as how effective service coordination could be scaled to other contexts.

6.4 Conclusions

Institutional environments, including political, social welfare, labour, health, educational, cultural and others, are deeply embedded in the fabric of society, and commonly considered a core component of our societal infrastructure [349]. The traditional health service delivery system in treating PLWH is no longer the sole institution responding to the HIV pandemic, considering the abundance of evidence on wider social and structural factors that are associated with suboptimal HIV care outcomes, particularly among PWUD. To this extent, different categories of organizations across institutions offer the potential for expanded actions to address the social-structural marginalization and barriers to services and care commonly experienced by PWUD. Although modern ART is an effective tool to prolong lives, a lack of congruence in the institutional environments might impede the creation of conditions that allow HIV-positive PWUD to adhere to ART, therefore preventing the

full benefit of scientific advances of the HIV treatment. The analyses in this dissertation describe important configurations of individual-institutional interactions at the micro-level (e.g., PWUD's engagement with specific organizations), meso-level (e.g., the synergy between organizations exhibiting the same function – for instance, health) and macro-level (e.g., the synergy across institutions exhibiting contrasting core functions). Specifically, an institutional framework is a useful conceptual approach to explore how institutional congruence, theorized as the alignment of rules, norms and cultural-cognitive beliefs across institutions, may improve HIV care outcomes among PWUD. Empirical studies in this dissertation have demonstrated that prescribing practices within the HIV domain of care and MMT-ART co-dispensation routines that integrate two domains of health were both significantly associated with achieving optimal adherence to ART. Although a wider set of institutions are correlated with material insecurity among PWUD, material insecurity was not significantly associated with adherence to ART, in the context of no-cost, free universal access to HIV care. Drawing from these studies, the misalignment between organizational and institutional structures, specifically as demonstrated by higher pill burden in ART prescribing practices, uncoordinated delivery, and service access barriers and criminal justice system involvement, collectively did not support PCC for PWUD, in terms of both optimal HIV treatment outcomes and material needs. As

regulative, normative and cultural-cognitive elements of institutional processes can be mutually reinforcing, the institutionalization of best practices through these processes is key in developing PCC public health approaches through which service coordination may reduce health inequities and promote optimal outcomes. A fuller understanding on how institutional environments are implicated in the implementation of HIV care among PWUD is critical to meet the overarching clinical and social needs of people living with HIV who use illicit drugs.

Bibliography

1. The Joint United Nations Program on HIV/AIDS (UNAIDS). 90-90-90: an ambitious treatment target to help end the AIDS epidemic. 2014. Available from: http://www.unaids.org/sites/default/files/media_asset/90-90-90_en.pdf
2. Gardner EM, McLees MP, Steiner JF, Del Rio C, Burman WJ. The spectrum of engagement in HIV care and its relevance to test-and-treat strategies for prevention of HIV infection. *Clin Infectious Dis*. 2011;52(6):793-800.
3. Risher K, Mayer KH, Beyrer C. HIV treatment cascade in MSM, people who inject drugs, and sex workers. *Curr Opin HIVAIDS*. 2015;10(6):420-9.
4. The Joint United Nations Program on HIV/AIDS (UNAIDS). The Gap Report. 2014. Available from http://files.unaids.org/en/media/unaids/contentassets/documents/unaidspublication/2014/UNAIDS_Gap_report_en.pdf
5. Bradley H, Hall HI, Wolitski RJ, Van Handel MM, Stone AE, LaFlam M, et al. Vital signs: HIV diagnosis, care, and treatment among persons living with HIV—United States, 2011. *MMWR Morb Mortal Wkly Rep*. 2014;63(47):1113-7.

6. Lourenço L, Colley G, Nosyk B, Shopin D, Montaner JS, Lima VD, et al. High levels of heterogeneity in the HIV cascade of care across different population subgroups in British Columbia, Canada. *PloS One*. 2014;9(12):e115277.
7. Helleberg M, Häggblom A, Sönnnerborg A, Obel N. HIV care in the Swedish-Danish HIV cohort 1995-2010, closing the gaps. *PloS One*. 2013;8(8):e72257.
8. Kato M, Long NH, Duong BD, Van Nguyen TT, Hai NH, Van NT, et al. Enhancing the benefits of antiretroviral therapy in Vietnam: towards ending AIDS. *Curr HIV/AIDS Rep*. 2014;11(4):487-95.
9. Degenhardt L, Mathers BM, Wirtz AL, Wolfe D, Kamarulzaman A, Carrieri MP, et al. What has been achieved in HIV prevention, treatment and care for people who inject drugs, 2010–2012? A review of the six highest burden countries. *Int J Drug Policy*. 2014;25(1):53-60.
10. British Columbia Centre for Excellence in HIV/AIDS. HIV Monitoring Quarterly Report for British Columbia. First Quarter 2018. Available from: <http://stophivaids.ca/qmr/2017-Q2/-/bc>.
11. Hinkin CH, Barclay TR, Castellon SA, Levine AJ, Durvasula RS, Marion SD, et al. Drug use and medication adherence among HIV-1 infected individuals. *AIDS Behav*. 2007;11(2):185-94.

12. Tucker JS, Burnam MA, Sherbourne CD, Kung F-Y, Gifford AL. Substance use and mental health correlates of nonadherence to antiretroviral medications in a sample of patients with human immunodeficiency virus infection. *Am J Med.* 2003;114(7):573-80.
13. Sharpe TT, Lee LM, Nakashima AK, Elam-Evans LD, Fleming PL. Crack cocaine use and adherence to antiretroviral treatment among HIV-infected black women. *J Community Health.* 2004;29(2):117-27.
14. Azar P, Wood E, Nguyen P, Luma M, Montaner J, Kerr T, et al. Drug use patterns associated with risk of non-adherence to antiretroviral therapy among HIV-positive illicit drug users in a Canadian setting: a longitudinal analysis. *BMC Infect Dis.* 2015;15(1):193.
15. Waldrop-Valverde D, Valverde E. Homelessness and psychological distress as contributors to antiretroviral nonadherence in HIV-positive injecting drug users. *AIDS Patient Care STDS.* 2005;19(5):326-34.
16. Palepu A, Milloy M, Kerr T, Zhang R, Wood E. Homelessness and adherence to antiretroviral therapy among a cohort of HIV-infected injection drug users. *J Urban Health.* 2011;88(3):545-55.

17. Surratt HL, O'Grady CL, Levi-Minzi MA, Kurtz SP. Medication adherence challenges among HIV positive substance abusers: The role of food and housing insecurity. *AIDS Care*. 2015;27(3):307-14.
18. Kidder DP, Wolitski RJ, Campsmith ML, Nakamura GV. Health status, health care use, medication use, and medication adherence among homeless and housed people living with HIV/AIDS. *Am J Public Health*. 2007;97(12):2238-45.
19. Chen Y, Kalichman SC. Synergistic effects of food insecurity and drug use on medication adherence among people living with HIV infection. *J Behav Med*. 2015;38(3):397-406.
20. Tran BX, Hwang J, Nguyen LH, Nguyen AT, Latkin NRK, Tran NK, et al. Impact of socioeconomic inequality on access, adherence, and outcomes of antiretroviral treatment Services for People Living with HIV/AIDS in Vietnam. *PloS One*. 2016;11(12):e0168687.
21. Milloy M, Kerr T, Buxton J, Rhodes T, Guillemi S, Hogg R, et al. Dose-response effect of incarceration events on nonadherence to HIV antiretroviral therapy among injection drug users. *J Infect Dis*. 2011;203(9):1215-21.

22. Small W, Wood E, Betteridge G, Montaner J, Kerr T. The impact of incarceration upon adherence to HIV treatment among HIV-positive injection drug users: a qualitative study. *AIDS Care*. 2009;21(6):708-14.
23. Brummel-Smith K, Butler D, Frieder M, Gibbs N, Henry M, et al. Person-centered care: A definition and essential elements. *J Am Geriatr Soc*. 2016;64(1):15-8.
24. World Health Organization (WHO). WHO global strategy on integrated people-centred health services 2016-2026. Placing people and communities at the centre of health services. Geneva. 2015. Available from: http://africahealthforum.afro.who.int/first-edition/IMG/pdf/the_global_strategy_for_integrated_people_centred_health_services.pdf
25. Weisner C, Schmidt LA. Expanding the frame of health services research in the drug abuse field. *Health Serv Res*. 1995;30(5):707.
26. Cheever LW. Engaging HIV-infected patients in care: their lives depend on it. The University of Chicago Press; 2007.
27. Ashman J, Conviser R, Pounds M. Associations between HIV-positive individuals' receipt of ancillary services and medical care receipt and retention. *AIDS Care*. 2002;14(sup1):109-18.

28. Wolitski RJ, Kidder DP, Pals SL, Royal S, Aidala A, Stall R, et al. Randomized Trial of the Effects of Housing Assistance on the Health and Risk Behaviors of Homeless and Unstably Housed People Living with HIV. *AIDS Behav.* 2010;14(3):493-503.
29. Nachega JB, Uthman OA, Peltzer K, Richardson LA, Mills EJ, Amekudzi K, et al. Association between antiretroviral therapy adherence and employment status: systematic review and meta-analysis. *Bull World Health Organ.* 2014;93:29-41.
30. Aggleton P, Wood K, Malcolm A, Parker R. HIV-related stigma discrimination and human rights violations: case studies of successful programmes. 2005.
31. Krüsi A, Wood E, Montaner J, Kerr T. Social and structural determinants of HAART access and adherence among injection drug users. *Int J Drug Policy.* 2010;21(1):4-9.
32. McNeil R, Small W, Wood E, Kerr T. Hospitals as a 'risk environment': an ethno-epidemiological study of voluntary and involuntary discharge from hospital against medical advice among people who inject drugs. *Soc Sci Med.* 2014;105:59-66.
33. Lang K, Neil J, Wright J, Dell CA, Berenbaum S, El-Aneed A. Qualitative investigation of barriers to accessing care by people who inject drugs in Saskatoon, Canada: perspectives of service providers. *Subst Abuse Treat Prev Policy.* 2013;8(1):35.

34. Westergaard RP, Kirk GD, Richesson DR, Galai N, Mehta SH. Incarceration predicts virologic failure for HIV-infected injection drug users receiving antiretroviral therapy. *Clin Infect Dis*. 2011;53(7):725-31.
35. Scott WR. Institutions and organizations: Ideas and interests. Sage; 2008.
36. United Nations Office on Drugs and Crime (UNODC). World Drug Report 2016. Available from: https://www.unodc.org/doc/wdr2016/WORLD_DRUG_REPORT_2016_web.pdf
37. Beyrer C, Malinowska-Sempruch K, Kamarulzaman A, Kazatchkine M, Sidibe M, Strathdee SA. Time to act: a call for comprehensive responses to HIV in people who use drugs. *Lancet*. 2010;376(9740):551-63.
38. UNAIDS, Health Canada. The Warsaw Declaration: A Framework for Effective Action on HIV/AIDS and Injecting Drug Use. Second International Policy Dialogue on HIV/AIDS. 2nd International Policy Dialogue on HIV/AIDS; November 12-14, 2003 November 12-14, 2003; Warsaw, Poland,.
39. Strathdee SA, Hallett TB, Bobrova N, Rhodes T, Booth R, Abdool R, et al. HIV and risk environment for injecting drug users: the past, present, and future. *Lancet*. 2010;376(9737):268-84.

40. Strathdee SA, Stockman JK. Epidemiology of HIV among injecting and non-injecting drug users: current trends and implications for interventions. *Curr HIV/AIDS Rep.* 2010;7(2):99-106.
41. Rhodes T, Singer M, Bourgois P, Friedman SR, Strathdee SA. The social structural production of HIV risk among injecting drug users. *Soc Sci Med.* 2005;61(5):1026-44.
42. Montaner JS, Lima VD, Barrios R, Yip B, Wood E, Kerr T, et al. Association of highly active antiretroviral therapy coverage, population viral load, and yearly new HIV diagnoses in British Columbia, Canada: a population-based study. *Lancet.* 2010;376(9740):532-9.
43. Zolopa AR, Andersen J, Komarow L, Sanne I, Sanchez A, Hogg E, et al. Early antiretroviral therapy reduces AIDS progression/death in individuals with acute opportunistic infections: a multicenter randomized strategy trial. *PloS One.* 2009;4(5):e5575.
44. Kitahata MM, Gange SJ, Abraham AG, Merriman B, Saag MS, Justice AC, et al. Effect of early versus deferred antiretroviral therapy for HIV on survival. *New Engl J Med.* 2009;360(18):1815-26.

45. Montaner J. Treatment as prevention: toward an AIDS-free generation. *Top Antivir Med.* 2013;21(3):110-4.
46. Gross R, Yip B, Re III VL, Wood E, Alexander CS, Harrigan PR, et al. A simple, dynamic measure of antiretroviral therapy adherence predicts failure to maintain HIV-1 suppression. *J Infect Dis.* 2006;194(8):1108-14.
47. Osterberg L, Blaschke T. Adherence to medication. *New Engl J Med.* 2005;353(5):487-97.
48. Paterson DL, Swindells S, Mohr J, Brester M, Vergis EN, Squier C, et al. Adherence to protease inhibitor therapy and outcomes in patients with HIV infection. *Ann Intern Med.* 2000;133(1):21-30.
49. Parienti J-J, Massari V, Descamps D, Vabret A, Bouvet E, Larouzé B, et al. Predictors of virologic failure and resistance in HIV-infected patients treated with nevirapine-or efavirenz-based antiretroviral therapy. *Clin Infect Dis.* 2004;38(9):1311-6.
50. Bangsberg DR, Perry S, Charlebois ED, Clark RA, Roberston M, Zolopa AR, et al. Non-adherence to highly active antiretroviral therapy predicts progression to AIDS. *AIDS.* 2001;15(9):1181-3.

51. Westergaard RP, Hess T, Astemborski J, Mehta SH, Kirk GD. Longitudinal changes in engagement in care and viral suppression for HIV-infected injection drug users. *AIDS*. 2013;27(16):2559.
52. Mehta S, Lucas G, Astemborski J, Kirk G, Vlahov D, Galai N. Early immunologic and virologic responses to highly active antiretroviral therapy and subsequent disease progression among HIV-infected injection drug users. *AIDS Care*. 2007;19(5):637-45.
53. Fairbairn N, Kerr T, Milloy M-J, Zhang R, Montaner J, Wood E. Crystal methamphetamine injection predicts slower HIV RNA suppression among injection drug users. *Addict Behav*. 2011;36(7):762-3.
54. Kerr T, Marshall BD, Milloy M-J, Zhang R, Guillemi S, Montaner JS, et al. Patterns of heroin and cocaine injection and plasma HIV-1 RNA suppression among a long-term cohort of injection drug users. *Drug Alcohol Depend*. 2012;124(1):108-12.
55. Sutton L, Cebulla A, Heaver C, Smith N. Drug and alcohol use as barriers to employment: a review of the literature. 2004. CRSP; 499s. Loughborough: Loughborough University.
56. Richardson L, Wood E, Li K, Kerr T. Factors associated with employment among a cohort of injection drug users. *Drug Alcohol Rev*. 2010;29(3):293-300.

57. Richardson LA, Kerr TH, Dobrer S, Puskas CM, Guillemi SA, Montaner JS, et al. Socioeconomic marginalization and plasma HIV-1 RNA nondetectability among individuals who use illicit drugs in a Canadian setting. *AIDS*. 2015;29(18):2487-95.
58. Milloy M-J, Kerr T, Bangsberg DR, Buxton J, Parashar S, Guillemi S, et al. Homelessness as a structural barrier to effective antiretroviral therapy among HIV-seropositive illicit drug users in a Canadian setting. *AIDS Patient Care STDS*. 2012;26(1):60-7.
59. Zivanovic R, Milloy M, Hayashi K, Dong H, Sutherland C, Kerr T, et al. Impact of unstable housing on all-cause mortality among persons who inject drugs. *BMC Public Health*. 2015;15(1):106.
60. Sarang A, Rhodes T, Sheon N. Systemic barriers accessing HIV treatment among people who inject drugs in Russia: a qualitative study. *Health Policy Plan*. 2013;28(7):681-91.
61. Degenhardt L, Glantz M, Evans-Lacko S, Sadikova E, Sampson N, Thornicroft G, et al. Estimating treatment coverage for people with substance use disorders: an analysis of data from the World Mental Health Surveys. *World Psychiatry*. 2017;16(3):299-307.

62. Earnshaw V, Smith L, Copenhaver M. Drug addiction stigma in the context of methadone maintenance therapy: an investigation into understudied sources of stigma. *Int J Ment Health Addict*. 2013;11(1):110-22.
63. Kourounis G, Richards BDW, Kyprianou E, Symeonidou E, Malliori M-M, Samartzis L. Opioid substitution therapy: lowering the treatment thresholds. *Drug Alcohol Depend*. 2016;161:1-8.
64. Nachega JB, Sam-Agudu NA, Mofenson LM, Schechter M, Mellors JW. Achieving Viral Suppression in 90% of People Living with HIV on Antiretroviral Therapy in Low-and Middle-Income Countries: Progress, Challenges, and Opportunities. *Clin Infect Dis*. 2018.
65. Green AR, Carrillo JE, Betancourt JR. Why the disease-based model of medicine fails our patients. *West J Med*. 2002;176(2):141.
66. World Health Organization (WHO). WHO global strategy on integrated people-centred health services 2016-2026. Placing people and communities at the centre of health services. Executive Summary. 2015. Available from: https://apps.who.int/iris/bitstream/handle/10665/180984/WHO_HIS_SDS_2015.20_en_g.pdf;jsessionid=CF18D7BC53BD3C720E92E823E4B6C69B?sequence=1

67. Barry MJ, Edgman-Levitan S. Shared decision making—the pinnacle of patient-centered care. *New Engl J Med*. 2012;366(9):780-1.
68. Dang BN, Westbrook RA, Njue SM, Giordano TP. Building trust and rapport early in the new doctor-patient relationship: a longitudinal qualitative study. *BMC Med Educ*. 2017;17(1):32.
69. Dang BN, Westbrook RA, Hartman CM, Giordano TP. Retaining HIV patients in care: the role of initial patient care experiences. *AIDS Behav*. 2016;20(10):2477-87.
70. Flickinger TE, Saha S, Moore RD, Beach MC. Higher quality communication and relationships are associated with improved patient engagement in HIV care. *J Acquir Immune Defic*. 2013;63(3):362-6.
71. Dang BN, Westbrook RA, Black WC, Rodriguez-Barradas MC, Giordano TP. Examining the link between patient satisfaction and adherence to HIV care: a structural equation model. *PLoS One*. 2013;8(1):e54729.
72. Bakken S, Holzemer WL, Brown M-A, Powell-Cope GM, Turner JG, Inouye J, et al. Relationships between perception of engagement with health care provider and demographic characteristics, health status, and adherence to therapeutic regimen in persons with HIV/AIDS. *AIDS Patient Care STDS*. 2000;14(4):189-97.

73. Salvalaggio G, McKim R, Taylor M, Wild TC. Patient–Provider Rapport in the Health Care of People Who Inject Drugs. *SAGE Open*. 2013;3(4):2158244013509252.
74. Campbell AN, Wolff M, Weaver L, Des Jarlais D, Tross S. “It’s Never Just About the HIV:” HIV Primary Care Providers’ Perception of Substance Use in the Era of “Universal” Antiretroviral Medication Treatment. *AIDS Behav*. 2018;22(3):1006-17.
75. Lloyd HM, Pearson M, Sheaff R, Asthana S, Wheat H, Sugavanam TP, et al. Collaborative action for person-centred coordinated care (P3C): an approach to support the development of a comprehensive system-wide solution to fragmented care. *Health Res Policy Syst*. 2017;15(1):98.
76. World Health Organization (WHO). WHO policy on collaborative TB/HIV activities: guidelines for national programmes and other stakeholders. 2012. Available from:
https://apps.who.int/iris/bitstream/handle/10665/44789/9789241503006_annexes_eng.pdf?sequence=2
77. World Health Organization (WHO). Scaling up of collaborative TB/HIV activities in concentrated HIV epidemic settings: a case study from India. 2015. Available from: <https://apps.who.int/iris/handle/10665/154076>

78. Tsemberis S, Gulcur L, Nakae M. Housing first, consumer choice, and harm reduction for homeless individuals with a dual diagnosis. *Am J Public Health*. 2004;94(4):651-6.
79. Marshall B, Kerr T. Housing and HIV/AIDS among people who inject drugs: Public health evidence for effective policy response. *Homelessness and health in Canada*. 2014:155-88.
80. Buchanan D, Kee R, Sadowski LS, Garcia D. The health impact of supportive housing for HIV-positive homeless patients: a randomized controlled trial. *Am J Public Health*. 2009;99(S3):S675-S80.
81. Kibicho J, Owczarzak J. A patient-centered pharmacy services model of HIV patient care in community pharmacy settings: a theoretical and empirical framework. *AIDS Patient Care STDS*. 2012;26(1):20-8.
82. Blumer H. *Symbolic interactionism: Perspective and method*: Univ of California Press; 1986.
83. McDonnell O, Lohan M, Hyde A, Porter S. *Social theory, health and healthcare*: Palgrave Macmillan; 2009.
84. Scott WR. *Institutions and organizations*: Sage Thousand Oaks, CA; 1995.

85. Hertzler JO. American social institutions: a sociological analysis: Allyn and Bacon; 1961.
86. Spencer H. The principles of sociology: Appleton; 1895.
87. Scott WR. The adolescence of institutional theory. *Adm Sci Q.* 1987;493-511.
88. Parsons T. Structure and process in modern societies: Free Pr; 1960.
89. Markus H, Zajonc RB. The cognitive perspective in social psychology. *Handbook of Social Psychology.* 1985;1:137-230.
90. Palthe J. Regulative, normative, and cognitive elements of organizations: Implications for managing change. *Management and Organizational Studies.* 2014;1(2):59.
91. Heise D, MacKinnon N. Self, identity, and social institutions: Springer; 2010.
92. Century IoMCoAtHotPits. The Future of the Public's Health in the 21st Century: National Academy Press; 2003.
93. Conway B, Prasad J, Reynolds R, Farley J, Jones M, Jutha S, et al. Directly observed therapy for the management of HIV-infected patients in a methadone program. *Clin Infect Dis.* 2004;38(Supplement 5):S402-S8.

94. Berg KM, Litwin A, Li X, Heo M, Arnsten JH. Directly observed antiretroviral therapy improves adherence and viral load in drug users attending methadone maintenance clinics: a randomized controlled trial. *Drug Alcohol Depend.* 2011;113(2):192-9.
95. WHO, UNODC, UNAIDS technical guide for countries to set targets for universal access to HIV prevention, treatment and care for injecting drug users. 2012. Available from: http://www.unaids.org/sites/default/files/sub_landing/idu_target_setting_guide_en.pdf
96. Conyers LM, Richardson LA, Datti PA, Koch LC, Misrok M. A critical review of health, social, and prevention outcomes associated with employment for people living with HIV. *AIDS Educ Prev.* 2017;29(5):475-90.
97. Conyers L, Boomer K. Examining the role of vocational rehabilitation on access to care and public health outcomes for people living with HIV/AIDS. *Disabil Rehabil.* 2014;36(14):1203-10.
98. Galtung J. The social functions of a prison. *Social Problems.* 1958;6(2):127-40.
99. Rubenstein LS, Amon JJ, McLemore M, Eba P, Dolan K, Lines R, et al. HIV, prisoners, and human rights. *Lancet.* 2016;388(10050):1202-14.

100. Meyer JP, Cepeda J, Wu J, Trestman RL, Altice FL, Springer SA. Optimization of human immunodeficiency virus treatment during incarceration: viral suppression at the prison gate. *JAMA Intern Med.* 2014;174(5):721-9.
101. Corerectional Service Canada. Evaluation Report: Correctional Service Canada (CSC)'s Health Services. 2017. Available from: <https://www.csc-scc.gc.ca/publications/005007-2017-eng.shtml>
102. Pai NP, Estes M, Moodie EE, Reingold AL, Tulskey JP. The impact of antiretroviral therapy in a cohort of HIV infected patients going in and out of the San Francisco county jail. *PLoS One.* 2009;4(9):e7115.
103. Iroh PA, Mayo H, Nijhawan AE. The HIV care cascade before, during, and after incarceration: a systematic review and data synthesis. *Am J Public Health.* 2015;105(7):e5-e16.
104. Mugavero MJ, Amico KR, Horn T, Thompson MA. The state of engagement in HIV care in the United States: from cascade to continuum to control. *Clin Infect Dis.* 2013;57(8):1164-71.
105. Bronfenbrenner U. The ecology of human development: Harvard University Press; 2009.

106. Curry N, Ham C. Clinical and service integration: the route to improved outcomes 2010. Available from: <https://www.kingsfund.org.uk/sites/files/kf/Clinical-and-service-integration-Natasha-Curry-Chris-Ham-22-November-2010.pdf>.
107. Pfeffer J, Salancik GR. The external control of organizations: A resource dependence perspective: Stanford University Press; 2003.
108. Campbell CI, Alexander JA. Health services for women in outpatient substance abuse treatment. *Health Serv Res.* 2005;40(3):781-810.
109. Johnson Jr BL. Resource Dependence Theory: A Political Economy Model of Organizations. 1995.
110. Rogers EM. Diffusion of preventive innovations. *Addict Behav.* 2002;27(6):989-93.
111. Miller RL. Innovation in HIV prevention: Organizational and intervention characteristics affecting program adoption. *Am J Community Psychol.* 2001;29(4):621-47.
112. Knudsen H, Oser C. Availability of HIV-related health services in adolescent substance abuse treatment programs. *AIDS Care.* 2009;21(10):1238-46.

113. Bui Q. A review of innovation diffusion theories and mechanisms. Proceedings of the Twentieth DIGIT 2015 Workshop. Available from: <https://aisel.aisnet.org/digit2015/11/>
114. Birken SA, Bungler AC, Powell BJ, Turner K, Clary AS, Klamon SL, et al. Organizational theory for dissemination and implementation research. *Implement Sci.* 2017;12(1):62.
115. McLeroy KR, Bibeau D, Steckler A, Glanz K. An ecological perspective on health promotion programs. *Health Educ Behav.* 1988;15(4):351-77.
116. DiMaggio P, Powell WW. The iron cage revisited: Collective rationality and institutional isomorphism in organizational fields. *Am Sociol Rev.* 1983;48(2):147-60.
117. Committee for Drug Evaluation and Therapy, British Columbia Centre for Excellence in HIV/AIDS. Therapeutic Guidelines. Antiretroviral treatment of adult HIV infection. 2018. Available from: [http://cfenet.ubc.ca/sites/default/files/uploads/Guidelines/Therapeutic-Guidelines-for-Antiretroviral-ARV-Treatment-of-Adult-HIV-Infection-\[07-JUN-2018\].pdf](http://cfenet.ubc.ca/sites/default/files/uploads/Guidelines/Therapeutic-Guidelines-for-Antiretroviral-ARV-Treatment-of-Adult-HIV-Infection-[07-JUN-2018].pdf)
118. Günthard HF, Aberg JA, Eron JJ, Hoy JF, Telenti A, Benson CA, et al. Antiretroviral treatment of adult HIV infection: 2014 recommendations of the International Antiviral Society–USA Panel. *JAMA.* 2014;312(4):410-25.

119. World Health Organization (WHO). Consolidated guidelines on HIV prevention, diagnosis, treatment and care for key populations: 2016 update. 2016. Available from: <https://www.who.int/hiv/pub/guidelines/keypopulations-2016/en/>
120. British Columbia Opioid Substitution Treatment System. Performance Measures.: Office of the Provincial Health Officer, British Columbia. 2014. Available from: <https://www2.gov.bc.ca/assets/gov/health/managing-your-health/methadone-2012-13.pdf>.
121. Flood AB, Fennell ML. Through the lenses of organizational sociology: the role of organizational theory and research in conceptualizing and examining our health care system. *J Health Soc Behav*. 1995:154-69.
122. Bouis S, Reif S, Whetten K, Scovil J, Murray A, Swartz M. An integrated, multidimensional treatment model for individuals living with HIV, mental illness, and substance abuse. *Health Soc Work*. 2007;32(4):268-78.
123. Hanson M. Institutional theory and educational change. *Educ Adm Q*. 2001;37(5):637-61.
124. Titler MG. The evidence for evidence-based practice implementation. 2008.

125. Shoveller J, DeBeck K, Montaner J. Developing Canada's Research Base for Harm Reduction and Health Equity Approaches to HIV Prevention and Treatment. *Can J Public Health*. 2010;442-4.
126. Kerr T, Mitra S, Kennedy MC, McNeil R. Supervised injection facilities in Canada: past, present, and future. *Harm Reduct J*. 2017;14(1):28.
127. D'Aunno T, Pollack HA, Jiang L, Metsch LR, Friedmann PD. HIV testing in the nation's opioid treatment programs, 2005-2011: the role of state regulations. *Health Serv Res*. 2014;49(1):230-48.
128. D'Aunno T, Sutton RI, Price RH. Isomorphism and external support in conflicting institutional environments: A study of drug abuse treatment units. *Acad Manage J*. 1991;34(3):636-61.
129. D'Aunno T, Vaughn TE, McElroy P. An institutional analysis of HIV prevention efforts by the nation's outpatient drug abuse treatment units. *J Health Soc Behav*. 1999:175-92.
130. Pollack HA, D'Aunno T, Lamar B. Outpatient substance abuse treatment and HIV prevention: An update. *J Subst Abuse Treat*. 2006;30(1):39-47.
131. Pollack HA, D'Aunno T. HIV testing and counseling in the nation's outpatient substance abuse treatment system, 1995-2005. *J Subst Abuse Treat*. 2010;38(4):307-16.

132. Frimpong JA, D'Aunno T, Helleringer S, Metsch LR. Low rates of adoption and implementation of rapid HIV testing in substance use disorder treatment programs. *J Subst Abuse Treat.* 2016;63:46-53.
133. Rhodes T. Risk environments and drug harms: a social science for harm reduction approach. *Int J Drug Policy.* 2009 ;20(3):193-201
134. Palepu A, Tyndall MW, Joy R, Kerr T, Wood E, Press N, et al. Antiretroviral adherence and HIV treatment outcomes among HIV/HCV co-infected injection drug users: the role of methadone maintenance therapy. *Drug Alcohol Depend.* 2006;84(2):188-94.
135. Reddon H, Milloy M-J, Simo A, Montaner J, Wood E, Kerr T. Methadone maintenance therapy decreases the rate of antiretroviral therapy discontinuation among HIV-positive illicit drug users. *AIDS Behav.* 2014;18(4):740-6.
136. House JS, editor Social support and social structure. *Sociological forum*; 1987: Springer.
137. Heaney CA, Israel BA. Social networks and social support. *Health behavior and health education: Theory, research, and practice.* 2008;4:189-210.

138. Witteveen E, van Ameijden EJ. Drug users and HIV-combination therapy (HAART): factors which impede or facilitate adherence. *Subst Use Misuse*. 2002;37(14):1905-25.
139. Sylla L, Bruce RD, Kamarulzaman A, Altice FL. Integration and co-location of HIV/AIDS, tuberculosis and drug treatment services. *Int J Drug Policy*. 2007;18(4):306-12.
140. Zaller N, Gillani F, Rich J. A model of integrated primary care for HIV-positive patients with underlying substance use and mental illness. *AIDS Care*. 2007;19(9):1128-33.
141. Meyer JP, Althoff AL, Altice FL. Optimizing care for HIV-infected people who use drugs: evidence-based approaches to overcoming healthcare disparities. *Clin Infect Dis*. 2013;57(9):1309-17.
142. Lucas GM, Mullen BA, Galai N, Moore RD, Cook K, McCaul ME, et al. Directly administered antiretroviral therapy for HIV-infected individuals in opioid treatment programs: results from a randomized clinical trial. *PloS One*. 2013;8(7):e68286.
143. Galea S, Vlahov D. Social determinants and the health of drug users: socioeconomic status, homelessness, and incarceration. *Public Health Rep*. 2002;117(Suppl 1):S135.

144. Blalock AC, Mcdaniel JS, Farber EW. Effect of employment on quality of life and psychological functioning in patients with HIV/AIDS. *Psychosomatics*. 2002;43(5):400-4.
145. Wood E, Hogg RS, Lima VD, Kerr T, Yip B, Marshall BD, et al. Highly active antiretroviral therapy and survival in HIV-infected injection drug users. *JAMA*. 2008;300(5):550-4.
146. Woolford A. Tainted Space: Representations of Injection Drug-Users and HIV/AIDS in Vancouver's Downtown Eastside. *BC Studies: The British Columbian Quarterly*. 2001(129):27-50.
147. Kerr T, Small W, Buchner C, Zhang R, Li K, Montaner J, et al. Syringe sharing and HIV incidence among injection drug users and increased access to sterile syringes. *Am J Public Health*. 2010;100(8):1449-53.
148. Strathdee SA, Palepu A, Cornelisse PG, Yip B, O'shaughnessy MV, Montaner JS, et al. Barriers to use of free antiretroviral therapy in injection drug users. *JAMA*. 1998;280(6):547-9.
149. Olding M, Enns B, Panagiotoglou D, Shoveller J, Harrigan PR, Barrios R, et al. A historical review of HIV prevention and care initiatives in British Columbia, Canada: 1996-2015. *J Int AIDS Soc*. 2017;20(1):21941.

150. CATIE. Maximally Assisted Therapy (MAT) Program. Available from: <https://www.catie.ca/en/pc/program/mat-program>.
151. Patterson S, Cescon A, Samji H, Cui Z, Yip B, Lepik KJ, et al. Cohort profile: HAART observational medical evaluation and research (HOMER) cohort. *Int J Epidemiol*. 2014;44(1):58-67.
152. Lappalainen L, Nolan S, Dobrer S, Puszczas C, Montaner J, Ahamad K, et al. Dose–response relationship between methadone dose and adherence to antiretroviral therapy among HIV-positive people who use illicit opioids. *Addiction*. 2015;110(8):1330-9.
153. Centers for Disease Control and Prevention. Understanding the HIV care continuum. 2014. Available from: http://www.cdc.gov/hiv/pdf/dhap_continuum.pdf.
154. Eaton EF, Saag MS, Mugavero M. Engagement in human immunodeficiency virus care: linkage, retention, and antiretroviral therapy adherence. *Infect Dis Clin North Am*. 2014;28(3):355-69.
155. Levi J, Raymond A, Pozniak A, Vernazza P, Kohler P, Hill A. Can the UNAIDS 90-90-90 target be achieved? A systematic analysis of national HIV treatment cascades. *BMJ Glob Health*. 2016;1(2):e000010.

156. Nosyk B, Montaner JS, Colley G, Lima VD, Chan K, Heath K, et al. The cascade of HIV care in British Columbia, Canada, 1996–2011: a population-based retrospective cohort study. *Lancet Infect Dis*. 2014;14(1):40-9.
157. Aaraj E, Jreij Abou Chrouch M. Drug policy and harm reduction in the Middle East and North Africa: The role of civil society. *Int J Drug Policy*. 2016;31:168-71.
158. Volkow ND, Montaner J. The urgency of providing comprehensive and integrated treatment for substance abusers with HIV. *Health Aff*. 2011;30(8):1411-9.
159. Mattick RP, Breen C, Kimber J, Davoli M. Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence. *Cochrane Database Syst Rev*. 2002;(4):CD002209.
160. Karki P, Shrestha R, Huedo-Medina TB, Copenhaver M. The impact of methadone maintenance treatment on HIV risk behaviors among high-risk injection drug users: a systematic review. *Evid Based Med Public Health*. 2016;2.
161. Nosyk B, Min JE, Evans E, Li L, Liu L, Lima VD, et al. The effects of opioid substitution treatment and highly active antiretroviral therapy on the cause-specific risk of mortality among HIV-positive people who inject drugs. *Clin Infect Dis*. 2015;61(7):1157-65.

162. Uhlmann S, Milloy MJ, Kerr T, Zhang R, Guillemi S, Marsh D, et al. Methadone maintenance therapy promotes initiation of antiretroviral therapy among injection drug users. *Addiction*. 2010;105(5):907-13.
163. Spire B, Lucas GM, Carrieri MP. Adherence to HIV treatment among IDUs and the role of opioid substitution treatment (OST). *Int J Drug Policy*. 2007;18(4):262-70.
164. Fiellin DA, O'connor PG, Chawarski M, Pakes JP, Pantalon MV, Schottenfeld RS. Methadone maintenance in primary care: a randomized controlled trial. *JAMA*. 2001;286(14):1724-31.
165. Carrieri PM, Michel L, Lions C, Cohen J, Vray M, Mora M, et al. Methadone induction in primary care for opioid dependence: a pragmatic randomized trial (ANRS Methaville). *PloS One*. 2014;9(11):e112328.
166. Fonseca J, Chang A, Chang F. Perceived Barriers and Facilitators to Providing Methadone Maintenance Treatment Among Rural Community Pharmacists in Southwestern Ontario. *J Rural Health*. 2018;34(1):23-30.
167. Haldane V, Cervero-Liceras F, Chuah FL, Ong SE, Murphy G, Sigfrid L, et al. Integrating HIV and substance use services: a systematic review. *J Int AIDS Soc*. 2017;20(1).

168. Low AJ, Mburu G, Welton NJ, May MT, Davies CF, French C, et al. Impact of opioid substitution therapy on antiretroviral therapy outcomes: a systematic review and meta-analysis. *Clin Infect Dis*. 2016;63(8):1094-104.
169. Binford MC, Kahana SY, Altice FL. A systematic review of antiretroviral adherence interventions for HIV-infected people who use drugs. *Curr HIV/AIDS Rep*. 2012;9(4):287-312.
170. World Health Organization (WHO). Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. 2016. Available from: <https://www.who.int/hiv/pub/arv/arv-2016/en/>
171. Kuchinad KE, Hutton HE, Monroe AK, Anderson G, Moore RD, Chander G. A qualitative study of barriers to and facilitators of optimal engagement in care among PLWH and substance use/misuse. *BMC Res Notes*. 2016;9(1):229.
172. George S, Garth B, Wohl AR, Galvan FH, Garland W, Myers HF. Sources and types of social support that influence engagement in HIV care among Latinos and African Americans. *J Health Care Poor Underserved*. 2009;20(4):1012.
173. Degenhardt L, Hall W. Extent of illicit drug use and dependence, and their contribution to the global burden of disease. *Lancet*. 2012;379(9810):55-70.

174. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med.* 2009;151(4):264-9.
175. Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ.* 2016;355:i4919.
176. Lappalainen L, Nolan S, Dobrer S, Puscas C, Montaner J, Ahamad K, et al. Dose-response relationship between methadone dose and adherence to antiretroviral therapy among HIV-positive people who use illicit opioids. *Addiction.* 2015;110(8):1330-9.
177. Pang L, Hao Y, Mi G, Wang C, Luo W, Rou K, et al. Effectiveness of first eight methadone maintenance treatment clinics in China. *AIDS.* 2007;21:S103-S7.
178. Tran BX, Nguyen LH, Nguyen LP, Nguyen CT, Phan HTT, Latkin CA. Methadone maintenance treatment promotes referral and uptake of HIV testing and counselling services amongst drug users and their partners. *PloS One.* 2016;11(4):e0152804.

179. Seewald R, Bruce RD, Elam R, Tio R, Lorenz S, Friedmann P, et al. Effectiveness and feasibility study of routine HIV rapid testing in an urban methadone maintenance treatment program. *Am J Drug Alcohol Abuse*. 2013;39(4):247-51.
180. Xia YH, Chen W, Tucker JD, Wang C, Ling L. HIV and hepatitis C virus test uptake at methadone clinics in Southern China: opportunities for expanding detection of bloodborne infections. *BMC Public Health*. 2013;13:899.
181. Achmad YM, Istiqomah AN, Iskandar S, Wisaksana R, van Crevel R, Hidayat T. Integration of methadone maintenance treatment and HIV care for injecting drug users: a cohort study in Bandung, Indonesia. *Acta Med Indones*. 2009;41 Suppl 1:23-7.
182. Hung V, Nguyen ST, Tieu VTT, Nguyen TTT, Duong TH, Lyss S, et al. Evaluation of the integrated clinic model for HIV/AIDS services in Ho Chi Minh City, Viet Nam, 2013-2014. *Public Health Action*. 2016;6(4):255-60.
183. Sanchez GV, Llibre JM, Torrens M, Sanvisens A, Mateu G, Knobel H, et al. Effectiveness of antiretroviral therapy in HIV-1-infected active drug users attended in a drug abuse outpatient treatment facility providing a multidisciplinary care strategy. *Curr HIV Res*. 2012;10(4):356-63.
184. Lucas GM, Mullen AB, Weidle PJ, Hader S, McCaul ME, Moore RD. Directly Administered Antiretroviral Therapy in Methadone Clinics Is Associated with

Improved HIV Treatment Outcomes, Compared with Outcomes among Concurrent Comparison Groups. *Clin Infect Dis*. 2006;42(11):1628-35.

185. Safren SA, O'Cleirigh CM, Bullis JR, Otto MW, Stein MD, Pollack MH. Cognitive behavioral therapy for adherence and depression (CBT-AD) in HIV-infected injection drug users: a randomized controlled trial. *J Consult Clin Psychol*. 2012;80(3):404-15.

186. Lambers FAE, Stolte IG, van den Berg CHSB, Coutinho RA, Prins M. Harm reduction intensity—Its role in HAART adherence amongst drug users in Amsterdam. *Int J Drug Policy*. 2011;22(3):210-8.

187. Rothman J, Rudnick D, Slifer M, Agins B, Heiner K, Birkhead G. Co-located substance use treatment and HIV prevention and primary care services, New York State, 1990–2002: a model for effective service delivery to a high-risk population. *J Urban Health*. 2007;84(2):226-42.

188. Bachireddy C, Soule MC, Izenberg JM, Dvoryak S, Dumchev K, Altice FL. Integration of health services improves multiple healthcare outcomes among HIV-infected people who inject drugs in Ukraine. *Drug Alcohol Depend*. 2014;134:106-14.

189. Cooperman NA, Heo M, Berg KM, Li X, Litwin AH, Nahvi S, et al. Impact of adherence counseling dose on antiretroviral adherence and HIV viral load among HIV-infected methadone maintained drug users. *AIDS Care*. 2012;24(7):828-35.
190. Parashar S, Palmer AK, O'Brien N, Chan K, Shen A, Coulter S, et al. Sticking to It: The Effect of Maximally Assisted Therapy on Antiretroviral Treatment Adherence Among Individuals Living with HIV Who are Unstably Housed. *AIDS Behav*. 2011;15(8):1612.
191. Sorensen JL, Haug NA, Delucchi KL, Gruber V, Kletter E, Batki SL, et al. Voucher reinforcement improves medication adherence in HIV-positive methadone patients: a randomized trial. *Drug Alcohol Depend*. 2007;88(1):54-63.
192. Simeone C, Shapiro B, Lum PJ. Integrated HIV care is associated with improved engagement in treatment in an urban methadone clinic. *Addict Sci Clin Pract*. 2017;12(1):19.
193. Fingerhood M, Rastegar DA, Jasinski D. Five year outcomes of a cohort of HIV-infected injection drug users in a primary care practice. *J Addict Dis*. 2006;25(2):33-8.
194. Ti L, Dong H, Kerr T, Turje R, Parashar S, Min J, et al. The effect of engagement in an HIV/AIDS integrated health programme on plasma HIV-1 RNA suppression

among HIV-positive people who use illicit drugs: a marginal structural modelling analysis. *HIV Med.* 2017.

195. Arnsten JH, Demas PA, Farzadegan H, Grant RW, Gourevitch MN, Chang C-J, et al. Antiretroviral therapy adherence and viral suppression in HIV-infected drug users: comparison of self-report and electronic monitoring. *Clin Infect Dis.* 2001;33(8):1417-23.

196. Bachireddy C, Soule MC, Izenberg JM, Dvoryak S, Dumchev K, Altice FL. Integration of health services improves multiple healthcare outcomes among HIV-infected people who inject drugs in Ukraine. *Drug Alcohol Depend.* 2014;134:106-14.

197. Bazazi AR, Vijay A, Crawford FW, Heimer R, Kamarulzaman A, Altice FL. HIV Testing and awareness of HIV status among people who inject drugs in greater Kuala Lumpur, Malaysia. *AIDS Care.* 2017:1-6.

198. Safren SA, O'cleirigh CM, Bullis JR, Otto MW, Stein MD, Pollack MH. Cognitive behavioral therapy for adherence and depression (CBT-AD) in HIV-infected injection drug users: a randomized controlled trial. *J Consult Clin Psychol.* 2012;80(3):404.

199. Berg KM, Litwin AH, Li X, Heo M, Arnsten JH. Lack of sustained improvement in adherence or viral load following a directly observed antiretroviral therapy intervention. *Clin Infect Dis*. 2011;53(9):936-43.
200. Cooperman NA, Heo M, Berg KM, Li X, Litwin AH, Nahvi S, et al. Impact of adherence counseling dose on antiretroviral adherence and HIV viral load among HIV-infected methadone maintained drug users. *AIDS Care*. 2012;24(7):828-35.
201. Dieterich D, Fusco J, Henegar C, D'Amico R, Schulman K, Zelt S, et al., editors. HIV/hepatitis C co-infected patients are significantly more complex to manage than HIV mono-infected patients in a large cohort of treatment-naive, HIV-positive individuals. *J Int AIDS Soc*.
202. Kamarulzaman A, Altice FL. The challenges in managing HIV in people who use drugs. *Curr Opin Infect Dis*. 2015;28(1):10.
203. Egan JE, Netherland J, Gass J, Finkelstein R, Weiss L, Collaborative B. Patient perspectives on buprenorphine/naloxone treatment in the context of HIV care. *JAIDS J Acquir Immune Defic Syndr*. 2011;56:S46-S53.
204. Kennedy MC, Kerr T, McNeil R, Parashar S, Montaner J, Wood E, et al. Residential eviction and risk of detectable plasma HIV-1 RNA viral load among HIV-positive people who use drugs. *AIDS Behav*. 2017;21(3):678-87.

205. Rumptz MH, Tobias C, Rajabiun S, Bradford J, Cabral H, Young R, et al. Factors associated with engaging socially marginalized HIV-positive persons in primary care. *AIDS Patient Care STDS*. 2007;21(S1):S-30-S-9.
206. Wang L, Panagiotoglou D, Min JE, DeBeck K, Milloy M, Kerr T, et al. Inability to access health and social services associated with mental health among people who inject drugs in a Canadian setting. *Drug Alcohol Depend*. 2016;168:22-9.
207. Dugosh K, Abraham A, Seymour B, McLoyd K, Chalk M, Festinger D. A systematic review on the use of psychosocial interventions in conjunction with medications for the treatment of opioid addiction. *J Addict Med*. 2016;10(2):91.
208. Hesse M, Pedersen MU. Easy-access services in low-threshold opiate agonist maintenance. *Int J Ment Health Addict*. 2008;6(3):316-24.
209. Ayon S, Ndimbii J, Jeneby F, Abdulrahman T, Mlewa O, Wang B, et al. Barriers and facilitators of access to HIV, harm reduction and sexual and reproductive health services by women who inject drugs: role of community-based outreach and drop-in centers. *AIDS Care*. 2018;30(4):480-7.
210. Des Jarlais DC, McKnight C, Feelemyer J, Arasteh K, Tross S, Campbell AN, et al. Heterosexual male and female disparities in HIV infection at the end of an

epidemic: HIV infection among persons who inject drugs in New York City, 2001-2005 and 2011-2015. *Drug Alcohol Depend.* 2018.

211. El-Bassel N, Strathdee SA. Women who use or inject drugs: an action agenda for women-specific, multilevel and combination HIV prevention and research. *J Acquir Immune Defic Syndr.* 2015;69(Suppl 2):S182.

212. Springer SA, Qiu J, Saber-Tehrani AS, Altice FL. Retention on buprenorphine is associated with high levels of maximal viral suppression among HIV-infected opioid dependent released prisoners. *PloS One.* 2012;7(5):e38335.

213. Abdool Karim SS, Naidoo K, Grobler A, Padayatchi N, Baxter C, Gray A, et al. Timing of initiation of antiretroviral drugs during tuberculosis therapy. *New Engl J Med.* 2010;362(8):697-706.

214. Montaner JS, Lima VD, Harrigan PR, Lourenço L, Yip B, Nosyk B, et al. Expansion of HAART coverage is associated with sustained decreases in HIV/AIDS morbidity, mortality and HIV transmission: the “HIV Treatment as Prevention” experience in a Canadian setting. *PloS One.* 2014;9(2):e87872.

215. Thompson MA, Aberg JA, Hoy JF, Telenti A, Benson C, Cahn P, et al. Antiretroviral treatment of adult HIV infection: 2012 recommendations of the International Antiviral Society–USA panel. *JAMA.* 2012;308(4):387-402.

216. Altice FL, Kamarulzaman A, Soriano VV, Schechter M, Friedland GH. Treatment of medical, psychiatric, and substance-use comorbidities in people infected with HIV who use drugs. *Lancet*. 2010;376(9738):367-87.
217. Palepu A, Horton NJ, Tibbetts N, Meli S, Samet JH. Uptake and adherence to highly active antiretroviral therapy among HIV-infected people with alcohol and other substance use problems: the impact of substance abuse treatment. *Addiction*. 2004;99(3):361-8.
218. Wood E, Montaner JS, Chan K, Tyndall MW, Schechter MT, Bangsberg D, et al. Socioeconomic status, access to triple therapy, and survival from HIV-disease since 1996. *AIDS*. 2002;16(15):2065-72.
219. Bouhnik A-D, Chesney M, Carrieri P, Gallais H, Moreau J, Moatti J-P, et al. Nonadherence among HIV-infected injecting drug users: the impact of social instability. *J Acquir Immune Defic Syndr*. 2002;31:S149-53.
220. Evans L, Strathdee SA. A roof is not enough: unstable housing, vulnerability to HIV infection and the plight of the SRO. *Int J Drug Policy*. 2006;17(2):115-7.
221. Ahern J, Stuber J, Galea S. Stigma, discrimination and the health of illicit drug users. *Drug Alcohol Depend*. 2007;88(2-3):188-96.

222. Stone VE, Jordan J, Tolson J, Miller R, Pilon T. Perspectives on adherence and simplicity for HIV-infected patients on antiretroviral therapy: self-report of the relative importance of multiple attributes of highly active antiretroviral therapy (HAART) regimens in predicting adherence. *J Acquir Immune Defic Syndr.* 2004;36(3):808-16.
223. Stone VE, Hogan JW, Schuman P, Rompalo AM, Howard AA, Korkontzelou C, et al. Antiretroviral regimen complexity, self-reported adherence, and HIV patients' understanding of their regimens: survey of women in the her study. *J Acquir Immune Defic Syndr.* 2001;28(2):124-31.
224. Buscher A, Hartman C, Kallen MA, Giordano TP. Impact of antiretroviral dosing frequency and pill burden on adherence among newly diagnosed, antiretroviral-naive HIV patients. *Int J STD AIDS.* 2012;23(5):351-5.
225. Bangsberg DR, Ragland K, Monk A, Deeks SG. A single tablet regimen is associated with higher adherence and viral suppression than multiple tablet regimens in HIV+ homeless and marginally housed people. *AIDS.* 2010;24(18):2835.
226. Parienti J-J, Bangsberg DR, Verdon R, Gardner EM. Better adherence with once-daily antiretroviral regimens: a meta-analysis. *Clin Infect Dis.* 2009;48(4):484-8.

227. Nachega JB, Parienti J-J, Uthman OA, Gross R, Dowdy DW, Sax PE, et al. Lower pill burden and once-daily antiretroviral treatment regimens for HIV infection: a meta-analysis of randomized controlled trials. *Clin Infect Dis*. 2014;58(9):1297-307.
228. Sax PE, Meyers JL, Mugavero M, Davis KL. Adherence to antiretroviral treatment and correlation with risk of hospitalization among commercially insured HIV patients in the United States. *PloS One*. 2012;7(2):e31591.
229. Hernández Arroyo M, Cabrera Figueroa S, Sepúlveda Correa R, Valverde Merino M, Luna Rodrigo G, Domínguez-Gil Hurlé A, et al. Influence of the number of daily pills and doses on adherence to antiretroviral treatment: a 7-year study. *J Clin Pharm Ther*. 2016;41(1):34-9.
230. Gianotti N, Galli L, Bocchiola B, Cahua T, Panzini P, Zandona D, et al. Number of daily pills, dosing schedule, self-reported adherence and health status in 2010: a large cross-sectional study of HIV-infected patients on antiretroviral therapy. *HIV Med*. 2013;14(3):153-60.
231. Gallant JE, DeJesus E, Arribas JR, Pozniak AL, Gazzard B, Campo RE, et al. Tenofovir DF, emtricitabine, and efavirenz vs. zidovudine, lamivudine, and efavirenz for HIV. *New Engl J Med*. 2006;354(3):251-60.

232. Portsmouth S, Osorio J, McCormick K, Gazzard B, Moyle G. Better maintained adherence on switching from twice-daily to once-daily therapy for HIV: a 24-week randomized trial of treatment simplification using stavudine prolonged-release capsules. *HIV Med.* 2005;6(3):185-90.
233. Tyndall MW, Currie S, Spittal P, Li K, Wood E, O'shaughnessy MV, et al. Intensive injection cocaine use as the primary risk factor in the Vancouver HIV-1 epidemic. *AIDS.* 2003;17(6):887-93.
234. Wood E, Hogg RS, Yip B, Harrigan PR, O'Shaughnessy MV, Montaner JS. Effect of medication adherence on survival of HIV-infected adults who start highly active antiretroviral therapy when the CD4+ cell count is 0.200 to 0.350× 10⁹ cells/L. *Ann Intern Med.* 2003;139(10):810-6.
235. Wood E, Montaner J, Yip B, Tyndall MW, Schechter MT, O'Shaughnessy MV, et al. Adherence to antiretroviral therapy and CD4 T-cell count responses among HIV-infected injection drug users. *Antivir Ther.* 2004;9(2):229-35.
236. Airoidi M, Zaccarelli M, Bisi L, Bini T, Antinori A, Mussini C, et al. One-pill once-a-day HAART: a simplification strategy that improves adherence and quality of life of HIV-infected subjects. *Patient Prefer Adherence.* 2010;4:115.

237. Platt L, Easterbrook P, Gower E, McDonald B, Sabin K, McGowan C, et al. Prevalence and burden of HCV co-infection in people living with HIV: a global systematic review and meta-analysis. *Lancet Infect Dis*. 2016;16(7):797-808.
238. Sulkowski MS. Hepatitis C virus infection in HIV-infected patients. *Curr Infect Dis Rep*. 2001;3(5):469-76.
239. Getahun H, Gunneberg C, Sculier D, Verster A, Raviglione M. Tuberculosis and HIV in people who inject drugs: evidence for action for tuberculosis, HIV, prison and harm reduction services. *Curr Opin HIV AIDS*. 2012;7(4):345-53.
240. Buckingham E, Schrage E, Cournos F. Why the treatment of mental disorders is an important component of HIV prevention among people who inject drugs. *Adv Prev Med*. 2013.
241. Ford N, Nachega JB, Engel ME, Mills EJ. Directly observed antiretroviral therapy: a systematic review and meta-analysis of randomised clinical trials. *Lancet*. 2010;374(9707):2064-71.
242. Hogg RS, Rhone SA, Yip B, Sherlock C, Conway B, Schechter MT, et al. Antiviral effect of double and triple drug combinations amongst HIV-infected adults: lessons from the implementation of viral load-driven antiretroviral therapy. *AIDS*. 1998;12(3):279-84.

243. Mugavero MJ, Amico KR, Westfall AO, Crane HM, Zinski A, Willig JH, et al. Early retention in HIV care and viral load suppression: implications for a test and treat approach to HIV prevention. *J Acquir Immune Defic Syndr*. 2012;59(1):86.
244. Sohler NL, Wong MD, Cunningham WE, Cabral H, Drainoni M-L, Cunningham CO. Type and pattern of illicit drug use and access to health care services for HIV-infected people. *AIDS Patient Care STDS*. 2007;21(S1):S-68-S-76.
245. Amato L, Davoli M, Perucci CA, Ferri M, Faggiano F, Mattick RP. An overview of systematic reviews of the effectiveness of opiate maintenance therapies: available evidence to inform clinical practice and research. *J Subst Abuse Treat*. 2005;28(4):321-9.
246. Wood E, Hogg RS, Kerr T, Palepu A, Zhang R, Montaner JS. Impact of accessing methadone on the time to initiating HIV treatment among antiretroviral-naive HIV-infected injection drug users. *AIDS*. 2005;19(8):837-9.
247. Ahamad K, Hayashi K, Nguyen P, Dobrer S, Kerr T, Schütz CG, et al. Effect of low-threshold methadone maintenance therapy for people who inject drugs on HIV incidence in Vancouver, BC, Canada: an observational cohort study. *Lancet HIV*. 2015;2(10):e445-e50.
248. Bart G. Maintenance medication for opiate addiction: the foundation of recovery. *J Addict Dis*. 2012;31(3):207-25.

249. D'Aunno T. The role of organization and management in substance abuse treatment: Review and roadmap. *J Subst Abuse Treat.* 2006;31(3):221-33.
250. Guise A, Seguin M, Mburu G, McLean S, Grenfell P, Islam Z, et al. Integrated opioid substitution therapy and HIV care: a qualitative systematic review and synthesis of client and provider experiences. *AIDS Care.* 2017;29(9):1119-28.
251. Nahvi S, Litwin AH, Heo M, Berg KM, Li X, Arnsten JH. Directly observed antiretroviral therapy eliminates adverse effects of active drug use on adherence. *Drug Alcohol Depend.* 2012;120(1-3):174-80.
252. Milloy M, Kerr T, Buxton J, Rhodes T, Krusi A, Guillemi S, et al. Social and environmental predictors of plasma HIV RNA rebound among injection drug users treated with antiretroviral therapy. *J Acquir Immune Defic Syndr.* 2012;59(4):393.
253. Austin PC, Stuart EA. Moving towards best practice when using inverse probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies. *Stat Med.* 2015;34(28):3661-79.
254. Petersen ML, Wang Y, Van Der Laan MJ, Bangsberg DR. Assessing the effectiveness of antiretroviral adherence interventions: using marginal structural models to replicate the findings of randomized controlled trials. *J Acquir Immune Defic Syndr.* 2006;43:S96-S103.

255. Cole SR, Hernán MA. Constructing inverse probability weights for marginal structural models. *Am J Epidemiol.* 2008;168(6):656-64.
256. Barker B, Adams E, Wood E, Kerr T, DeBeck K, Dong H, et al. Engagement in Maximally-Assisted Therapy and Adherence to Antiretroviral Therapy Among a Cohort of Indigenous People Who Use Illicit Drugs. *AIDS Behav.* 2018:1-9.
257. Goggin K, Liston RJ, Mitty JA. Modified directly observed therapy for antiretroviral therapy: a primer from the field. *Public Health Rep.* 2007;122(4):472-81.
258. Lin C, Cao X, Li L. Integrating antiretroviral therapy in methadone maintenance therapy clinics: service provider perceptions. *Int J Drug Policy.* 2014;25(6):1066-70.
259. European Centre for Disease Prevention and Control, European Monitoring Centre for Drugs and Drug Addiction. Thematic report: People who inject drugs. Monitoring implementation of the Dublin Declaration on Partnership to Fight HIV/AIDS in Europe and Central Asia: 2014 progress report.
260. Altice FL, Maru DS-R, Bruce DR, Springer SA, Friedland GH. Superiority of Directly Administered Antiretroviral Therapy over Self-Administered Therapy among HIV-Infected Drug Users: A Prospective, Randomized, Controlled Trial. *Clin Infect Dis.* 2007;45(6):770-8.

261. Bobrova N, Sarang A, Stuikyte R, Lezhentsev K. Obstacles in provision of anti-retroviral treatment to drug users in Central and Eastern Europe and Central Asia: a regional overview. *Int J Drug Policy*. 2007;18(4):313-8.
262. Wagstaff A. Poverty and health sector inequalities. *Bull World Health Organ*. 2002;80:97-105.
263. Jaffe K, Dong H, Godefroy A, Boutang D, Hayashi K, Milloy M-J, et al. Informal recycling, income generation and risk: Health and social harms among people who use drugs. *Int J Drug Policy*. 2018;60:40-6.
264. Bradshaw J, Finch N. Overlaps in dimensions of poverty. *J Soc Policy*. 2003;32(4):513-25.
265. Long C, DeBeck K, Feng C, Montaner J, Wood E, Kerr T. Income level and drug related harm among people who use injection drugs in a Canadian setting. *Int J Drug Policy*. 2014;25(3):458-64.
266. Iceland J, Bauman KJ. Income poverty and material hardship: how strong is the association? *J Socio Econ*. 2007;36(3):376-96.
267. World Health Organization (WHO). A conceptual framework for action on the social determinants of health. 2010. Available from:

https://www.who.int/sdhconference/resources/ConceptualframeworkforactiononSDH_eng.pdf

268. Ompad DC, Nandi V, Cerdá M, Crawford N, Galea S, Vlahov D. Beyond income: Material resources among drug users in economically-disadvantaged New York City neighborhoods. *Drug Alcohol Depend.* 2012;120(1-3):127-34.

269. Klein S. Long overdue: why BC needs a poverty reduction plan: Canadian Centre for Policy Alternatives; 2017.

270. Druyts E, Rachlis B, Lima V, Harvard S, Zhang W, Brandson E, et al. Mortality is influenced by locality in a major HIV/AIDS epidemic. *HIV Med.* 2009;10(5):274-81.

271. Prosperity for All through a Healthy Communities Approach. Vancouver's Recommendations to the Federal Government's National Poverty Reduction Strategy – July 2017. In: Vancouver Co, editor. 2017. Available from: <https://vancouver.ca/files/cov/prosperity-for-all-through-a-healthy-communities-approach.pdf>

272. Ompad DC, Palamar JJ, Krause KD, Kapadia F, Halkitis PN. Reliability and Validity of a Material Resources Scale and Its Association With Depression Among Young Men Who Have Sex With Men: The P18 Cohort Study. *Am J Mens Health.* 2016:1557988316651206.

273. Dunst CJ, Leet HE. Measuring the adequacy of resources in households with young children. *Child Care Health Dev.* 1987;13(2):111-25.
274. van Draanen J, Hayashi, K., Milloy, M.J., Shulha, H., Richardson, L. Advances in Measurement of Material Security and its Effect on Exposure to Violence Among People Who Use Drugs. Manuscript submitted for publication.
275. Joseph B, Kerr T, Puskas CM, Montaner J, Wood E, Milloy M-J. Factors linked to transitions in adherence to antiretroviral therapy among HIV-infected illicit drug users in a Canadian setting. *AIDS Care.* 2015;27(9):1128-36.
276. Krishnan A, Wickersham JA, Chitsaz E, Springer SA, Jordan AO, Zaller N, et al. Post-release substance abuse outcomes among HIV-infected jail detainees: results from a multisite study. *AIDS Behav.* 2013;17(2):171-80.
277. Freudenberg N, Daniels J, Crum M, Perkins T, Richie BE. Coming home from jail: the social and health consequences of community reentry for women, male adolescents, and their families and communities. *Am J Public Health.* 2008;98(Supplement_1):S191-S202.
278. Van Olphen J, Eliason MJ, Freudenberg N, Barnes M. Nowhere to go: How stigma limits the options of female drug users after release from jail. *Subst Abuse Treat Prev Policy.* 2009;4(1):10.

279. DeBeck K, Shannon K, Wood E, Li K, Montaner J, Kerr T. Income generating activities of people who inject drugs. *Drug Alcohol Depend.* 2007;91(1):50-6.
280. Bozinoff N, DeBeck K, Milloy M, Nosova E, Fairbairn N, Wood E, et al. Utilization of opioid agonist therapy among incarcerated persons with opioid use disorder in Vancouver, Canada. *Drug Alcohol Depend.* 2018;193:42-7.
281. Tyler ET, Brockmann B. Returning Home: Incarceration, Reentry, Stigma and the Perpetuation of Racial and Socioeconomic Health Inequity. *J Law Med Ethics.* 2017;45(4):545-57.
282. Pinard M. Collateral consequences of criminal convictions: Confronting issues of race and dignity. *NYUL Rev.* 2010;85:457.
283. United Nations Children's Funds (UNICEF). UNICEF social protection strategic framework. New York: UNICEF. 2012. Available from: [https://www.unicef.org/socialpolicy/files/UNICEF Social Protection Strategic Framework full doc std.pdf](https://www.unicef.org/socialpolicy/files/UNICEF_Social_Protection_Strategic_Framework_full_doc_std.pdf)
284. Elliott R. Support for survival: barriers to income security for people living with HIV/AIDS and directions for reform: Canadian HIV/AIDS Legal Network; 2005. Available from: <http://www.aidslaw.ca/site/wp-content/uploads/2013/11/Income+Security+-+Rpt+-+ENG.pdf>

285. Peters DH, Garg A, Bloom G, Walker DG, Brieger WR, Rahman MH. Poverty and access to health care in developing countries. *Ann N Y Acad Sci.* 2008;1136(1):161-71.
286. Shi L, Stevens GD. Vulnerability and unmet health care needs: the influence of multiple risk factors. *J General Intern Med.* 2005;20(2):148-54.
287. Weiser J, Beer L, Frazier EL, Patel R, Dempsey A, Hauck H, et al. Service delivery and patient outcomes in Ryan White HIV/AIDS Program-funded and-nonfunded health care facilities in the United States. *JAMA Intern Med.* 2015;175(10):1650-9.
288. Sibley LM, Glazier RH. Reasons for self-reported unmet healthcare needs in Canada: a population-based provincial comparison. *Healthcare Policy.* 2009;5(1):87.
289. Reif S, Golin C, Smith S. Barriers to accessing HIV/AIDS care in North Carolina: Rural and urban differences. *AIDS Care.* 2005;17(5):558-65.
290. Tuller DM, Bangsberg DR, Senkungu J, Ware NC, Emenyonu N, Weiser SD. Transportation costs impede sustained adherence and access to HAART in a clinic population in southwestern Uganda: a qualitative study. *AIDS Behav.* 2010;14(4):778-84.

291. Williams CT, Latkin CA. Neighborhood socioeconomic status, personal network attributes, and use of heroin and cocaine. *Am J Prev Med.* 2007;32(6):S203-S10.
292. Das J, Do Q-T, Friedman J, McKenzie D, Scott K. Mental health and poverty in developing countries: Revisiting the relationship. *Soc Sci Med.* 2007;65(3):467-80.
293. Saxena S, Thornicroft G, Knapp M, Whiteford H. Resources for mental health: scarcity, inequity, and inefficiency. *Lancet.* 2007;370(9590):878-89.
294. Ammassari A, Trotta MP, Murri R, Castelli F, Narciso P, Noto P, et al. Correlates and predictors of adherence to highly active antiretroviral therapy: overview of published literature. *J Acquir Immune Defic Syndr.* 2002;31:S123-7.
295. Wohl AR, Carlos J-A, Tejero J, Dierst-Davies R, Daar ES, Khanlou H, et al. Barriers and unmet need for supportive services for HIV patients in care in Los Angeles County, California. *AIDS Patient Care STDS.* 2011;25(9):525-32.
296. Spire B, Duran S, Souville M, Leport C, Raffi F, Moatti J-P. Adherence to highly active antiretroviral therapies (HAART) in HIV-infected patients: from a predictive to a dynamic approach. *Soc Sci Med.* 2002;54(10):1481-96.
297. Burch LS, Smith CJ, Anderson J, Sherr L, Rodger AJ, O'Connell R, et al. Socioeconomic status and treatment outcomes for individuals with HIV on

antiretroviral treatment in the UK: cross-sectional and longitudinal analyses. *Lancet Public Health*. 2016;1(1):e26-e36.

298. Kalichman SC, Grebler T. Stress and poverty predictors of treatment adherence among people with low-literacy living with HIV/AIDS. *Psychosom Med*. 2010;72(8):810.

299. Surratt HL, Kurtz SP, Levi-Minzi MA, Chen M. Environmental influences on HIV medication adherence: The role of neighborhood disorder. *Am J Public Health*. 2015;105(8):1660-6.

300. Dombrowski JC, Simoni JM, Katz DA, Golden MR. Barriers to HIV care and treatment among participants in a public health HIV care relinkage program. *AIDS Patient Care STDS*. 2015;29(5):279-87.

301. Kushel M, Colfax G, Ragland K, Heineman A, Palacio H, Bangsberg DR. Case management is associated with improved antiretroviral adherence and CD4+ cell counts in homeless and marginally housed individuals with HIV infection. *Clin Infect Dis*. 2006;43(2):234-42.

302. Degenhardt L, Mathers B, Vickerman P, Rhodes T, Latkin C, Hickman M. Prevention of HIV infection for people who inject drugs: why individual, structural, and combination approaches are needed. *Lancet*. 2010;376(9737):285-301.

303. Knowlton AR, Arnsten JH, Eldred LJ, Wilkinson JD, Shade SB, Bohnert AS, et al. Antiretroviral use among active injection-drug users: the role of patient-provider engagement and structural factors. *AIDS Patient Care STDS*. 2010;24(7):421-8.
304. Milloy M, Marshall B, Kerr T, Buxton J, Rhodes T, Montaner J, et al. Social and structural factors associated with HIV disease progression among illicit drug users: a systematic review. *AIDS*. 2012;26(9):1049.
305. World Health Organization (WHO). Integrating collaborative TB and HIV services within a comprehensive package of care for people who inject drugs: consolidated guidelines. 2016. Available from: <https://apps.who.int/iris/handle/10665/204484>
306. Strauss SM, Mino M. Addressing the HIV-related needs of substance misusers in New York State: the benefits and barriers to implementing a “one-stop shopping” model. *Subst Use Misuse*. 2011;46(2-3):171-80.
307. Tran BX, Nguyen LH, Phan HTT, Nguyen LK, Latkin CA. Preference of methadone maintenance patients for the integrative and decentralized service delivery models in Vietnam. *Harm Reduct J*. 2015;12(1):29.
308. Kredo T, Ford N, Adeniyi FB, Garner P. Decentralising HIV treatment in lower- and middle-income countries. *Cochrane Database Syst Rev*. 2013(6):CD009987.

309. Curtis M. Building integrated care services for injection drug users in Ukraine. 2010. Available from: http://www.euro.who.int/_data/assets/pdf_file/0016/130651/e94651.pdf
310. Drainoni M-L, Farrell C, Sorensen-Alawad A, Palmisano JN, Chaisson C, Walley AY. Patient perspectives of an integrated program of medical care and substance use treatment. *AIDS Patient Care STDS*. 2014;28(2):71-81.
311. Hogan SR, Unick GJ, Speiglmann R, Norris JC. Social welfare policy and public assistance for low-income substance abusers: The impact of 1996 welfare reform legislation on the economic security of former Supplemental Security Income drug addiction and alcoholism beneficiaries. *J Socio Soc Welf*. 2008;35(1):221.
312. Delgado J, Heath KV, Yip B, Marion S, Alfonso V, Montaner J, et al. Highly active antiretroviral therapy: physician experience and enhanced adherence to prescription refill. *Antivir Ther*. 2003;8(5):471-8.
313. Sangsari S, Milloy M, Ibrahim A, Kerr T, Zhang R, Montaner J, et al. Physician experience and rates of plasma HIV-1 RNA suppression among illicit drug users: an observational study. *BMC Infect Dis*. 2012;12(1):22.

314. Landon BE, Wilson IB, McInnes K, Landrum MB, Hirschhorn LR, Marsden PV, et al. Physician specialization and the quality of care for human immunodeficiency virus infection. *Arch Intern Med.* 2005;165(10):1133-9.
315. Kitahata MM, Van SR, Shields AW. Physician experience in the care of HIV-infected persons is associated with earlier adoption of new antiretroviral therapy. *J Acquir Immune Defic Synd.* 2000;24(2):106-14.
316. Miller LG, Liu H, Hays RD, Golin CE, Beck CK, Asch SM, et al. How well do clinicians estimate patients' adherence to combination antiretroviral therapy? *J Gen Intern Med.* 2002;17(1):1-11.
317. Altice FL, Sullivan LE, Smith-Rohrberg D, Basu S, Stancliff S, Eldred L. The potential role of buprenorphine in the treatment of opioid dependence in HIV-infected individuals and in HIV infection prevention. *Clin Infect Dis.* 2006;43(Supplement_4):S178-S83.
318. Eibl JK, Morin K, Leinonen E, Marsh DC. The state of opioid agonist therapy in Canada 20 years after federal oversight. *Can J Psychiatry.* 2017;62(7):444-50.
319. Collins AB, Parashar S, Hogg RS, Fernando S, Worthington C, McDougall P, et al. Integrated HIV care and service engagement among people living with HIV who

use drugs in a setting with a community-wide treatment as prevention initiative: a qualitative study in Vancouver, Canada. *J Int AIDS Soc.* 2017;20(1).

320. Nosyk B, Anglin MD, Brissette S, Kerr T, Marsh DC, Schackman BR, et al. A call for evidence-based medical treatment of opioid dependence in the United States and Canada. *Health Aff.* 2013;32(8):1462-9.

321. Neale J, Tompkins C, Sheard L. Barriers to accessing generic health and social care services: a qualitative study of injecting drug users. *Health Soc Care Community.* 2008;16(2):147-54.

322. Raphael D. Social determinants of health: Canadian perspectives: Canadian Scholars' Press; 2009.

323. Chavkin W, Wise PH. The data are in: health matters in welfare policy. *Am J Public Health;* 2002.

324. Poundstone KE, Strathdee SA, Celentano DD. The social epidemiology of human immunodeficiency virus/acquired immunodeficiency syndrome. *Epidemiol Rev.* 2004;26(1):22-35.

325. Crane J, Quirk K, Van der Straten A. "Come back when you're dying:" the commodification of AIDS among California's urban poor. *Soc Sci Med.* 2002;55(7):1115-27.

326. Roe GW. Vancouver's Downtown Eastside and the Community of Clients. *BC Stud.* 2009(164):75-101.
327. Parkhurst JO. Understanding the correlations between wealth, poverty and human immunodeficiency virus infection in African countries. *Bull World Health Organ.* 2010;88:519-26.
328. Moreno-Serra R, Smith PC. Does progress towards universal health coverage improve population health? *Lancet.* 2012;380(9845):917-23.
329. World Health Organization (WHO). Arguing for universal health coverage. 2013. Available from: https://www.who.int/health_financing/UHC_ENvs_BD.PDF?ua=1
330. United Nations Programme on HIV/AIDS (UNAIDS). 2006 report on the global AIDS epidemic: a UNAIDS 10th anniversary special edition: World Health Organization; 2006. Available from: http://data.unaids.org/pub/globalreport/2006/2006_gr-executivesummary_en.pdf
331. Tantivess S, Walt G. The role of state and non-state actors in the policy process: the contribution of policy networks to the scale-up of antiretroviral therapy in Thailand. *Health Policy Plan.* 2008;23(5):328-38.

332. Worthington C, O'Brien K, Myers T, Nixon S, Cockerill R. Expanding the lens of HIV services provision in Canada: results of a national survey of HIV health professionals. *AIDS Care*. 2009;21(11):1371-80.
333. Kresina TF, Lubran R, Clark HW, Cheever LW. Substance abuse treatment, HIV/AIDS, and the continuum of response for people who inject drugs. *Advances Prev Med*. 2012;2012.
334. Pierson P. *Politics in time: History, institutions, and social analysis*: Princeton University Press; 2011.
335. Connock M, Juarez-Garcia A, Jowett S, Frew E, Liu Z, Taylor R, et al. Methadone and buprenorphine for the management of opioid dependence: a systematic review and economic evaluation. NIHR Health Technology Assessment Programme: Executive Summaries. 2007.
336. Ball JC, Ross A. *The effectiveness of methadone maintenance treatment: patients, programs, services, and outcome*: Springer Science & Business Media; 2012.
337. Torrens M, Fonseca F, Castillo C, Domingo-Salvany A. Methadone maintenance treatment in Spain: the success of a harm reduction approach. *Bull World Health Organ*. 2013;91:136-41.

338. Rao R, Agrawal A, Kishore K, Ambekar A. Delivery models of opioid agonist maintenance treatment in South Asia: a good beginning. *Bull World Health Organ.* 2013;91:150-3.
339. Mohamad N, Bakar NH, Musa N, Talib N, Ismail R. Better retention of Malaysian opiate dependents treated with high dose methadone in methadone maintenance therapy. *Harm Reduct J.* 2010;7(1):30.
340. Socías ME, Wood E, Small W, Dong H, Shoveller J, Kerr T, et al. Methadone maintenance therapy and viral suppression among HIV-infected opioid users: The impacts of crack and injection cocaine use. *Drug Alcohol Depend.* 2016;168:211-8.
341. Carpenter CC, Cooper DA, Fischl MA, Gatell JM, Gazzard BG, Hammer SM, et al. Antiretroviral therapy in adults: updated recommendations of the International AIDS Society–USA Panel. *JAMA.* 2000;283(3):381-90.
342. Westergaard RP, Ambrose BK, Mehta SH, Kirk GD. Provider and clinic-level correlates of deferring antiretroviral therapy for people who inject drugs: a survey of North American HIV providers. *J Int AIDS Soc.* 2012;15(1):10.
343. Abraham AJ, O'Brien LA, Bride BE, Roman PM. HIV/AIDS services in private substance abuse treatment programs. *Drug Alcohol Depend.* 2011;115(1-2):16-22.

344. Novotná G, Dobbins M, Henderson J. Institutionalization of evidence-informed practices in healthcare settings. *Implement Sci.* 2012;7(1):112.
345. Shoveller J, Viehbeck S, Di Ruggiero E, Greyson D, Thomson K, Knight R. A critical examination of representations of context within research on population health interventions. *Crit Public Health.* 2016;26(5):487-500.
346. Chillag K, Bartholow K, Cordeiro J, Swanson S, Patterson J, Stebbins S, et al. Factors affecting the delivery of HIV/AIDS prevention programs by community-based organizations. *AIDS Educ Prev.* 2002;14(3 Supplement):27-37.
347. López M, Hofer K, Bumgarner E, Taylor D. Developing Culturally Responsive Approaches to Serving Diverse Populations: A Resource Guide for Community-Based Organizations. National Research Centre on Hispanic Children and Families. 2017;3. Available from: <https://www.nsvrc.org/sites/default/files/2017-06/cultural-competence-guide.pdf>
348. Bogart LM, Wagner GJ, Mutchler MG, Risley B, McDavitt BW, McKay T, et al. Community HIV treatment advocacy programs may support treatment adherence. *AIDS Educ Prev.* 2012;24(1):1-14.
349. Giddens A, Duneier M, Appelbaum RP, Carr DS. Introduction to sociology: WW Norton; 1996

Appendices

Appendix A Search strategy sample

Table 6.1 Sample: Search strategy for MEDLINE

PICO	Categories	Search
Key Population: People Who Use Drugs Living with HIV	Types of drugs	<ol style="list-style-type: none"> 1. exp street drugs/ 2. exp Opioid-Related Disorders/ OR Opioid Dependence* OR opioid use* or Heroin Dependence/ or Heroin/ 3. Cocaine-Related Disorders/ 4. Amphetamine-Related Disorders/ 5. (Heroin OR cocaine OR crack OR opioid* OR amphetamine OR morphine OR "amphetamine-type stimulant*" OR "Cocaine Related Disorder*" OR "Cocaine Abuse*" OR "Cocaine Dependence*" OR "Cocaine Addiction" OR "Amphetamine Related Disorder*" OR "Amphetamine Abuse*" OR "Amphetamine Addiction" OR "Amphetamine Dependence*" OR "Morphine Addiction" OR "Morphine Abuse" OR "Heroin Dependence" OR "Heroin Addiction" OR "Heroin Abuse*" OR "Opioid Dependence*").ti,ab
	Drug Use	<ol style="list-style-type: none"> 6. ("drug use*" OR "illicit drug use*" OR "illicit drug*" OR "people who use drug*" OR "pwud" OR "drug abuse" OR "drug dependence*").ti,ab.
	Injecting Drug Use	<ol style="list-style-type: none"> 7. substance abuse, intravenous/ 8. needle sharing/ 9. (PWID or people who inject drug* or inject* drug* or intravenous drug* or injecting drug use* or IDU).ti,ab.
	DRUG USE	10. OR/1-9
		<ol style="list-style-type: none"> 11. exp HIV/ or HIV infections/ or AIDS Serodiagnosis/ or HIV seropositivity/ 12. (HIV or "HIV infect*" or "HIV?positive" or "PLHIV" or "People Living with HIV" or AIDS or "acquired immunodeficiency syndrome").ti,ab. 13. ((human immun*) AND (deficiency virus)).ti,ab. 14. ((HIV or AIDS) adj2 (seropositivity or positive or status)).ti,ab.
	HIV	15. OR/11-14
Service Provision	Substance abuse treatment	<ol style="list-style-type: none"> 16. substance abuse treatment centers/ or opiate substitution treatment/ 17. Methadone/or Analgesics, Opioid/ 18. (opioid replace* or opioid substitut*).ti,ab. 19. methadone.mp
	Social and Community Services	<ol style="list-style-type: none"> 20. assisted living facilities/ or community pharmacy services/ or voluntary programs/ or group homes/

		21. (community?based or non?profit or non?government* or residential or "home-based care" or "housing support" or "housing assistance" or "literacy program" or "educational program" or "life skill train*" or "vocational train*" or "income generation" or "case management" or "peer education" or "social support" or "peer support" or "community mobilization").ti,ab.
	Access to health care	22. comprehensive health care/ or "delivery of health care"/ or health services accessibility/ or "quality of health care"/ or point-of-care systems/
	SERVICE PROVISION	23. or/16-22
Stage 1 HIV Testing *proportion of those who accepted testing, received results and proportions of newly diagnosed		24. (HIV test* or HIV screen* or" HIV Testing Services" or HTS or HIV rapid test* or HIV rapid screen* or point-of-care test* or HIV rapid diagnostic test* or "HIV testing and counselling" or "HTC" or "Voluntary Counselling and Testing" or "VCT").ti,ab. 25. (provider-administered test* or self?test* or home?based test* or home test* or anti?body laboratory test* or community?based test* or community test* or primary?care test* or outreach test*).ti,ab.
	HIV TESTING	26. OR/16-17
	DRUG USE and HIV and HIV TESTING and SERVICE PROVISION	27. 10 and 15 and 23 and 26 remove duplicates limit to yr="2006-Current", English
Stage 2 HIV Treatment (exposure and adherence) *Time to ART initiation, proportions of PWUD initiated and received ART, adherence to ART		28. exp Antiretroviral Therapy, Highly Active/ 29. (antiretrovir* or anti?retrovir* or "anti?retroviral therapy" or "highly active anti?retroviral" or HAART or ART* or ARV* or "HIV treatment" or "combined antiretroviral therapy" or cART).ti,ab. 30. (zidovudine or stavudine or lamivudine or nevirapine or efavirenz or Atripla or Complera or Stribild or Combivir or Emtriva or Epivir or Epzicom or Hivid or Retrovir or Trizivir or Truvada or Videx EC or Videx or Viread or Zerit or Ziagen or Agenerase or Aptivus or Crixivan or Fortovase or Invirase or Kaletra or Lexiva or Norvir or Prezista or Reyataz or Viracept or Fuzeon or Selzentry or Isentress or Edurant or Intelence or Sustiva or Rescriptor or Viramune or emtricitabine or abacavir or didanosine or tenofovir or stavudine or rilpivirine or etravirine or delavirdine or efavirenz or nevirapine or amprenavir or tipranavir or indinavir or squinavir or lopinavir or ritonavir or darunavir or atazanavir or nelfinavir or enfuvirtide or maraviroc or raltegravir or elvitegravir or zalcitabine or dideoxycytidine or azidothymidine or saquinavir or Fosamprenavir or cobicistat).ti,ab.
	ART	31. or/20-22
	DRUG USE and HIV and ART	32. 10 and 15 and 23 and 31 remove duplicates

		limit to yr="2006-Current", English
		33. exp Compliance/ 34. exp Medication adherence/ 35. (adheren* or complian* or retention or pill count* or directly administered anti?retroviral therapy or medication assisted therapy or MAT or DAART or electronic pill bottle caps or MEMS caps or self?reported adheren* or prescription* refill or electronic data or electronic records or physiologic marker* or patient diary or patient diaries or pharmacy refill data or pharmacy records or dispensation records).ti,ab.
	ADHERENCE	36. or/25-27
	DRUG USE and HIV and ART and ADHERENCE	37. 10 and 15 and 23 and 31 and 36 remove duplicates limit to yr="2006-Current", English
Stage 3 Viral Load Suppression		38. exp Viral Load/ 39. exp Treatment Outcome/ 40. undetect* adj3 viral load.ti,ab. 41. non?detect adj3 viral load.ti,ab. 42. Suppress* adj3 viral load.ti,ab. 43. ("anti?retroviral outcome*" or "viral load change*" or "virologic* respon*" or "virologic* success" or "immunologic* success").ti,ab.
	VIRAL LOAD	44. or/30-35
	DRUG USE and HIV and VIRAL LOAD	45. 10 and 15 and 23 and 44 remove duplicates limit to yr="2006-Current"

Appendix B Risk of bias assessments

B.1 Non-randomized studies of interventions

Table 6.2 Risk of bias in non-randomized studies of interventions

<i>Study</i>	Bias due to confounding	Bias in selection of participants	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall
<i>Rothman et al. (2007)</i>	Moderate	Moderate	Moderate	Moderate	Low	Low	Moderate	Moderate
<i>Tran et al. (2016)</i>	Moderate	Moderate	Low	Low	Low	Low	Moderate	Moderate
<i>Xia et al. (2013)</i>	Moderate	Moderate	Moderate	Low	Moderate	Low	Moderate	Moderate
<i>Pang et al. (2007)</i>	Moderate	Moderate	Moderate	Low	Low	Low	Moderate	Moderate
<i>Seewald et al. (2013)</i>	Moderate	Moderate	Low	Low	Low	Low	Moderate	Moderate
<i>Bachireddy et al.(2014)</i>	Moderate	Moderate	Low	Moderate	Low	Low	Moderate	Moderate
<i>Lambers et al. (2011)</i>	Moderate	Moderate	Low	Moderate	Low	Low	Moderate	Moderate
<i>Lappalainen et al. (2015)</i>	Moderate	Moderate	Low	Moderate	Low	Low	Moderate	Moderate
<i>Parashar et al. (2011)</i>	Moderate	Moderate	Low	Low	Low	Low	Moderate	Moderate

<i>Sanchez et al. (2012)</i>	Moderate	Moderate	Low	Low	Low	Low	Moderate	Moderate
<i>Simeone et al. (2017)</i>	Moderate	Moderate	Low	Low	Low	Low	Moderate	Moderate
<i>Fingerhood et al. (2006)</i>	Moderate	Moderate	Moderate	Low	Low	Low	Moderate	Moderate
<i>Ti et al. (2017)</i>	Moderate	Moderate	Low	Moderate	Low	Low	Moderate	Moderate
<i>Achmad et al. (2009)</i>	Moderate	Moderate	Low	Low	Moderate	Low	Moderate	Moderate
<i>Hung et al. (2016)</i>	Moderate	Moderate	Low	Low	Low	Low	Moderate	Moderate
<i>Lucas et al. (2006)</i>	Moderate	Moderate	Low	Moderate	Low	Low	Moderate	Moderate

Note: Moderate=the study is sound for a non-randomized study with regard to this domain but cannot be considered comparable to a well-performed randomized trial; Low=the study is comparable to a well-performed randomized trial with regard to this domain

B.2 Randomized trials

Table 6.3 Risk of bias in randomized trials

<i>Study</i>	Random sequence generation	Allocation concealment	Selective reporting	Other sources of bias	Blinding participants and personnel	Blinding outcome assessment	Incomplete outcome data	Overall
<i>Safren et al. (2013)</i>	Low	Low	Unclear	Low	Low	Low	Low	Good quality
<i>Sorensen et al. (2007)</i>	Low	Low	Unclear	Low	Low	Low	Low	Good quality
<i>Berg et al. (2012)</i>	Low	Low	Unclear	Low	Low	Low	Low	Good quality
<i>Cooperman et al. (2012)</i>	Low	Low	Unclear	Low	Low	Low	Low	Good quality

Note: **Good quality:** All criteria met (i.e. low for each domain). Using the Cochrane ROB tool, it is possible for a criterion to be met even when the element was technically not part of the method. For instance, a judgment that knowledge of the allocated interventions was adequately prevented can be made even if the study was not blinded, if EPC team members judge that the outcome and the outcome measurement are not likely to be influenced by lack of blinding. **Fair quality:** One criterion not met (i.e. high risk of bias for one domain) or two criteria unclear, and the assessment that this was unlikely to have biased the outcome, and there is no known important limitation that could invalidate the results **Poor quality:** One criterion not met (i.e. high risk of bias for one domain) or two criteria unclear, and the assessment that this was likely to have biased the outcome, and there are important limitations that could invalidate the results. Two or more criteria listed as high or unclear risk of bias

Appendix C Supplementary Material for Chapter 4

C.1 Data analysis for Chapter 4

Bivariate analyses

Primary and secondary explanatory variables that were associated with $\geq 95\%$ adherence in bivariate analyses at p -value < 0.10 : MMT-ART co-dispensation, age, gender, ancestry, prohibited income, heavy alcohol use, daily heroin use, daily crack use, daily cannabis use and CD4 cell count

Multivariate analyses

As a first step, a full model with all the above variables (p -value < 0.10) was built. Variables were then dropped one at a time, recording parameter estimate for MMT-ART co-dispensation variable each time. The relative change (absolute delta) in the coefficient for the MMT-ART co-dispensation variable was then compared. The variable that produced the lowest change was removed. The same process was continued until the minimum change from the full model exceeded 5%

Step 1:

Variables out of the model	Estimate for MMT-ART co-dispensation	Delta (%)	Absolute Delta (%)	Final removal (Produced the lowest change)
FULL MODEL	0.45066			
age	0.43315	-3.89	3.89	
gender	0.44442	-1.38	1.38	
ancestry	0.44705	-0.80	0.80	
prohibited income	0.45019	-0.10	0.10	Remove
heavy alcohol use	0.45378	0.69	0.69	
daily heroin use	0.45639	1.27	1.27	
daily crack use	0.45237	0.38	0.38	
daily cannabis use	0.43244	-4.04	4.04	
CD4 cell count	0.47001	4.29	4.29	

Step 2:

Variables out of the model	Estimate for MMT-ART co-dispensation	Delta (%)	Absolute Delta (%)	Final removal (Produced the lowest change)
FULL MODEL	0.45019			
age	0.43121	-4.22	4.22	
gender	0.44391	-1.39	1.39	
ancestry	0.44617	-0.89	0.89	
prohibited income				Removed
heavy alcohol use	0.45369	0.78	0.78	Remove
daily heroin use	0.45797	1.73	1.73	
daily crack use	0.45264	0.54	0.54	
daily cannabis use	0.43214	-4.01	4.01	
CD4 cell count	0.46897	4.17	4.17	

Step 3:

Variables out of the model	Estimate for MMT-ART co-dispensation	Delta (%)	Absolute Delta (%)	Final removal (Produced the lowest change)
FULL MODEL	0.45369			
age	0.43507	-4.1	4.1	
gender	0.44521	-1.87	1.87	
ancestry	0.44901	-1.03	1.03	
prohibited income				Removed
heavy alcohol use				Removed
daily heroin use	0.46349	2.16	2.16	
daily crack use	0.45542	0.38	0.38	Remove
daily cannabis use	0.43650	-3.79	3.79	
CD4 cell count	0.47233	4.11	4.11	

Step 4:

Variables out of the model	Estimate for MMT-ART co-dispensation	Delta (%)	Absolute Delta (%)	Final removal (Produced the lowest change)
FULL MODEL	0.45542			
age	0.43786	-3.86	3.86	
gender	0.44514	-2.26	2.26	
ancestry	0.45076	-1.02	1.02	Remove
prohibited income				Removed
heavy alcohol use				Removed
daily heroin use	0.46775	2.71	2.71	
daily crack use				Removed
daily cannabis use	0.43946	-3.5	3.5	
CD4 cell count	0.473480	3.97	3.97	

Step 5:

Variables out of the model	Estimate for MMT-ART co-dispensation	Delta (%)	Absolute Delta (%)	Final removal (Produced the lowest change)
FULL MODEL	0.45076			
age	0.42955	-4.71	4.71	
gender	0.43705	-3.04	3.04	
ancestry				Removed
prohibited income				Removed
heavy alcohol use				Removed
daily heroin use	0.46316	2.75	2.75	Remove
daily crack use				Removed
daily cannabis use	0.43497	-3.5	3.5	
CD4 cell count	0.46863	3.96	3.96	

Step 6:

Variables out of the model	Estimate for MMT-ART co-dispensation	Delta (%)	Absolute Delta (%)	Final removal (Produced the lowest change)
FULL MODEL	0.46316			
age	0.44249	-4.46	4.46	
gender	0.44851	-3.16	3.16	
ancestry				Removed
prohibited income				Removed
heavy alcohol use				Removed
daily heroin use				Removed
daily crack use				Removed
daily cannabis use	0.44964	-2.92	2.92	Remove
CD4 cell count	0.48037	3.71	3.71	

Step 7:

Variables out of the model	Estimate for MMT-ART co-dispensation	Delta (%)	Absolute Delta (%)	Final removal (Produced the lowest change)
FULL MODEL	0.44964			
age	0.43266	-3.78	3.78	Remove
gender	0.42843	-4.72	4.72	
ancestry				Removed
prohibited income				Removed
heavy alcohol use				Removed
daily heroin use				Removed
daily crack use				Removed
daily cannabis use				Removed
CD4 cell count	0.466930	3.85	3.85	

Step 8:

Variables out of the model	Estimate for MMT-ART co-dispensation	Delta (%)	Absolute Delta (%)	Final removal (Produced the lowest change)
FULL MODEL	0.43266			
age				Removed
gender	0.40462	-6.48	6.48	
ancestry				Removed
prohibited income				Removed
heavy alcohol use				Removed
daily heroin use				Removed
daily crack use				Removed
daily cannabis use				Removed
CD4 cell count	0.44857	3.68	3.68	Remove

Final Model (include secondary explanatory variable(s) that produce at least 5% relative change)

Variables out of the model	Estimate for MMT-ART co-dispensation	Delta (%)	Absolute Delta (%)	Final removal (Produced the lowest change)
FULL MODEL	0.43266			
age				Removed
gender	0.40462	-6.48	6.48	
ancestry				Removed
prohibited income				Removed
heavy alcohol use				Removed
daily heroin use				Removed
daily crack use				Removed
daily cannabis use				Removed
CD4 cell count				Removed

Goodness of fit test

The Hosmer-Lemeshow goodness of fit test for logistic regression was used.

$$\chi^2 = 0.90035, p\text{-value} = 0.3427$$

Failed to reject H_0 (Model fits well), thus there was lack of evidence of poor fit.

Appendix D Supplementary material for Chapter 5

D.1 18-item set of questions, modified from the 30-item Family Resource Scale

		Never (0% of the time)	Occasionally (25% of the time or less)	Sometimes (26% to 74% of the time)	Usually (75% of the time or more)	Always (100% of the time)
1.	Food for two meals a day	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2.	A house or apartment	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3.	Indoor plumbing and water	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4.	Money to buy necessities	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5.	Enough clothes for yourself (& family)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
6.	Heat for your house or apartment	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
7.	Money to pay monthly bills	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
8.	A job for yourself (or your partner)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
9.	Access to medical care for yourself (& family)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
10.	Social assistance (EI, IA, PPMB, PWD, CPP, OAS, etc.)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
11.	Access to dependable transportation	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
12.	Time to get enough sleep/rest	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
13.	Adequate furniture for your house or apartment	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
14.	Telephone	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
15.	Access to adequate dental care for yourself (& family)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
16.	Money to buy things for yourself	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
17.	Money for entertainment	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
18.	Money to save	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

D.2 Data analysis for explanatory model in Chapter 5

Bivariate analyses

Explanatory variables that were associated with $\geq 95\%$ adherence in bivariate analyses at p -value < 0.10 : gender, hepatitis C, access to substance use facilities, illicit income generation, mental illness, sex work, access to general facilities, daily heroin injection, recent incarceration, street-based income, unmet health needs, age, total income (per \$1000), access to social service facilities, employment and unmet social needs.

Multivariate analyses

The selection of this model was based on: Akaike Information Criterion (AIC) and p -values. These two criteria balance the model choice on finding the best explanatory model (lower p -values indicate more significance) and at the same time a model with the best goodness-of-fit statistic (lower AIC values indicate better fit). At each step of the iterative process, the AIC value and the Type III p -values of each variable were recorded. At each step the variable with the highest Type III p -value is dropped until no variables were left in the model. The final model is the model with the lowest AIC.

Comparison of AIC values across models:

	AIC Value	Lowest <i>p</i> -value	Variable removed
Model 1:	2820.882495	0.84	gender
Model 2	2829.849582	0.29	hepatitis C
Model 3	2824.743764	0.28	access to substance use facilities
Model 4	2818.301753	0.2	illicit income generation
Model 5	2812.715579	0.07	mental illness
Model 6	2880.163675	0.08	sex work
Model 7	2876.796328	0.04	access to general facilities
Model 8	2884.286658	0.01	daily heroin injection
Model 9	2883.776144	<0.01	recent incarceration
Model 10	2891.353179	<0.01	street-based income
Model 11	2893.644762	<0.01	unmet health needs
Model 12	2897.595301	<0.01	age
Model 13	2900.917838	<0.01	total income (per \$1000)
Model 14	3044.015923	<0.01	access to social service facilities
Model 15	3054.281735	<0.01	employment

Model 5 was selected based on the lowest AIC value, excluding gender, hepatitis C, access to substance use facilities and illicit income generation.

Goodness of fit test

Pearson $\chi^2 = 0.10$

D.3 Data analysis for multivariate model in Chapter 5

Since there were no significant associations between material security and adherence for overall score and each of the factors in bivariable analyses, multivariate models were built instead of confounding models.

Goodness of fit test

Pearson $\chi^2 = 0.61$