

**Barriers to antiretroviral therapy use among people who inject
drugs: A systematic review**

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Executive Summary

Poor access to ART among people who inject drugs remains a concern

Injecting drug use is an important contributor to the spread of HIV worldwide – there are an estimated 15.9 million people who inject drugs (PWID), about 3 million are HIV positive. While antiretroviral therapy (ART) has reduced morbidity and mortality for people living with HIV/AIDS and appears to reduce HIV transmission risk, disparities remain in terms of ART coverage for PWID relative to other populations living with HIV. Global data show that only two-thirds of countries have ART available for PWID in 2010 and even where ART is available for PWID, coverage rates are low. This is a concern as poor access to ART leads to delays in initiating ART and contributes to less than optimal adherence to ART regimens. These findings provide a strong argument for improving access to ART among PWID as a means to curb the growth of the HIV/AIDS pandemic. However this important public health goal will only be realised if barriers that impede access to ART for PWID are removed. To remove these barriers, service providers and policy makers need a good understanding of the factors that impede ART use among PWID and how best to deliver ART to this vulnerable population.

Purpose of this report

This report hopes to improve current understanding of ART use among PWID by 1) systematically reviewing the global literature for factors associated with access and adherence to ART among PWID and 2) reviewing the literature on health system approaches to HIV treatment delivery for PWID. It is hoped that findings from this report will be used to inform public health interventions to improve the uptake and use of ART among PWID.

Method

This report presents findings from two systematic reviews of the global literature: the first, examined barriers and facilitators to ART access and adherence among PWID; the second review focused on ways of delivering ART to PWID. Systematic searches were conducted of

several electronic databases (from 1 January 2000 to 11 August 2011). We supplemented these searches by manually searching for relevant reports within the published conference abstracts and the websites of international agencies and civil society organizations working with PWID, by contacting experts within the International Reference Group to the UN on HIV and Injecting Drug Use as well as country experts to request relevant reports, and by hand-searched the reference lists of all selected studies (as well as reports, commentaries and review articles) for additional citations. Studies identified through these procedures were entered into the review databases if they met our eligibility criteria. For eligible studies, data extraction was conducted using standardised forms. Data were independently extracted by authors who then met to compare data extraction sheets and resolve differences of opinion.

Key findings and recommendations

Despite improvements in the global availability of ART for PWID, this report clearly indicates that PWID still experience numerous barriers to initiating ART that also reduce the likelihood of adherence to these life saving medications. More specifically, this review found that:

- Gender and ethnic disparities in the use of ART among PWID exist; with women and ethnic minorities who inject drugs less likely to initiate and more at risk for poor adherence than other PWID. Interventions to address these disparities are urgently needed to ensure PWID benefit from ART.
- Social instability (due to homelessness or unstable housing) hampers access and adherence to ART among PWID. There is evidence that interventions that improve the social stability of PWID also improve engagement in health services and HIV service use. Investment in efforts to improve the social stability of PWID (through drug dependence treatment and through social interventions) may yield benefits for ART initiation and adherence rates among PWID.

- Untreated depression and other untreated mental disorders act as barriers to ART initiation and adherence among PWID. There is evidence that providing treatment for co-occurring mental disorders improves the uptake of and adherence to ART for PWID. Given this finding, PWID with these co-occurring problems should be provided with mental health treatment. Stronger linkages between mental health, HIV and drug treatment services may facilitate access to these needed services.
- Access to and the use of opioid substitution treatment (OST) is the most important facilitator of ART initiation and adherence among PWID. Not only does OST use reduce the risk of HIV transmission due to reductions in risky drug use, but OST also increases rates of ART initiation among treatment naïve PWID. Findings also indicate that OST use improves ART adherence levels, by reducing drug use severity and improving the social stability of PWID. In addition, there is evidence that adherence is supported when OST is administered in conjunction with ART. Given this strong evidence, access to OST needs to be improved for PWID.
- Poor patient-provider relationships (characterised by mutual distrust and stigma) discourage PWID from seeking and remaining in HIV care. However, findings also suggest that where patient-provider relationships are good, providers are able to facilitate adherence self-efficacy among PWID and thereby help PWID achieve optimal adherence. Given the potentially positive impact that health providers have on ART adherence, considerable effort needs to be invested in improving the quality of patient-provider relationships in all country contexts.
- Health care system factors also limit the use of ART by PWID. Evidence indicates that in countries where there is institutionalised stigma within health care systems towards PWID, this results in delayed or denied access to ART. In such contexts, urgent health care reforms are needed. Pressure should be brought to bear on

countries where PWID are denied access to ART or are subject to discrimination, long wait times or additional user fees as a result of their status as a PWID. In addition, evidence suggests that several countries require PWID to co-finance their HIV treatment including covering the costs associated with HIV testing and monitoring, treatment for opportunistic infections and ART-related side-effects, and routine medical examinations. Efforts need to be made to remove these health cost barriers to HIV treatment.

- Policies and practices that promote the social exclusion of PWID from mainstream society separate PWID from HIV care and reduce the likelihood of ART initiation and adherence. To improve the use of ART among PWID, legal and regulatory frameworks that promote the social exclusion of and stigma towards PWID in many countries must be reformed. Similarly health system factors that entrench the social exclusion of PWID must be reviewed.
- Enforcement-oriented drug policies that allow for police harassment of PWID, place PWID on drug user registries that limit their social rights, and lead to the social exclusion of PWID are major barriers to ART use among PWID. In countries with such policies, attempts to improve access to and the use of ART among PWID should include concerted political efforts to change these drug policies and laws that stigmatise PWID and separate them from needed health services.
- All forms of detention pose significant risks for delayed, denied or interrupted use of ART among PWID. In many countries, access to ART is still limited in detention facilities, especially in pre-trial detention but also in prisons and compulsory drug “rehabilitation” facilities. For PWID already on ART, treatment gets interrupted when they enter detention but also when they are transferred from one detention facility to another and/or when they are released (due to limited continuity of care). To improve access to and the use of ART among PWID, detention of PWID in

compulsory drug “rehabilitation” facilities should be ended. Enforcement-oriented drug policies that allow short-term detention at the hands of law enforcement or lengthy periods of pre-trial detention (with no access to ART or medical services) also need to be stopped. For PWID who are incarcerated, prison health services and in particular HIV and TB services should be closely linked to public health services.

- Access and adherence to ART among PWID is facilitated by well-integrated HIV, harm reduction, and OST services. Despite this, evidence suggests that many of these essential services for PWID remain compartmentalized, with little service integration occurring. Health services should work towards greater integration of essential services for PWID. While the provision of co-located services remains an ideal for improving access to comprehensive care for PWID, strategies to improve the integration of services through case management and patient navigation may yield benefits for engagement in care where co-located service delivery is not feasible.

Findings from this review suggest that although the provision of ART for PWID remains a challenge, many of the identified barriers to ART use among PWID are mutable.

Addressing these barriers is of critical importance as failure to do so may limit the promise that ART holds in terms of improving health-outcomes for HIV-infected PWID. Findings also indicate that interventions to improve ART uptake and adherence should be multi-pronged and address both patient-level and systemic barriers to the effective use of ART among PWID.

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1. Introduction

Injecting drug use is an important contributor to the spread of HIV worldwide (1). Estimates suggest that with the exception of sub-Saharan Africa, injecting drug use accounts for about a third of new HIV infections (2). This proportion is greater in some regions, such as Eastern Europe and Central Asia, where in 2010 about half of new HIV infections were due to needle sharing among people who inject drugs (PWID; 3). Globally, around 20 percent of people who inject drugs are living with HIV/AIDS (3). However, the absence of data in certain regions, as well as the illegality of drug use in most countries, makes it difficult to determine the exact prevalence rates of injection drug use (1). Nevertheless, extrapolated estimates suggest that globally approximately 15.9 million people inject drugs, of which about 3 million are HIV positive (1).

The most effective way of managing HIV/AIDS among PWID is through the use of highly active antiretroviral therapy (HAART). Since its introduction in the late 1990s, HAART has reduced morbidity and mortality and improved quality of life for people living with HIV/AIDS. When used as prescribed, HAART reduces HIV-1 RNA viral load and improves CD4+ cell counts thereby delaying progression to AIDS and extending lives (3-77). While an extensive review of the benefits of HAART for PWID is beyond the scope of the current report, it is important to note that the benefits associated with HAART use extend to PWID. Research has consistently demonstrated that the use of HAART increases life expectancy (5, 8) and enhances virologic outcomes (such as viral suppression; 9) for HIV-positive PWID. For example, a Swiss cohort study found that the introduction of HAART significantly decreased the standard mortality ratio from 98.2 to 40.9 among 3853 HIV-positive PWID (10). A further study found that HIV-positive PWID using HAART had significantly longer life expectancies (24.5 additional years at age 20) compared to HIV-positive PWID who were not using HAART (19.1 years at age 20; 11). In addition, one study reported comparable mortality rates, after adjusting for potential confounding variables including baseline CD4+ count and HAART adherence, between HIV-positive PWID and persons who did not inject drugs (82). In addition, PWID living with HIV have

no greater odds of developing antiretroviral resistance than other populations living with HIV, despite concerns by physicians (12). Related to this, there is no evidence that HAART use among PWID leads to negative, such as needle sharing (83).

Yet the benefits of antiretroviral therapy (ART) use often are not realised for PWID. A high proportion of HIV/AIDS morbidity and mortality is attributable to late or no access to HAART; especially among marginalised populations such as PWID (16-17, 84). A recent review of global data on access to ART for PWID, reported that only two-thirds of participating countries had ART available for HIV-positive PWID in 2010, with 33 out of 96 countries reporting that ART was not available for PWID (84). In addition, even where ART is available for PWID, the number of HIV-positive people with access to ART is poor. A recent global review of ART coverage rates for PWID found low rates of coverage with fewer than one in six HIV-positive PWID having access to ART (18). Access is particularly poor in developing and transitional countries; with HAART largely unavailable to former or current injection drug users in about one third of these countries (19). There is also converging evidence that PWID have suboptimal access to HAART compared to persons exposed to HIV by other modes of transmission (5, 9, 19-22). Even in countries that have a national policy of universal access to free HAART (e.g. Brazil, Canada, and China among others), PWID have disproportionately low rates of ART uptake in comparison to other people living with HIV (9, 23-25, 85). For example, despite universal access to free HAART in Brazil, PWID were less likely to receive HAART, had lower CD4+ counts, and had higher viral loads when initiating care compared to men who have sex with men; resulting in higher rates of HIV/AIDS-related mortality among PWID (85). Poor access to HAART not only leads to failure to initiate and delays in initiating HAART among PWID, but also contributes to less than optimal adherence to ART regimens for PWID who are able to initiate treatment (16, 22, 24, 26-31).

Poor adherence may take the form of less than optimal adherence to HAART (taking less than 90-95% of the doses as prescribed), short-term non-scheduled treatment

interruptions, longer periods of non-scheduled treatment interruptions, and treatment discontinuation. This is worrisome as adherence is closely tied to HIV viral suppression and CD4+ cell count responses to HAART and therefore is a key predictor of positive treatment outcomes (16, 31-33). For instance, poor adherence has been associated with clinical progression to AIDS (32) and mortality (33). Evidence suggests that optimising adherence is particularly important in the first six months of HAART use as this sets the stage for long-term viral suppression (34). Moderate deviations from high adherence (88-99%) after six months of HAART use seem to have less negative impact on HIV viral load than deviations that occur when first starting HAART (35). Although newer simpler treatment regimens have enhanced adherence, specific at-risk populations (such as PWID) continue to face barriers to adhering to ART. For example, several studies have noted suboptimal adherence to HAART among PWID (for example 17, 32, 36-40) as well as high levels of treatment discontinuation (8, 40). In contrast, a recent systematic review and meta-analysis found that adherence rates for HIV positive people who use drugs was 60%- well within the range noted for people living with HIV/AIDS (41). While this adherence rate is lower than optimal, new evidence suggests that viral suppression and improved clinical outcomes are possible among patients with moderate adherence (54% to 100%) to more potent medications, such as non-nucleoside reverse-transcriptase-inhibitor regimens (42). However perfect adherence still remains an important therapeutic goal as this is associated with the best immunologic and virologic outcomes (42).

Apart from the consequences that poor access and adherence to HAART has for disease outcomes among individuals who inject drugs and their sexual partners, there is a growing evidence that poor access to HAART among vulnerable populations may negatively impact on global efforts to curb HIV incidence and prevent new infections (86). There is an increasing amount of evidence that adequate HAART coverage among infected populations prevents HIV transmission (13-15) in vertical, sexual and injection drug use settings (46, 86-89). For example, a recent meta-analysis of several randomized controlled trials found that HAART use decreases plasma HIV-1 RNA to undetectable levels in a sustained way.

This results in decreased levels of HIV-1 RNA in sexual secretions and therefore diminishes the risk of sexual transmission among serodiscordant couples (13). Similarly, there is evidence that HAART use among PWID prevents new infections within this population. For example, one study found that within a cohort of PWID, reductions in community viral load as a result of HAART use was the most powerful determinant of reduced HIV incidence - even after adjusting for traditional risk factors such as unsafe sexual behaviours and needle sharing (14). In addition, an analysis of administrative records found that population level increases in HAART coverage were significantly associated with decreases in HIV incidence, including a 50% decrease in new HIV infections among people with a history of IDU (15). These findings provide a strong argument for improving access to HAART among PWID as a means to curb the growth of the HIV/AIDS pandemic.

Evidence that the timely initiation and effective use of HAART among PWID leads to reduced morbidity, mortality and HIV transmission provides a strong rationale for intensifying efforts to improve access to HAART for all medically eligible HIV-infected PWID. However this important public health goal will only be realised if the barriers that impede access to HAART and the continued use of HAART are removed. To facilitate expanded access for PWID, service providers and policy makers need a good understanding of the barriers and facilitators to the optimal use of HAART as well as information about how best to deliver HAART to this vulnerable population. Evidence about factors that impede HAART use among PWID and ways in which health systems can be strengthened to respond to HIV among PWID is vital for the development of interventions to optimise the use HAART among PWID.

While there have been several previous reviews of factors associated with HAART use among PWID, these reviews have (for the most part) not been systematic reviews of the global literature. Generally, previous reviews have been limited in focus to either developed (7) or developing/transitional countries (9) or to a few types of barriers to access (44). Similarly, prior reviews on adherence among PWID have focused narrowly on

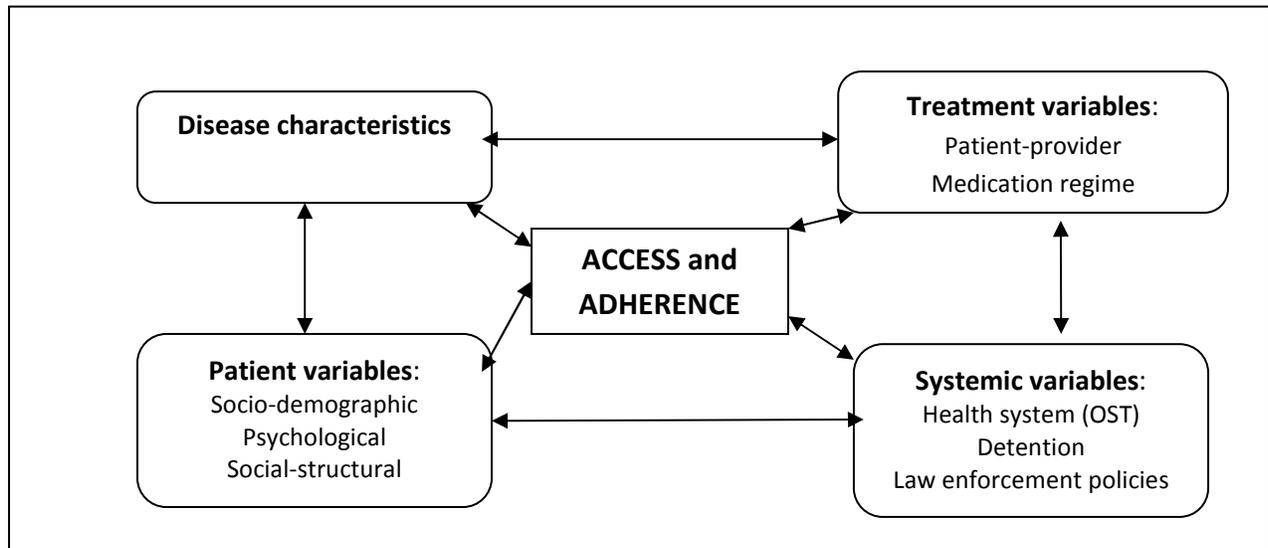
describing adherence rates among PWID, with most reviews failing to fully elucidate the factors affecting HAART compliance among PWID. Although there have been some exceptions to this (e.g. 34, 47), these reviews have had serious limitations. For instance, Spire et al.'s (34) review was not systematic in nature and focused largely on evidence from developed country settings. In addition, Malta et al.'s (47) systematic review focused on drug- using populations in general rather than PWID specifically. To the best of our knowledge there has only been one systematic review of the factors associated with both access and adherence to HAART as well as ways of optimising HAART service delivery for PWID (8). Even this more comprehensive review is relatively dated and it is quite possible that some of the barriers and facilitators to ART use may have changed since the introduction of newer treatment regimens. This current review aims to redress some of the gaps and limitations of prior reviews by systematically examining the global literature for factors associated with access and adherence to HAART among PWID. In addition, this review adds to the current body of literature by expanding the frame to examine both individual and structural-systemic barriers to HAART use among PWID. Given the important role that health systems play in facilitating or hindering the effective use of HAART for PWID, this report also aims to review the literature on health system approaches to HIV treatment delivery for PWID.

1.1. Conceptual framework for the review

The conceptual framework (Figure 1) used to organise and classify factors associated with HAART use is a modified version of Ickovics' system for classifying determinants of adherence (48). In the original system, Ickovics grouped barriers and facilitators for adherence into patient variables that include socio-demographic factors and psychosocial factors (including depression and mental illness, active substance use, social support, and self-efficacy) as well as factors associated with the treatment regimen; with the disease (including symptom severity, immunologic status); with the patient-provider relationship; and with the clinical setting, including access to reliable primary care, clinical environment, convenience, and confidentiality (48).

We made several revisions to this original framework; both in terms of content and application. First, while this classification system was originally developed to examine adherence behaviours, we expanded this application to include barriers and facilitators to HAART access. As earlier reviews describe individual, provider-level and structural factors associated with access (8), Ickovics' classification system is easily applied to the study of HAART initiation. Second, as the original model fails to recognize the important social, structural and systemic influences on adherence for PWID (44), we broadened Ickovic's original framework to take better account of these structural and systemic influences. More specifically we expanded the patient-level barriers to include not only socio-demographic and psychological variables but also social-structural influences on access and adherence, such as social support and indicators of social status and social stability (44). We also incorporated the "clinical setting" category of barriers and facilitators into a broader category, termed "systemic factors". This large category of barriers and facilitators includes characteristics of the health care system (such as stigma and discrimination towards PWID, availability of ART, and access to opioid substitution treatment), detention facilities (which incorporates all aspects of detention), and law enforcement policies that impact on ART access and adherence for PWID. In terms of other content revisions, the two categories referring to the treatment regime and patient-provider characteristics were incorporated into a single category termed "treatment factors" (Figure 1). When access is the focus of the study, medication regime factors will not be relevant as the patient is still treatment naïve.

Figure 1: Conceptual framework for examining factors associated with the use of ART for people who inject drugs (modified from Ickovics & Meade, 2002).



The following section describes the methods used to conduct the systematic review. Thereafter, the remainder of the report reviews: 1) barriers and facilitators to HAART initiation among PWID, 2) factors associated with optimal adherence among PWID and 3) health system approaches for delivering HAART to PWID.

2. Methods

We conducted two reviews of the literature. The first, a systematic review, examined barriers and facilitators to the effective use of HAART among PWID. The second review focused on ways of optimising HAART delivery to PWID.

To ensure the methodological quality of the systematic reviews, we followed principles for the assessment of multiple systematic reviews outlined in the Assessment of Multiple Systematic Reviews (AMSTAR) measurement tool (49). As most of the primary studies included in this review were longitudinal cohort, case-control or cross-sectional observational studies, we also followed recommendations for conducting and reporting systematic reviews (50), and meta-analyses of observational studies (51).

2.1. Inclusion and exclusion criteria

To be included in the first review, studies had to either examine correlates of access to antiretroviral therapy (ART) or adherence to ART among PWID as a primary outcome. To be included in the second review, studies had to describe health system factors associated with improved HAART use among PWID and have rates of ART initiation or adherence rates as outcomes. For both reviews, PWID were defined as those individuals who had injected any drug over the last 12 months. Access was defined as any initiation of ART during the course of the study period. Qualitative studies were included in the reviews, primarily because these studies are able to shed light on potential structural and political barriers to accessing and adhering to ART. Studies were excluded if they were commentaries or reviews and did not present primary data. Studies were also excluded if they assessed access or adherence to HIV treatment among other populations without disaggregating PWID from the overall sample.

2.2 Search strategy

Search strategies were developed using systematic automated and manual searches. First we conducted a comprehensive automated search of six electronic bibliographic databases

including PubMed Central, SciELO, EbscoHost, ScienceDirect, ISI Web of Science and LILACS (Latin American and Caribbean Health Sciences). These databases were searched from 1 January 2000 to 11 August 2011 by three of the authors of this review (BM, ZP, and SP). For the first review, the search consisted of standardised search terms (keywords and medical subject heading (MeSH) terms) that reflect the following domains: a) injection drug use; b) antiretroviral therapy (i.e. ART, HAART, ARV); and c) barriers to access (i.e. initiation, uptake) and/or adherence (i.e. adherence, compliance, interrupted treatment). Citations that address all three of these domains were downloaded into the study database. The search terms and search strategy are reflected in Box 1.

Box 1: Search Terms and Strategy for review on use of HAART:

<p>Terms:</p> <ol style="list-style-type: none">1. Inject*2. HIV treatment3. ARV4. ART5. HAART6. antiretroviral7. access8. initiat*9. uptake10. barrier11. adhere*12. compliance	<p style="text-align: center;">Search Strategy:</p> <p>A: [1] AND</p> <p>B: [2 or 3 or 4 or 5 or 6] AND</p> <p>C: [7 or 8 or 9 or 10 or 11 or 12]</p>	<p>For the second review, the search comprised standardised search terms (keywords and medical subject heading (MeSH) terms) that reflect the following domains: a) injection drug use; b) antiretroviral therapy (i.e.</p>
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ART, HAART, ARV); and c) service delivery interventions (i.e. treatment services and treatment outcomes). Citations that addressed all three domains were downloaded into a second study database. The search terms and search strategy for this review are reflected in Box 2.

Terms were included as full text for both of these searches, with truncation used where possible to capture variation in the terminology. The searches were not limited to the English language nor were they restricted in any other manner (apart from the aforementioned year of publication).

Box 2: Search Terms and Strategy for review on interventions to improve HAART use:

<p>Terms:</p> <ol style="list-style-type: none">1. Inject*2. HIV treatment3. ARV4. ART5. HAART6. antiretroviral7. treatment8. service9. outcome10. delivery11. intervention*	<p>Search Strategy:</p> <p>A: [1] AND</p> <p>B: [2 or 3 or 4 or 5 or 6] AND</p> <p>C: [7 or 8 or 9 or 10 or 11]</p>
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To reduce the risk of publication bias and address potential gaps in the automated searches, we supplemented these searches with several additional search strategies to identify studies that were not yet published in peer-reviewed journals.

These supplementary searches used the same domains and key terms as the automated searches. First, the published conference abstracts from HIV/AIDS and drug use conferences held between January 2008 and August 2011 were searched for relevant abstracts and the authors were asked for copies of their posters or presentations. Second, we searched the websites of international organizations working with people who inject drugs (such as Harm Reduction International, Human Rights Watch, Open Society Institute, and the Asian-Pacific Network for people who are HIV positive, UNAIDS, UNODc, and World Health Organisation) for relevant research reports related to access to ART for PWID (or interventions to improve access). Third, we contacted authors of selected papers to request copies of upcoming publications. Fourth, we contacted experts within the International Reference Group to the UN on HIV and Injecting Drug Use as well as country experts from various regions to request relevant reports. Finally, we hand-searched the reference lists of all selected studies (as well as reports, commentaries and review articles) for additional citations. Studies identified through these procedures were entered into the review databases if they met our eligibility criteria.

2.3. Study selection

Using a pre-defined protocol (available on request), four investigators (SD, BM, SP, & ZP) independently scrutinized the abstracts of papers, reports and conference proceedings, obtained through the aforementioned search strategies, for suitability before obtaining the full text of relevant articles. After obtaining the full text of all relevant articles, these investigators then independently assessed whether each article was eligible to be included in the study. The investigators then met to discuss any differences in their selections and reach consensus about what to include or exclude. This process was followed for both reviews.

2.4. Data Extraction

Data extraction was conducted using standardised forms. For the first review, data were extracted about study characteristics (including study date, location, design, and recruitment setting), participant characteristics (including age, gender, race/ethnicity, and percentage of the sample who injected drugs), correlates of access to ART, and correlates of adherence to ART regimens. Data extraction was performed by four authors. Two authors (SP & ZP) independently extracted data for the first 22 articles and two further authors (SD & BM) independently extracted data for the remainder of the articles. The four authors then met to compare data extraction sheets and differences of opinion were resolved by discussion and re-reviewing the articles or reports.

For the second review, data were extracted about study characteristics (including study date, location, design, and recruitment setting), type of service to improve access or adherence to ART, and outcomes on ART uptake and adherence (where these were reported). Data extraction was performed by two authors (AP and BM). The authors then met to compare data extraction sheets and differences of opinion were resolved by discussion.

3. Factors associated with the effective use of HAART among PWID

This section presents key findings for the systematic review of barriers and facilitators to HAART access and adherence for people who inject drugs. These findings are grouped into factors associated with access and factors associated with adherence to HAART for PWID.

3.1. Results of the systematic review

The various searches identified 1752 abstracts of potentially relevant studies. After removing duplicates and screening the abstracts for studies that clearly did not meet the review's inclusion criteria, 1654 abstracts were excluded from further review. The full-text papers for the remaining 98 abstracts were then obtained and screened for eligibility. In this second screening, 12 studies were excluded because they were reviews, commentaries or opinion pieces and did not present primary data. A third screening excluded 6 further studies because they did not report results disaggregated by injection drug use. In addition, 7 studies because they reported exclusively on biological outcomes (such as HIV-1 RNA viral load and CD4+ cell counts) rather than the use of ART. We thus included 73 eligible papers for full data extraction (Figure 2).

3.1.1. Study characteristics

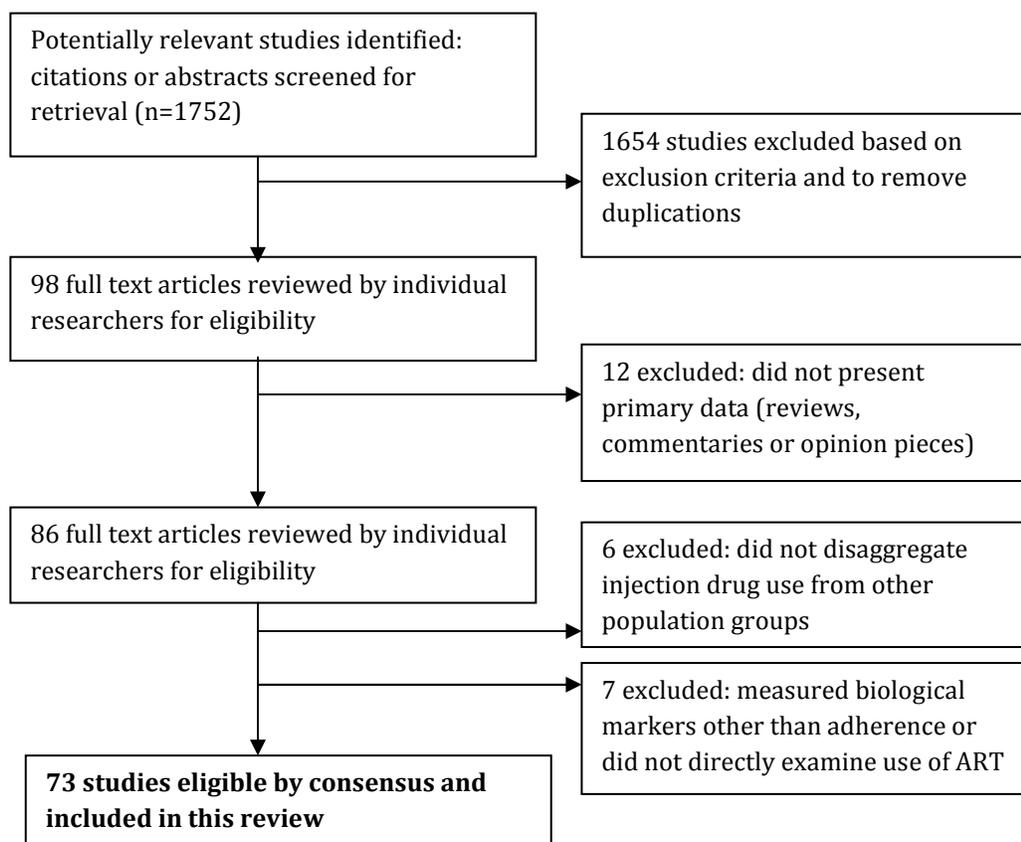
Seventy-three studies were considered which examined a total of 53, 706 participants (range 12-8660, median 252), the majority of whom were PWID (n= 29,151, 54.3%). Characteristics of the selected studies are summarized in Table 1. In spite of searching for papers and reports published in other languages, almost all the identified studies that met our inclusion criteria were in English.

Study origin

The large majority (54, 74.0%) of the papers originated from studies conducted in developed countries. Of the papers that were included in this review, 28(38.4%) were from studies conducted in North America, 16 (21.9%) were from Canada, and 10 (13.7%) were from Europe. Of the European studies, one was from Ireland [68], four were from

France [60, 65, 102, 106], two from Spain [27, 97], one from Italy [52], one from Switzerland [121] and one from Poland [103]. There was some emerging research from less developed regions including South America (3, 4.1%), Eastern Europe and Northern and Central Asia (9, 12.3%), and East and South-East Asia (7, 9.6%). More specifically, there were three studies included from the South Americas: two from Brazil [63, 70] and one from Mexico [62]. There were six studies from the Eastern Europe, Northern and Central Asia region: two from Russia [54, 107], two from Ukraine [76, 94], one from Kyrgyzstan [71], and two multi-country studies that covered Azerbaijan, Russia, Georgia and the Ukraine [96] and 21 countries in the region [59]. When studies from East and South East (SE) Asia were considered, there was one multi-country study that covered India, China, Indonesia, Myanmar, Nepal and Vietnam [56]; one study from Vietnam [91], one from Thailand [75], and three from China [77, 108, 109]. We were unable to identify any studies conducted in Africa or the Middle East that met the eligibility criteria for this review (Table 1).

Figure 2: Flow diagram of studies included in the review.



Study design

When the types of studies included in the review were examined, there was a preponderance of longitudinal cohort studies (n= 35). These accounted for 47.9% of the studies included in the review. While most of these studies were prospective studies assessing primary data, two were retrospective and analysed secondary data from administrative and medical records. For the remainder of the studies, there were two (2.7%) randomized controlled trials, one (1.4%) case control study, 18 (24.7%) cross-sectional studies, three (4.1%) mixed methods designs (that included a cross sectional survey and a qualitative component), and 14 (19.1%) qualitative studies included in the review. Almost all the longitudinal cohort studies originated from North America, Canada or Europe. Most of the qualitative studies originated from Central and Eastern Europe, Central Asia or East and SE Asia (Table 1).

Population characteristics

All of the studies included in this review focused on adult populations (at least 18 years old). When studies that did not report the gender distribution of participants were excluded from the analysis (n=15), females comprised 30.1% (12,841) of the total population of 42,679 participants. Similarly, when studies that did not report on the ethnicity of participants were excluded from the review (n =39), ethnic minorities (such as aboriginal, African American, Hispanic) comprised 68.0% (14,683) of the total population of 21, 595 participants (Table 1). Studies that did not report on ethnicity mostly originated from countries other than North America and Canada.

The included studies represented participants recruited from a broad range of settings. A total of 36 (49.3%) studies recruited 15,165 participants from community-based settings. These participants represented 28.2% of the total number of participants. A further 12 (16.4%) studies recruited 14, 666 participants (27.3% of the total number of participants) from HIV care services. Eight (11.0%) studies recruited 2876 participants from hospitals

representing 5.4% of the study population. Three (4.1%) studies recruited 6128 participants (representing 11.4% of the total number of participants) from primary health care services, four (5.5%) recruited 4162 participants from mixed settings and two (2.7%) studies were located in prisons where 1758 participants were recruited.

3.2. Barriers and facilitators to the initiation of ART among PWID

Tables 2-4 summarise the factors associated with access to and the initiation of ART among PWID. As there were large variations in the types of methods used to assess access, we were unable to conduct a meta-analysis to pool the results of the included studies. As such, this section provides a narrative synthesis of the key factors associated with access. These factors are categorised into patient-level (Table 2), disease and treatment-related (Table 3) and systemic (Table 4) barriers and facilitators to the use of ART.

3.2.1. Patient-level barriers and facilitators

Patient-level barriers and facilitators to the use of ART among PWID were noted in 29 studies (Table 2). These barriers and facilitators are grouped into socio-demographic, psychological and social -structural factors.

Socio-demographic factors associated with access to ART

Nine studies identified socio-demographic factors associated with ART use among PWID (21, 55, 67, 81, 105, 113, 123, 126-127; Table 2). These included age, education, gender, and ethnicity. After adjusting for the influence of other covariates, age was significantly associated with access to ART in only four studies (21, 67, 81, 105) where it was a weak predictor of access to ART. In all of these studies being older was associated with greater likelihood of ART uptake.

Table 1. Characteristics of selected studies (2000-2011)

Source	Country	Setting	Study objectives	Study design	Sample size	Population%	Age, years (range)	Ethnicity (%)	Female (%)
Aloisi et al. (2002) (52)	Italy	Hospital-based	Adherence	Prospective cohort study(1997-2000)	366	IDU 100%	>18 years of age	Not reported	114 (31.1%)
Altice et al. (2003) (53)	USA	Community	Access	Prospective cohort study(1997-1998)	13	100% IDU	34-48	Black 5 (38.5%) Hispanic 2 (23.1%) White 5 (38.5%)	7 (54%)
Amirkhanian et al. (2011) (54)	Russia	Community	Adherence	Cross-sectional (2008-2009)	492	312 (63.4%)	30.2 (29) overall 29.7 (29) IDU	Not reported	Not reported
Andersen et al. (2000) (55)	USA	General health service	Access	Prospective Cohort study (1996-1997)	2776	100% IDU	18-45	White 1359 (48.9%) African American 928 (33.4%) Hispanic 399(14.4%) Other 90 (3.2%)	819 (29.5%)
APN+ (2011) (56)	6 in Asia (India, China, Indonesia, Myanmar, Nepal,Vietnam	Community	Access	Mixed (Cross-sectional and Qualitative) (2008)	945 survey 27 in focus group	100% IDU	Mean 31.1 (30.7-31.5)	Not reported	187 (19.8%)
Arnsten et al (2007) (57)	USA	Community	Adherence	RCT (2001-2003)	636	100% IDU	>40 years 60.3%	Non-hispanic white 43 (7.0%) Nonhispanic black 412 (66.0%) Hispanic 124(20.0%) Nonhispanic other 42 (7.0%)	223 (35.0%)
Berg et al. (2004) (58)	USA	Drug Service	Adherence	Prospective Cohort study (1998-2001)	113	100% IDU 51% current	30-50	Hispanic 75(66%) Black 25(22%) White 24 (12%)	55 (49%)

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Source	Country	Setting	Study objectives	Study design	Sample size	Population%	Age, years (range)	Ethnicity (%)	Female (%)
Bobrova et al (2007) (59)	21 countries in Central and Eastern Europe and Central Asia	Multiple settings	Access	Cross-sectional	55	Service providers	Not reported	Not reported	Not reported
Bouhnik et al. (2002) (60)	France	Hospital-based	Adherence	Prospective cohort study (1997-1999)	210	100% IDU	median 35 (IQR 32-38)	Not reported	58 (27.5%)
Broadhead et al. (2002) (61)	USA	Community	Adherence	Qualitative (2001)	15	100% IDU	26-47	White 4 (29%) African American 10 (71%)	7 (46%)
Brouwer et al. (2009) (62)	Mexico	Community	access & adherence	Cross sectional (2005)	222	100% IDU (past month use)	29-40	Not reported	17 (8%)
Campos et al. (2008) (63)	Brazil	HIV service	adherence	Cross sectional (2001-2002)	293	3.4% IDU	Not reported	Not reported	99 (34%)
Carrico, et al (2010) (64)	USA	Community	Adherence	Cross-sectional	122	44% IDU	26-51	African American 39 (32%) Hispanic 17(14%) Caucasian 50(41%) multicultural 11(9%) Asian 2(2%) Native American 2(2%)	0 (0%)
Carrieri et al. (2003) (65)	France	Hospital-based	adherence	Prospective cohort study (1995-1999)	96	100% IDU	>18 years of age	Not reported	30 (31.2%)
Celentano et al. (2001) (20)	USA	Community	Access	Prospective cohort study (1996-1999)	528	100% IDU	Mean age 40	African American 496 (94%)	138(26.1%)
Chakeapani et al. (2008) (66)	India	Community	Access	Qualitative	23	100% IDU	26-48 (Mean 35)	100% Tamil	Not reported

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Source	Country	Setting	Study objectives	Study design	Sample size	Population%	Age, years (range)	Ethnicity (%)	Female (%)
Chander et al. (2006) (67)	USA	Hospital-based	Access & adherence	Prospective cohort study (1998-2003)	1711	100% IDU	Mean age 38 (35-50)	Caucasian 327 (19.1%) African American 1384 (80.9%)	618(36.1%)
Clarke et al (2003) (68)	Dublin, Ireland	Hospital-based	Access	Cross-sectional (2000)	150	100% IDU	19-29	Not reported	63(42%)
De Joncheere et al (2009) (69)	Latvia	HIV service	Access	Qualitative (2009)	12	Service provider	Not reported	Not reported	Not reported
de Melo et al (2006) (70)	Brazil	HIV service	Access	Retrospective cohort study (AIDS registry) (1986-2002)	170	Stratified by IDU status: NIDU:57.1% IDU:39.4%	mean age 30.0 (IQR 25-36)	Not reported	Overall: 19 (28.2%) IDU: 56 (57.7%) NIDU
Dzhalbieva et al (2009) (71)	Krygyzstan	Community	Access	Qualitative (2007-2008)	73	100% IDU	Median 26-35 (48%)	Kyrgyz 7 Russian 52 Uzbek 27 Other 14	73 (100%)
Eramova et al (2010) (72)	Lithuania	HIV service	Access	Qualitative (2010)	14	Service provider	Not reported	Not reported	Not reported
Gardner et al. (2002) (73)	USA	Drug service	Access	Cross-sectional (1993-1995)	273	100% IDU	18-45	Not reported	273 (100%)
Gebo et al. (2003) (74)	USA	HIV service	Adherence	Cross-sectional (1999-2000)	196	48.9% IDU	Mean age: 37.0	African American 151 (77%)	61(31.0%)
Himelhoch et al. (2007) (21)	USA	Drug service	Access	Cross-sectional (2001)	5119	1561 (30.5%) IDU	Median age 41.6	Caucasian 3501 (68.4%)	1556(30.4%)

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Source	Country	Setting	Study objectives	Study design	Sample size	Population%	Age, years (range)	Ethnicity (%)	Female (%)
Human rights Watch/TTAG (2007) (75)	Thailand	Community	access	Qualitative	43	100% IDU (current and former)	Not reported	Not reported	Not reported
Human Rights Watch (2006) (76)	Ukraine	Multiple settings	access	Qualitative (2005)	101	Injection Drug users, sex workers and people living with HIV	Not reported	Not reported	Not reported
Human Rights Watch (2010) (77)	China	Drug Service	Access and adherence	Qualitative (2010)	33	Current and former IDU	Not reported	Not reported	Not reported
Johnson, et al (2003) (78)	USA	Drug service	Adherence	Cross-sectional (2000-2002)	2765	221 (8%) IDU	17-92	African American 1368 (49%) Hispanic 510 (49%) White 719 (49%) Other 168 (6%)	664 (24%)
Jones et al. (2010) (79)	USA	Community	Access	Cross-sectional (1999-2006)	416	247 (59%) IDU (stratified by IDU and HIV status)	38.16 (7.05)	African American 231 (56%) Hispanic 100 (24%) White 104(25%)	183 (44.%)
Kavasery et al (2009) (80)	USA	Community	Adherence	Prospective cohort study (1996-2006)	335	100% IDU	40-47	African American 322(96%)	94 (28%)
Kerr et al. (2004) (36)	Canada	Community	Adherence	Prospective cohort study (2000-2001)	108	100% IDU	Mean 39 (7.1) (26-56)	Not reported	49 (45.4%)
Kerr et al. (2005) (40)	Canada	Community	Adherence	Prospective cohort study (2000-2001)	160	100% IDU	Mean 39 (7.0) (26-56)	Not reported	69 (43%)

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Source	Country	Setting	Study objectives	Study design	Sample size	Population%	Age, years (range)	Ethnicity (%)	Female (%)
Knowlton et al. (2010) (81)	USA	Community	Access	Prospective cohort study (2001-2005)	807	100% IDU in past 12 months	Median age 42.5 years	Nonhispanic black 605 (75%)	307 (38%)
Loughlin & Metsch (2004) (90)	USA	HIV service	Access	Cross sectional (2000-2001)	420	Service providers to IDU	46.6% 25-44 years; 53.4% were 45 years or older	White 263 (62.7%) African American 63 (62.7%) Other 94 (22.4%)	189(45%)
Maher et al. (2007) (91)	Vietnam	Community	Access and adherence	Qualitative (2006)	Not reported	100% IDU	Not reported	Not reported	Not reported
Milloy et al (2011) (92)	Canada	Community	Adherence	Prospective cohort study (1996-2009)	490	100% IDU	Not reported	192 (39.2%) aboriginal	201 (41%)
Milloy et al (2011) (93)	Canada	Community	Adherence	Prospective cohort study (1996-2009)	247	100% IDU	Not reported	111 (46%) aboriginal	112 (47%)
Mimiaga et al. (2010) (94)	Ukraine	HIV service	Adherence	Qualitative	16	100% IDU	31.6 (7.0)	Not reported	5 (31%)
Morris et al (2007) (95)	USA	Community	Access	Prospective cohort study MACS 1998—2003 WIHS 1994-2002 ALIVE 1988-1994	2266	Stratified by IDU status: IDU 843 (37.2%) Non-IDU 1423 (66.8%)	Not reported	African American IDU 523(62%) African American NIDU 498(35%) Hispanic IDU 194(23%) Hispanic NIDU 640 (45%)	IDU 556(66%) NIDU 847(59.5%)

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Source	Country	Setting	Study objectives	Study design	Sample size	Population%	Age, years (range)	Ethnicity (%)	Female (%)
Open Society Institute (2009) (96)	Azerbaijan Russia, Georgia Ukraine	Community	Access	Mixed methods (2007-2008) Qualitative interviews and cross-sectional survey	701 (376 in survey)	100% IDU	Not reported	Not reported	Not reported
Orejudo et al (2009) (97)	Spain	Drug Service	Adherence	Prospective cohort study (2003-2004)	100	100% IDU	Mean 37 (20-49)	Not reported	20 (20%)
Palepu et al (2004) (98)	USA	General health service	Access and adherence	Prospective cohort study (1997-2001)	349	59% IDU 41% NIDU	Mean 41	Non-White 121 (62.4%)	40 (20.6%)
Palepu et al (2004a) (99)	Canada	Prison	Adherence	Prospective cohort (1997-2002)	1746	101 prison 1645 not incarcerated IDU ex/IDU 395 Never IDU 1351	Incarcerated: 34 (29-40) Not incarcerated: 37 (32-44)	Not reported	Incarcerated: 10 (10%) Not incarcerated: 296 (18%)
Palepu et al (2006) (100)	Canada	Community	Adherence	Prospective cohort study (1996-2003)	278	100% IDU (276 (99.3%) HIV and HCV co-infected)	Adherent: 36.3 (32.7, 42.3) Nonadherent: 35 (28-42)	Adherent aboriginal 41 (31.1%) Nonadherent aboriginal 41 (31.1%)	Adherent: 48 (37.2%) Nonadherent 70 (46.9%)
Palepu et al (2011) (101)	Canada	Community	Adherence	Prospective cohort study (1996-2008)	543	100% IDU stratified by housing status	Homeless: Mean 35.8 Non-homeless mean 37.9	Homeless: Aboriginal: 32.9% Non-homeless aboriginal 33.4%	Homeless: (33.6%) Non-homeless: 38.8%
Peretti-Watel (2006) (102)	France	HIV Service	Adherence	Cross-sectional (2003)	2932	447 (15.2%) IDU	Non-adherent mean 40.9% Adherent: mean 44.6%	Not reported	Non-adherent 287 (28.6%) Adherent: 393 (26.6%)

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Source	Country	Setting	Study objectives	Study design	Sample size	Population%	Age, years (range)	Ethnicity (%)	Female (%)
Piekarska-Mankiewicz & Cholewinska (2009) (103)	Poland	Drug Service	Adherence	Case-control (2008)	60	50% IDU on MMT 50% NIDU who HIV positive	Not reported	Not reported	Not reported
Roberson et al. (2009) (104)	USA	Prison	Adherence	Qualitative (2004-2005)	12	100% IDU from prison health services	22-45	Not reported	12 (100%)
Rodriguez-Arenas et al. (2006) (27)	Spain	Hospital-based	Access	Prospective cohort study (1997-2003)	4643	Stratified by IDU status: 2621 (56.4%) IDU 2022 (43.6%) NIDU	IDU median: 34 (IQR 31-37) Total sample: median 35 (IQR 31-39),	Not reported	588 (22.4% of IDU) Overall sample 1300 (27%)
Rompalo et al. (2001) (105)	USA	Community	Access	Cross-sectional (1993-1995)	579	Stratified by IDU status: IDU 299 Sexual transmission 280	16-55	African American 349 (60.3%) White 122 (21.0%) Latina 95 (16.4%)	579 (100%)
Roux et al (2008) (106)	France	Hospital-based	Adherence	Prospective cohort study (1995-2000)	276	100% IDU	median 35 years (IQR 32-38)	Not reported	78(27.5%)
Rusakova et al (2008) (107)	Russia	Mixed settings	Access and adherence	Mixed methods (Cross-sectional survey and qualitative)	551 survey 26 focus group	More than 60% IDU	St Petersburg median 25-29 Orenburg median (20-24)	Not reported	(61.7%) St Petersburg (70.5%) Orenburg

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Source	Country	Setting	Study objectives	Study design	Sample size	Population%	Age, years (range)	Ethnicity (%)	Female (%)
Sabin et al. (2008) (108)	China	Hospital-based	adherence	Qualitative (2005-2006)	36	21 (58.3%) IDU 15 (41.7%) NIDU	23-55	Not reported	17 (47.2%) of which 2 (11.8%) were IDU
Sambamoorthi et al (2000) (109)	USA	General health service	Access	Retrospective cohort study (1988-1996)	2600	100% IDU who were Medicaid beneficiaries	11.9% between 18-29 51.1% between 30 and 39, 31.5% between 40 and 49	African American 1649(63%) white 517(19.9%), latino 434(16.7%)	947(36.4%)
Shannon et al (2005) (110)	Canada	Community	Adherence	Prospective cohort study (2002-2004)	184	109 (59.2%) current IDU	Non-adherent 41 (36-46) Adherent 43 (41-50) Overall 42 (37-48)	Aboriginal 72 (39%)	Non-adherent 46 (37%) Adherent 12 (22%)
Small et al (2009) (111)	Canada	HIV service	adherence	Qualitative (2006-2007)	12	100% IDU	Mean 38 years (25-60)	White 7(58.3%) black 1(8.3%) aboriginal 1(8.3%), asian 2(16.6%) Hispanic 1(8.3%)	0 (0%)
Stein et al (2000)(112)	USA	Drug service	adherence	Cross-sectional (1997-1998)	42	100% IDU in MMT	Not reported	White 14 (33%) African American 18 (43%) Latino 6 (14%)	15(36%)
Tapp et al. (2011)(113)	Canada	Community	access and adherence	Prospective cohort study (1996-2008)	545	100% IDU	> 24 years old: 97% male and 88% female	Not aboriginal: 249 (73%) male 110 (54%) female	204 (37%)
Turner et al. (2001) (114)	USA	Community	access	Prospective cohort study (1996-1997)	2267	531 (24%) history of injection drug use	Majority 26-49 years old	50% minority ethnic racial groups	567(25%)

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Source	Country	Setting	Study objectives	Study design	Sample size	Population%	Age, years (range)	Ethnicity (%)	Female (%)
Uhlmann et al (2010) (115)	Canada	Community	Access and adherence	Prospective cohort study (1996-2008)	231	100% IDU in 12 months preceding study	<24 years old: 18 (7.8%) 25 years of older 213 (92.2%)	nonaboriginal 153(66.2%) Aboriginal: 78 (23.8%)	87 (37.7%)
Wagner & Ryan (2004) (116)	USA	Community	Adherence	Cross-sectional (2003)	51	100% IDU	mean 39 (22-57)	white 17(33%) african American 22(43%) latino 9(18%)	5(10%)
Waldrop-Valverde et al. (2005) (117)	USA	Community	Adherence	Cross-sectional	58	100% IDU	Non-homeless: Homeless:	African American 52 (89.6%)	Non-homeless: 14 (24%) Homeless:0 (0%)
Waldrop-Valverde et al. (2008) (118)	USA	Community	Adherence	Cross-sectional	57	100% IDU	42.7 (5.6)	African American 51 (89.4%)	13 (22.8%)
Wang et al. (2010) (119)	China	HIV service	Adherence	RCT (2007-2008)	116	100% IDU	Mean: 36.7 (SD 5.6) (24-54 years)	Not reported	19(16.4%)
Ware et al. (2005) (120)	USA	Multiple settings	Adherence	Qualitative (2005)	52	100% active drug users	Mean: 41 years (30-51)	White 25 (48%) African American 20 (38%) Latin 5 (10%) Other 2 (4%)	14 (27%)

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Source	Country	Setting	Study objectives	Study design	Sample size	Population%	Age, years (range)	Ethnicity (%)	Female (%)
Weber et al. (2009) (121)	Switzerland	HIV service	Access and adherence	Prospective Cohort study (1997-2006)	8660	NIDU: 6091 (70.3%) IDU: 2569 (29.7%) IDU transmission stratified by drug use status: NoDMT and no IDU: 1080 (12.5%) Drug maintenance treatment (DMT) and no IDU: 741 (8.6%) DMT & IDU: 607 (7.0%) IDU and no DMT (141 (1.6%)	Not reported	Not reported	Not reported
Westergaard et al. (2011) (122)	USA	Community	Adherence	Prospective cohort study (1998-2009)	437	100% IDU stratified by incarceration history	>18 years old	95% African American	31%
Wood, Kerr et al. (2006) (123)	Canada	Community	Access	Prospective cohort study (1996-2003)	91	100% IDU Stratified by ethnicity	Not reported	Aboriginal Nonaboriginal	Not reported

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Source	Country	Setting	Study objectives	Study design	Sample size	Population%	Age, years (range)	Ethnicity (%)	Female (%)
Wood, Montaner et al. (2004) (124)	Canada	HIV service	adherence	Prospective cohort study (1996-2000)	1422	IDU: 359 (25.2%) NIDU: 1063 (74.8%)	IDU: Median 37.6 (32.3-43) NIDU: Median 37.1 (31.9-44.0)	Not reported	IDU: 85 (23.7%) NIDU: 139 (13.1%)
Wood, Hogg et al. (2005) (125)	Canada	Community	access	Prospective cohort study (1996-2003)	234	100% IDU Stratified by MMT on baseline versus no MMT at baseline	Not reported	Not reported	Not reported
Wood Kerr Zhang et al. (2008) (126)	Canada	Community-based	adherence	Prospective cohort study (1996-2003)	460	100% IDU	Median 34 years old (IQR: 28-40).	Non White 215 (46.7%) Nonwhite self-identified as Aboriginal [171; 37.2%], Asian [17; 3.7%], Black [10; 2.1%] and other [17; 3.6%].	198 (43.0%)
Wood, Kerr Hogg et al (2006) (127)	Canada	Community-based	access	Prospective cohort study (1996-2003)	105	100% IDU : Stratified by receipt of test results: 64 (61%) receive test within 8 month of baseline 41 (39%) not receive test results	Median: 34 years [IQR 28-40];	Not reported	Not reported

Similarly, after adjusting for the influence of other covariates, length of education was (weakly) associated with ART uptake among PWID in only two studies (55, 81). Both of these studies found that PWID who had not completed high school had significantly diminished odds of accessing ART compared to those who had completed high school.

In contrast, gender and ethnicity were more strongly associated with ART initiation among PWID. After adjusting for the influence of other variables (including need for ART), gender was significantly associated with ART initiation in five cohort studies (21, 55, 67, 113, 126). In three of these studies, men who inject drugs had significantly higher odds of accessing ART than their female counterparts (21, 67, 113). The remaining two studies (55, 126) noted that women who inject drugs had significantly lower rates of ART uptake compared to men. Six cohort studies (21, 55, 67, 105, 123, 126) also reported that ethnicity was associated with access to ART, even after controlling for the influence of potential confounders. These studies found that belonging to an ethnic minority (such as being African American, Hispanic or Aboriginal) was associated with significantly reduced odds of ART access (21, 55, 67, 105, 123) or slower rates of ART initiation (126) compared to White participants.

Importantly, PWID who belong to several marginalised populations appear the most vulnerable in terms of not accessing ART. For example, one study (55) found that the odds of not accessing ART increased when gender, education and ethnicity were examined simultaneously. This study found that marginalised populations (such as women and ethnic minorities) had fewer financial resources compared to less marginalised groups, decreasing the odds of ART use in contexts where there is not universal access to free health care (55). Yet, as similar findings were found in settings where there is universal access to free health care (113, 123, 126), limited access to ART for women and ethnic minorities cannot be attributed entirely to greater financial and economic barriers in these populations. Regardless of the reasons for these findings, it is clear that gender and ethnicity are associated with differential access to ART, with women and ethnic minorities who inject drugs particularly affected by issues of access. Increased efforts are required to

close the gap between systems of HIV treatment delivery and these vulnerable populations. This will necessitate more research into the specific barriers to ART that women and ethnic minorities that inject drugs face and whether these barriers exist at the point of treatment or within the community. Future studies, including qualitative research methods, will be useful for identifying these population-specific barriers.

Psychological factors associated with access

Psychological barriers and facilitators to the use of ART among PWID were identified by 20 studies (20-21, 27, 53-4, 56, 66-67, 70, 73, 75, 79, 81, 95, 105, 107, 114, 121, 126-7; Table 2). These psychological factors include cognitive processes (such as self-efficacy regarding the use of ART and management of side-effects), the presence of co-occurring mental illness, and substance use history and severity. After adjusting for the influence of other variables, the most frequently reported psychological factor associated with ART use among PWID was the current use of alcohol and other drugs. Twelve studies (20, 27, 66-7, 70, 73, 75, 81, 95, 105, 107, 121) found that current substance use significantly reduced the likelihood of accessing ART compared to individuals who had never used drugs or who reported a history of injection drug use (IDU). Although individuals who currently injected drugs had less likelihood of accessing ART than individuals with a prior history of IDU, two studies (92, 94) found that individuals with a history of IDU had worse access to ART than those who had never injected drugs.

Some of the included studies (20, 67, 107, 121) suggest that the odds of accessing ART are further reduced when drug problems are severe as indicated by severity of dependence scores (107), consistent injection drug use (20), multiple drug use (67), or daily drug use (121). In support of this, one prospective cohort study (65) found a dose-response relationship between alcohol problem severity in combination with illicit drug use: as the severity of the alcohol problems increased for current IDU, the likelihood of accessing ART declined. There are several confounding variables that may partially account for the relationship between drug problem severity and poor access to ART for PWID, including

service providers' concerns about adherence to HAART among active drug users (27, 81), high levels of social instability that may accompany active illicit drug use (20), PWID' concerns about being treated punitively in the health care system (9), and rigid regulations that hamper access to HIV treatment for PWID in many countries (53). Yet the negative impacts of drug problem severity on rates of ART initiation for PWID persist even after adjusting for many of these confounding factors. The high risks for poor or delayed ART use among PWID with high levels of drug problem severity, point to the need for strategies to improve HAART use among this population. One promising avenue for intervention is to reduce drug problem severity through drug dependence treatment including opiate substitution therapy (OST). While the impact of OST on the uptake of ART among PWID will be discussed later in this report, it is useful to note that these treatments attenuate the impact of active drug use on the uptake of ART (121).

A further psychological factor associated with ART use among PWID was the presence of (untreated) co-occurring mental health problems; specifically depression. Despite clear evidence that untreated depression is a major barrier to the use of HAART among non-drug using populations (see 128-130), this was not a powerful predictor of HAART initiation among PWID. After controlling for the influence of other patient-level and treatment variables in multivariate analyses only three studies (21, 54, 79) identified depression as a risk for not initiating ART among PWID. In all of these studies, the relationship between depression and HAART uptake was weak, especially after current substance use had been taken into account. While mental illness may not contribute much to the likelihood of ART use among PWID, findings from at least one study that compared ART uptake among PWID with and without mental illness (21) suggest that the presence of untreated mental illness worsens the already low rates of ART uptake among PWID. Consequently, it is important to expand access to mental health services for PWID, especially as there is evidence that engagement in these services may improve access to HAART (130).

Cognitive factors also were associated with the initiation of ART among PWID. After adjusting for the influence of other variables, five studies (53, 56, 66, 81, 107) found

outcome expectancies associated with ART use among PWID (Table 2). One study (81) noted that PWID with positive outcome expectancies (such as beliefs that ART will provide health benefits) had greater odds of using ART than people with negative outcome expectancies. In contrast, PWID with negative outcome expectancies (such as beliefs that ART will “eat up methadone”, concerns about side effects and drug-ART interactions, and beliefs that ART will not work) were less likely to seek treatment for HIV (53, 56, 66, 107). In addition, two studies from developing countries reported that inadequate knowledge of ART was associated with low uptake of this treatment (56, 66). These beliefs and concerns are not unique to PWID and are commonly cited as barriers to HAART initiation among other populations (131). While these cognitive factors were not the most powerful predictors of ART use among PWID, findings from this review still point to the need to address these barriers to ART use among PWID. Other studies among non-drug using populations have found that a good patient-provider relationship where the provider adequately prepares the patient for HAART and a strong support network with other HIV positive people attenuates the effect of negative beliefs about HAART on treatment uptake (132). The importance of the patient-provider relationship is discussed in detail later on in this report.

Readiness to accept HIV status (as indicated by early receipt of HIV test results) was a final psychological factor associated with the uptake of HAART among PWID. Early receipt of HIV test results was positively associated with the uptake of ART in one cohort study (127). In this study, after controlling for the influence of all other covariates, PWID who received their HIV tests results soon after testing initiated ART at an elevated rate compared to PWID who delayed the receipt of the test results.

Table 2. Patient-level factors associated with access to and the initiation of ART among PWID: findings from selected studies (2000-2011)

Source	Country	Study design	Sample size	Social structural	Psychological (including cognitive)	Socio-demographic
Altice et al. (2003) [53]	USA	Prospective cohort study(1997-1998)	13		<i>Non-access associated with</i> <u>Negative Outcome expectations:</u> <u>Beliefs</u> would make sick or would “eat up their methadone”	
Amirkhanian et al. (2011) [54]	Russia	Cross-sectional (2008-2009)	492	<i>Non-access associated with</i> <u>Social isolation due to stigma:</u> Number of discrimination experiences (AOR 1.06, CI 1.10-1.12)	<i>Non-access associated with</i> <u>Depression</u> (AOR 1.05, CI 1-1.10)	
Andersen et al. (2000)[55]	USA	Cohort study (1996-1997)	2776	<i>Access associated with:</i> <u>Poverty:</u> Current income< \$25 000 (AOR .64; p <0.01).		<i>Access associated with:</i> <u>Gender:</u> Female IDU: (AOR 0.58 (p <0.01) <u>Education:</u> (Less than high school education AOR 0.57 (p <0.01). <u>Ethnicity</u> (African American less likely than White (AOR 0.44, p <0.01)
APN+ (2011) [56]	6 in SE Asia	Mixed (Cross-sectional and Qualitative) (2008)	945 survey 27 in focus group		<i>Non-access associated with:</i> <u>Lack of adequate knowledge of ART</u> (26.7%), <u>Negative outcome expectancies:</u> fear of side effects (10.4%) fear of ART and drug interactions (10.0%).	

Source	Country	Study design	Sample size	Social structural	Psychological (including cognitive)	Socio-demographic
Brouwer et al. (2009) [62]	Mexico	Cross sectional (2005)	222	<u>Non-access associated with:</u> <u>Vulnerable social status:</u> Deportees/migrants access to public health (OR 0.41, CI 0.19-0.89) and, medical care (OR: 0.37, CI: 0.13-1.00)		
Celentano et al. (2001) [20]	USA	Prospective cohort study (1996-1999)	528	<u>Access associated with:</u> <u>Social stability and income:</u> Health insurance (ARH 2.05, CI: 1.21-3.49).	<u>Delayed access associated with:</u> <u>Consistent injection use</u> (ARH 2.76, CI 0.28-0.63)	
Chakeapani et al. (66)	India	Qualitative	23	<u>No access associated with:</u> <u>Unmet basic needs.</u> Unstable social circumstances: food and shelter. Meeting basic needs is a priority	<u>No access associated with:</u> <u>Active drug use</u> which prevents PWID from taking care of their health <u>Lack of self-efficacy and low motivation</u> <u>Negative beliefs about HAART-</u> based on inadequate and incorrect knowledge	
Chander et al. (2006) [67]	USA	Prospective cohort study (1998-2003)	1711		<u>Access associated with:</u> <u>Active drug use:</u> (AOR 0.58, CI 0.49-0.70) Compared to alcohol only, drug user (AOR 0.54, CI: 0.43-0.68), drug use and moderate alcohol (AOR 0.68, CI: 0.54-0.88), Drug use and hazardous alcohol (AOR 0.40, CI: 0.29-0.57)	<u>Access associated with</u> <u>Age:</u> Older (>36) (AOR 1.38 CI 1.15-1.66) <u>Gender:</u> Being <u>male</u> associated (AOR 1.33, CI 1.11-1.59) <u>Ethnicity:</u> African American (AOR 0.53, CI 0.41-0.69)
de Melo et al (2006) [70]	Brazil	Retrospective cohort study (AIDS registry) (1986-2002)	170		<u>Access associated with:</u> <u>Drug use:</u> IDU significantly less chance of receiving ART prescription than NIDU (77.3% vs 61.2% p = 0.03)	

Source	Country	Study design	Sample size	Social structural	Psychological (including cognitive)	Socio-demographic
Gardner et al. (2002) [73]	USA	Cross-sectional (1993-1995)	273		<i>Access associated with:</i> <u>Active drug use:</u> Current injection drug users low rates of ART initiation	
Himelhoch et al. (2007)[21]	USA	Cross-sectional (2001)	5119		<i>Access associated with</i> <u>Severe Mental illness:</u> (AOR 0.85 , CI:0.71-1.23) <u>Mental illness and IDU</u> (AOR 0.52 ,CI 0.41-0.81) <u>Continued IDU</u> (AOR 0.64,CI: 0.58-0.85)	<i>Access associated with</i> <u>Gender:</u> Male (AOR 1.41, CI: 1.10-1.03) <u>Ethnicity:</u> Black less likely than White (AOR 0.87,CI 0.75-1.16). <u>Age</u> (AOR 1.02, CI: (1.01-1.03)
Human Rights Watch/TTAG (2007) [75]	Thailand	Qualitative	43		<i>Access associated with</i> <u>Drug use status:</u> Former drug user (71.7%) more likely to initiate ART than current drug users (38.7%) (p <0.001)	
Jones et al (2010) [79]	USA	Cross sectional (1999-2006)	416		<i>Access associated with</i> Lower levels of <u>depression</u> among people who access ART compared to IDU with no ART F (1, 15) = 3.56, p <0.04.	
Knowlton et al. (2010) [81]	USA	Prospective cohort study (2001-2005)	807	<i>Access associated with</i> <u>social stability:</u> -Any health care coverage (AOR 2.29; CI: 1.57-3.34) -Stable housing (AOR 1.90; CI: 1.15-3.15)	<i>Access associated with</i> <u>Current drug use</u> (AOR 0.65; CI: 0.5-0.86) <u>Positive outcome expectancies</u> for HAART (AOR: 1.45, CI 1.07-1.98)	<i>Access associated with</i> <u>Education</u> less than grade 8 (AOR 0.55, CI: 0.36-0.83) Age (AOR 1.02; CI:1-1.05)

Source	Country	Study design	Sample size	Social structural	Psychological (including cognitive)	Socio-demographic
Maier et al. (2007) [91]	Vietnam	Qualitative (2006)	Not reported	<p><i>Access associated with</i> <u>Social stability:</u> -Unstable housing associated lower access as priority to secure shelter -Poverty-unable to afford costs associated with ART (treatment for side effects, for OI, CD4 and viral load tests)</p> <p><u>Social support:</u> Limited family support due to shame of being HIV positive drug user and fear of stigma leads to difficulties in getting resources for ART</p>		
Morris et al (2007) [95]	USA	Prospective cohort study	2266		<p><i>Non-Access associated with</i> <u>Current IDU:</u> IDU (AOR 1.78; CI:1.53-2.06)</p>	
Palepu et al. (2004) [98]	USA	Prospective cohort study (1997-2001)	349	<p><i>Access associated with</i> <u>Social stability:</u> Not being homeless (AOR 2.27 CI: 1.34-3.79).</p>		
Rodriguez-Arenas et al. (2006) [27]	Spain	Prospective cohort study (1997-2003)	4643		<p><i>Access associated with:</i> <u>Current drug use:</u> HAART uptake lower among treatment naïve current IDU compared to other transmission categories (AHR 0.67; CI: 0.57-0.79).</p>	

Source	Country	Study design	Sample size	Social structural	Psychological (including cognitive)	Socio-demographic
Rompalo et al. (2001) [105]	USA	Cross-sectional (1993-1995)	579		Access associated with <u>History of IDU</u> (AOR 0.54, CI: 0.38-0.79),	Access associated with <u>Ethnicity</u> : black (AOR: 0.50, CI: 0.34-0.74). <u>Age</u> : > 38 years of age, AOR 1.74, CI: 1.20-2.51)
Rusakova et al (2008)[107]	Russia	Mixed methods	577		Access associated with <u>Outcome expectations about HAART</u> : Fears about poor treatment tolerance, side effects, and belief that it will not work, belief that ART requires changes in drug use are reasons for not seeking treatment	
Tapp et al. (2011) [113]	Canada	Prospective cohort study (1996-2008)	545			Access associated with <u>Gender</u> : Male more likely to access ART than females (39% vs 30%, p = 0.042).
Turner et al. (2001) [114]	USA	Prospective cohort study (1996-1997)	2267		Access associated with <u>Current drug dependence</u> : (AOR 0.40, CI: 0.27-0.59); Any current <u>heroin</u> use (AOR 0.40 CI: 0.22-0.72). <u>Severity</u> of drug abuse ART (AOR 0.38, CI 0.24-0.58). <u>IDU history</u> If exposed to HIV via IDU (AOR: 0.50 CI: 0.38-0.66).	

Source	Country	Study design	Sample size	Social structural	Psychological (including cognitive)	Socio-demographic
Weber et al. (2009) [121]	Switzerland	Prospective Cohort study (1997-2006)	8660		Access associated with <u>Current Drug use</u> : Individuals in DMT with injecting drug use (AOR 0.79 CI: 0.71-0.89) Current IDU (AOR 0.80 CI 0.67-0.96)	
Wood, Kerr et al. (2006) [123]	Canada	Prospective cohort study (1996-2003)	91			Access associated with <u>Ethnicity</u> : Aboriginal participants initiated ART at slower rate (ARH 0.37 CI: 0.15-0.93)
Wood, Kerr Hogg et al (2006) [127]	Canada	Prospective cohort study (1996-2003)	105		Access associated with <u>Readiness to accept HIV status</u> : Early Receipt of HIV test results initiate ART at an elevated rate compared to those who receive late (ARH 1.87, CI: 1.05-3.33).	
Wood Kerr Zhang et al. (2008) [126]	Canada	Prospective cohort study (1996-2003)	460		Access associated with <u>Current drug use</u> : Daily heroin use (AOR 0.72, CI 0.61–0.85) associated with CD ⁴ monitoring.	Access associated with <u>Gender</u> : female gender (AOR 0.71, CI 0.57–0.89), <u>Ethnicity</u> : non-White (AOR 0.75, CI 0.60–0.94) associated with CD ⁴ monitoring,

RH = relative hazard, ARH adjusted relative hazard; CI= 95%confidence interval

OR = odds ratio; AOR odds ratio adjusted for confounders and covariates

Social -structural factors associated with the use of ART

Eight studies described social-structural barriers and facilitators to the use of ART among PWID (54-55, 62, 66, 81,91, 95; Table 2). These barriers include social support, social isolation, and indicators of social stability (such as stable housing, employment, and income). Substance use (particularly IDU) remains deeply moralised in many societies and those who use drugs face stigma, discrimination and social exclusion (133-134). Social isolation and social exclusion arising from a marginal social status were reported as barriers to ART initiation in two studies (54, 62). One study (54) noted that as the number of discriminatory experiences increased, the likelihood of not utilising ART grew. Another noted that having a doubly marginal social status such as being a PWID and being a refugee or migrant further reduces access to medical and health care services including ART (62). This is probably because people who are socially isolated and excluded from opportunities in mainstream society lack extensive social support networks that facilitate access to health services (44, 62). In addition, PWID who fear social isolation and exclusion may remain hidden from health services and may fail to initiate HIV care.

Another social- structural factor associated with the low uptake of ART among PWID is social instability, as indicated by social deprivation (poverty, low income, lack of employment) and lack of stable housing. After controlling for the influence of other variables on ART access, six studies (55, 61, 66, 81, 91, 98) identified some form of social instability as a risk factor for the poor uptake of ART. While existing HIV treatment research has given limited attention to the impact of housing on access to HAART among PWID (44), this review found emerging evidence of a relationship between these two variables. Unstable housing was associated with reduced likelihood of accessing ART in four studies (66, 81,91, 98; Table 2). Two of these studies found that PWID who were homeless were twice as likely not to access ART compared to those with stable housing. These findings are cause for concern as PWID living with HIV/AIDS are often economically disadvantaged and challenged by homelessness or unstable housing (135-6). Two qualitative studies (66, 91) suggest possible ways in which unstable housing reduces the likelihood of ART use. First, PWID with unstable housing often have multiple survival

needs (including food insecurity) and addressing these immediate needs for food and shelter is often viewed as more urgent than seeking health services (66, 91). In addition, meeting these competing priorities is often time consuming and there may be little time left for seeking health services [81].

Like unstable housing, social deprivation (as evidenced by food insecurity, low income and unemployment) contributes to low rates of ART use among PWID. Social deprivation was associated with reduced odds of ART use among PWID in four studies (55, 62, 81, 91). In countries where there is limited availability of free health care (e.g. the costs of health care for opportunistic infections and the costs of HIV disease monitoring are borne by the patients), low income limits access to services (91). However in countries with free access to HIV-related care, low income was also associated with less chance of ART initiation (55, 81). Apart from limiting the ability to afford health care costs, low income and deprivation may make the costs of transport to health services unaffordable. The limited income available to PWID may be used to secure other scarce resources such as food rather than on accessing health services (137-8). Taken together, these findings suggest that efforts to improve the social stability and reduce the social deprivation of PWID may hold benefits for HIV treatment initiation, especially as findings from a systematic review show that stable housing facilitates engagement in HIV care (135).

One social-structural factor that may buffer against the social instability associated with drug use is social support. When the influence of other variables associated with HAART use were controlled for, only one study identified the provision of social support as a facilitator of ART uptake (81). This qualitative study noted that when families provide tangible and emotional support for HIV treatment and care, this support encourages people to engage in HIV services and initiate HAART. Despite the few number of studies that examined the role of social support among PWID, many other studies among non-drug using populations have reported that social support (particularly by HIV positive peers) facilitates access to ART (132, 138). Further research on the potential buffering effect of

social support on barriers to accessing HAART among PWID may suggest promising avenues for interventions to improve HAART use among PWID.

3.2.2. Disease-level facilitators to the use of ART

HIV symptom severity and other disease outcomes are important indicators of need for HAART (55). Seven studies noted objective, need-related factors associated with HAART initiation (20-1, 54-55, 81, 105, 115; Table 3). All of these studies found that greater need for HAART among PWID was associated with a better likelihood of initiating HAART. Most of these studies identified HIV severity as a facilitator to ART initiation, with lower CD4 counts (20-1, 55, 81, 105, 115) and higher HIV RNA viral loads (115) associated with a greater likelihood of ART uptake, even after controlling for the influence of other variables. One reason for this may be that PWID who start to be bothered by HIV-related symptoms may drive people to seek HIV treatment. This explanation is supported by one study which reported an inverse relationship between HIV symptom severity and the use of ART (54).

While these findings suggest that access to HAART is related to objective need for these medications, it is important to note that in all of the aforementioned studies, the strength of the associations between CD4+ counts, HIV-1 RNA levels and HAART initiation for PWID is diminished when other potential barriers to access are considered. This suggests that while need for HAART (as indicated by disease-level factors) is an important and powerful determinant of HAART initiation among PWID, other barriers impinge on whether this need translates into HAART uptake. This clearly highlights the need for interventions to reduce barriers to HAART use among PWID.

3.2.3. Treatment-level barriers and facilitators to the use of ART

Treatment-related barriers and facilitators to the use of ART among PWID were noted in eleven studies (20, 56, 66, 69, 73, 75-76, 81, 90, 96, 107; Table 3). These barriers and facilitators centre on the quality of the patient-provider relationship. Findings from these studies suggest that good patient-provider relationships characterised by clear communication and information sharing, confidence in the providers' ability to treat HIV,

patient involvement in decision making, and a supportive and caring relationship facilitate the regular use of HIV services (an important condition for HAART initiation), better management of HIV and mitigate some of the other barriers to access (20,81). At least one study found that having a regular source of HIV care and having continuity with a service provider facilitates the rapid initiation of ART among PWID (20). Another factor associated with the rapid initiation of ART is having access to an HIV specialist physician rather than a general health provider (73). This may be because specialist physicians are better equipped to treat HIV positive PWID and less likely to delay access to care because of adherence concerns or unrealistic demands that the patient needs to stop using drugs before starting HAART (27).

On the other hand, a poor patient-provider relationship is an important barrier to the use of ART (56, 66, 69, 75-76, 90, 96, 107). Several studies found that service providers hold negative perceptions towards PWID and may deny or delay access to HAART until a person stops using drugs due to adherence concerns (76, 90, 96, 107). In some contexts, service providers may even deny access to ART to former IDU due to misinformation and bias towards people with a history of drug use (66, 79, 96, 107). These negative beliefs persist even though the World Health Organization has recommended that physicians not discriminate on the basis of current or former IDU status (139). While additional clinical training for physicians delivering ART to PWID may ameliorate some of these biases (2), a focus on increased training may mask some of the systemic factors that influence patient-provider relationships. Qualitative studies in this review show that where there is systemic stigma towards PWID, health care providers openly mistreat HIV positive PWID, not only denying them care but not providing confidential care and making them wait for lengthy periods for services (56, 66, 69, 75-76, 90, 96, 107). For PWID, this discrimination acts as a disincentive for ART use or any other kind of engagement with health services (56, 66, 69, 75-76, 90). These systemic influences on the uptake of ART among PWID are discussed more fully in the next section. Taken together these findings suggest that interventions are needed to promote better interactions between PWID and HIV service providers as a means of improving access to HAART.

Table 3. Disease and Treatment-related factors associated with access to ART: findings from selected studies (2000-2011).

Source	Country	Study design	Sample size	Treatment characteristics (Patient - provider)	Disease characteristics
Amirkhanian et al. (2011) [54]	Russia	Cross-sectional (2008-2009)	492		<i>No Access associated with <u>HIV symptom severity</u> (AOR 0.21, CI: 0.1-0.46) (reference no symptoms)</i>
Andersen et al. (2000) [55]	USA	Cohort study (1996-1997)	2776		<i>Access associated with <u>Disease severity</u>: CD⁴ <200 (AOR 4.56, p <0.01)</i>
APN+ (2011) [56]	6 in SE Asia	Mixed (Cross-sectional and Qualitative) (2008)	945 survey 27 in focus group	<i>Low access associated with <u>Poor patient-provider relationship and discrimination towards drug users</u>: Negative attitudes to drug users in health care system discourage treatment seeking. Drug users denied care or kept waiting for services-discourages treatment seeking.</i>	
Celentano et al. (2001) [20]	USA	Prospective cohort study (1996-1999)	528	<i>Access associated with: <u>Relationship with a provider</u>: Continuity and regular source of care associated with rapid initiation of ART (ARH 1.74, CI: 1.01-3.00).</i>	<i>Access associated with <u>Disease severity</u> CD⁴ count inversely associated increased probability of initiating ART (ARH 0.85, CI 0.75-0.96).</i>
Chakeapani et al. (66)	India	Qualitative	23	<i>No access associated with: <u>Patient-provider relationship</u>: Discrimination towards drug users and negative attitudes to drug users so drug users reluctant to seek treatment</i>	

Source	Country	Study design	Sample size	Treatment characteristics (Patient - provider)	Disease characteristics
De Joncheere et al. (2009) [69]	Latvia	Qualitative	12	<i>Poor access associated with:</i> <u>Patient-provider relationships</u> : highly stigmatizing attitudes of providers towards PWID	
Gardner et al. (2002) [73]	USA	Cross-sectional (1993-1995)	273	<i>Low access associated with</i> <u>Not having an HIV specialist</u> : lower rate of ART compared to those with specialist care (p<0.001)	
Himelhoch et al. (2007)[21]	USA	Cross-sectional (2001)	5119		<i>Access associated with</i> <u>Disease severity</u> CD ⁴ count <200 (AOR 2.52; CI: 3.54-5.87)
Human Rights Watch/TTAG (2007) [75]	Thailand	Qualitative	43	<i>No Access associated with</i> <u>Patient-provider relationship is poor</u> : stigma and discrimination towards drug users, deny treatment until stop using drugs. Stigma and discrimination from health workers greater towards current drug users (35.8%) than former drug users (24.0%; p <0.01) <u>Negative perceptions and attitudes to drug users</u> : Service providers deny access to ART to current drug users as well as drug users on MMT on basis of adherence concerns.	

Source	Country	Study design	Sample size	Treatment characteristics (Patient - provider)	Disease characteristics
Human Rights Watch (2006) [76]	Ukraine	Qualitative (2005)	101	<p><i>No Access associated with</i> <u>Patient-provider relationship is poor</u>: stigma and discrimination towards drug users, deny treatment until stop using drugs. Also ill-treated when seeking care and have to wait for lengthy periods of time- discourages treatment seeking and reduces trust in health care providers</p> <p><u>Negative perceptions and attitudes to drug users:</u> Service providers deny access to ART to current drug users due to adherence concerns.</p>	
Knowlton et al. (2010) [81]	USA	Prospective cohort study (2001-2005)	807	<p><i>"Better" access associated with</i> <u>Patient-provider relationship</u>: "Perfect" patient - provider engagement (AOR 1.45, CI:1.09-1.93)</p>	<p><i>Access associated with</i> <u>Disease severity</u> CD⁴ count < 350 (AOR 1.70; CI: 1.28-25)</p>
Loughlin & Metsch (2004)[90]	USA	Cross sectional (2000-2001)	420	<p><i>No access associated with</i> <u>Negative perceptions of drug users by physicians:</u> Perceptions that homeless IDU less likely to adhere (AOR 2.12 (CI: 1.36-3.29), Perceptions that current IDU less likely to adhere (AOR 6.31 (CI: 3.56-11.2)</p>	

Source	Country	Study design	Sample size	Treatment characteristics (Patient - provider)	Disease characteristics
Open Society Institute (2009) [96]	Azerbaijan Russia, Georgia Ukraine	Mixed methods (2007-2008) Qualitative interviews and cross-sectional survey	701 (376 in survey)	<i>No Access associated with <u>Patient-provider relationship is poor</u>: stigma and discrimination towards drug users, deny treatment until stop using drugs.</i> <i><u>Negative perceptions of drug users</u>: often deny current and ex-IDU access to ART (decided by a health committee) as concerned about lack of adherence and unstable lives.</i>	
Rompalo et al. (2001) [105]	USA	Cross-sectional (1993-1995)	579		<i>Access associated with <u>Disease severity</u> CD⁴ count < 500 (AOR 4.59, CI: 2.92-6.92).</i>
Rusakova et al (2008) [107]	Russia	Mixed methods	577	<i>No Access associated with <u>Negative provider' perceptions</u> about drug users: Concerns about adherence among drug users cited as common reason for denying meds.</i>	
Uhlmann et al (2010) [115]	Canada	Prospective cohort study (1996-2008)	231		<i>Access associated with <u>Disease severity</u> -CD⁴ count <200 (ARH 1.93, CI: 1.22-3.04) -HIV RNA viral load >100 000 copies/ml (ARH 1.87 CI 1.26-2.78),,</i>

RH = relative hazard, ARH adjusted relative hazard; CI= 95% confidence interval

OR = odds ratio; AOR odds ratio adjusted for confounders and covariates

3.2.4. Systemic barriers and facilitators to the use of ART

Systemic barriers and facilitators to the use of ART among PWID were noted in 26 studies (Table 4). These barriers and facilitators were grouped into factors associated with the health care system, detention, and law enforcement policies related to drug use.

Characteristics of the health care system

Health care system barriers and facilitators to the use of ART among PWID were identified by 25 studies (20, 27, 55-6, 59, 66, 68-9, 70-72, 75-7, 81, 91, 96, 98, 105, 107, 109, 115, 121, 125-6; Table 4). Access to and the use of OST was the most frequently reported facilitator for ART initiation; with seven studies noting that OST was strongly associated with improved uptake of ART among PWID (20, 98, 109, 115, 121, 125-6). All of these studies noted that people who use OST have significantly greater odds of accessing ART compared to people who continue to inject drugs and do not access OST. This effect persists even after controlling for the influence of other patient and treatment -related influences on access. Although there are many possible reasons for the relationship between OST and the uptake of ART, one possibility is that OST influences the uptake of ART through reducing active IDU. This explanation is supported by the finding that people who accessed OST and stopped IDU had better odds of initiating ART than people who accessed OST and continued to inject (121).

While the mechanisms that explain these findings are likely to be multi-factorial, having patients enrolled in OST does allow regular contact with the health care system which facilitates the more frequent monitoring of CD4+ cell counts which is an important factor in the timing ART initiation [115]. Enrolment in OST also may provide PWID with positive experiences of health providers that may encourage PWID to engage in HIV care (115). Findings from earlier studies that OST use increases the percentage of kept health care appointments (140-1) provides some support for this claim. In addition, reducing IDU (which involves large amounts of time spent sourcing, using and recovering from drug use), may free up more time to access health services and may increase social stability which supports engagement in HIV services (115). On the other hand, service providers

are probably more likely to start PWID on HAART if they are engaged in drug dependence treatment services which provide some form of structure to their lives that could facilitate adherence to complex medication regimens. Regardless of how OST facilitates ART initiation among PWID, these findings clearly point to the need to expand access and coverage of OST programmes, especially in country settings where new HIV infections are largely attributable to IDU and where there is low or no access to OST (18).

Furthermore, several studies noted that the organisation of health care systems constitutes a major barrier to accessing comprehensive HIV treatment and care for PWID (59, 71-2, 76, 96, 107). Several countries (e.g. Russia, Ukraine) still have highly centralized health care systems in which speciality services are vertically organized and are completely distinct from each other. These compartmentalised services are a major hindrance to receiving adequate care as there is little coordination between these services which means that it is up to the patient to figure out how to navigate these multiple systems of care (59, 71-2, 76, 96, 107). This is often confusing and difficult, especially for treatment-naïve patients, as each specialty service has its own complex eligibility criteria (59, 71-2, 76, 96, 107). For instance, in some former Soviet countries, people cannot access ART if they have opportunistic infections (such as TB) as these infections need to be treated first. However some of the TB services will not provide services to HIV positive PWID (96, 107). In addition, as people need to travel between various facilities for these services, it is time consuming and leads to out of pocket travel expenses (59, 71-2, 76, 96, 107). This acts as a further disincentive for PWID to initiate ART.

Even in countries which have better co-ordination of drug, HIV and other health services, it seems that health care systems are often difficult to navigate for PWID, especially if they have no former experience of the HIV service system. One study found that PWID with prior experience of ART and HIV services have faster rates of ART initiation than people who are treatment naïve with little knowledge of how to access these systems of care (27). These findings clearly point to the need to improve the co-ordination and integration of HIV, drug and other health services, especially in health care systems where highly

compartmentalized care acts as a significant barrier to accessing ART for PWID but also in countries where services are less compartmentalized but still difficult to navigate for vulnerable populations.

Other features of health systems also act as barriers to ART use among PWID. Availability of free HIV services is a challenge with several studies reporting that PWID have limited access to HIV testing, as well as HIV monitoring via regular CD4+ counts and viral load tests (70-1, 91, 96, 126). This is a barrier to the initiation of ART, mainly because people do not know their HIV status nor when they are eligible to start ART (70-1, 91, 96). In addition, some studies note that PWID have fewer CD4+ counts and viral load tests and experience longer wait times between their first contact with HIV services and their first viral load test than people exposed to HIV via other routes (70, 126). This is concerning as there is evidence that regular contact with HIV primary health care services (which includes HIV monitoring) is associated with greater odds of ART utilisation (81). While there are probably multiple reasons for this lack of monitoring, including that PWID often have limited engagement with health services (81), another reason is that while ART is freely available in public health settings in many countries, CD4+ counts and viral load tests are not free in many settings. Six studies noted that these additional health care costs associated with HIV monitoring hinder access to these services which are a precursor for ART initiation (56, 59, 72, 76, 91, 96).

Related to this, the availability of free ARV medication in the public health sector is not always constant in developing countries, with stock out-ages and medication shortages frequently occurring. Although ART is available in the private sector there is considerable cost involved, placing it out of reach of most PWID. The inconsistent availability of free ART leads to considerable delays in the initiation of care for those who are eligible and is a disincentive for seeking treatment (56, 69, 71-2, 91, 107). Apart from the limited availability of free HIV testing, monitoring and treatment, there are other health care costs associated with public health service use in many developing and transitional countries. Some countries (especially in Eastern Europe) have poorly financed public health care

systems. As a result, citizens are charged user fees for public health services which hamper access to health services for people of limited means. In addition, doctors may also charge patients “informal” fees. These “informal” fees vary in amount according to the type of service needed and the characteristics of the patient; with stigma towards drug users often resulting in PWID being charged higher fees (71, 76, 96). PWID are also required to pay more for confidential medical services and to prevent being registered as a drug user. This relates directly to the stigma and discrimination that PWID face within the health care system which in itself is a major deterrent to ART initiation.

Nine studies reported that stigma and discrimination towards HIV positive drug users within the health care system is a major hindrance to ART initiation (56, 59, 71, 72, 75-76, 91, 96, 107). These mainly qualitative studies were conducted in countries (such as Russia, Ukraine, Vietnam) where drug policies have a law enforcement focus and aim to sanction and control people who use drugs. This policy framework and socio-political environment has influenced how health systems within these countries respond to PWID. All of these studies noted that HIV positive PWID are commonly discriminated against in the health care system. This discrimination takes the form of ill-treatment (and denial of confidential care), denial of care and refusal to treat PWID, and delayed treatment with PWID being made to wait for services. In addition, these studies report that health care providers in many of these countries alert the police to patients who actively use drugs. Together these factors leads to PWID avoiding contact with the health care system, including ART services (56, 71,72, 75-76, 91, 96, 107). Taken together these findings clearly point to the need for health system interventions that address health care financing barriers, ensure the availability of HIV testing, monitoring and free ART, and remove institutionalized stigma and discrimination towards PWID. To achieve such health system reforms will require supportive policy and legislative frameworks. The following section examines how punitive legislative frameworks can deter the use of ART among PWID.

Drug policies, legislation and access to ART for PWID

There are only a limited number of studies that explore how drug policy approaches which prioritise law enforcement over public health-focused interventions, impede access to HAART among PWID. Eight studies identified policy and legislation-related barriers that restrict ART uptake among PWID (52, 66, 69, 71, 75-6, 91, 96). All of these studies were conducted in countries that have a law enforcement-focused drug policy that criminalises and stigmatises people who use drugs. These studies found that PWID residing in countries with law enforcement -focused policies and legislative frameworks are treated with little regard for their human rights. For example, once identified as a potential drug user, they are placed on drug registries and subject to police monitoring. Police often harass people who use drugs and may send them to compulsory drug treatment services (where available). People who use drugs are afraid to be placed on national drug registries because they then run the risk of harassment, ill-treatment and violence at the hands of police and law enforcement especially during periods of intensified police activity (52, 66, 69, 71, 75-6, 91, 96). Several studies found that drug user registries in combination with police harassment and social exclusion drives PWID underground and separates PWID from health services, including HIV services (66, 69, 71, 75-6). This is because police monitor services frequented by PWID but also because health providers in some settings work closely with the police and are known to call the police when someone is identified as PWID. Consequently, PWID may avoid or limit their use of health and drug services in case they are identified as drug users (66, 71, 75). Another factor that contributes to the avoidance of health services is that the boundaries between health care providers and the police are blurred in some countries, with doctors accompanying police on drug raids and conducting compulsory HIV testing on people who use drugs. This compulsory testing is not accompanied by any information or counseling regarding HIV services. This reduces trust in the health care system and is another hindrance to HIV service use (52, 71, 75).

In summary these findings indicate that national drug strategies which focus on the use of criminal sanctions and the social exclusion of PWID as strategies to deter drug use create hidden populations of PWID that are extremely difficult to reach and connect with health

services (44). As such it is vital that attempts to improve access to and the use of ART among PWID include concerted political efforts to reform drug policies and laws that stigmatise vulnerable and marginalized populations and separate them from needed health services. Without these changes to the policy and legislative framework, the health disparities between PWID and other HIV infected populations in these settings will continue to increase.

Detention and access to ART

While many studies have examined incarceration as a risk for treatment interruption or ART discontinuation among people living with HIV, few have examined whether incarceration or detention is a risk for the delayed initiation of ART among PWID. Only four studies (all conducted in SE Asia) noted detention-related barriers to the initiation of ART (66, 75, 77, 91; Table 4). Most of these studies focused on detention in compulsory drug rehabilitation centres which are common in China and South East Asia. In countries which run compulsory drug “rehabilitation facilities”, detention in these facilities is associated with delays in initiating ART. Although HIV testing occurs in these facilities, people are not given their test results and if HIV positive are not given access to ART. They often have to wait several years until their rehabilitation is complete before they can access ART (71, 73, 79). Apart from not offering any form of evidence-based drug dependence treatment, these detention facilities clearly are major barriers to the timely initiation of HAART and deny PWID their right to life saving medicines. Countries that have compulsory detention facilities needs to be pressurized to end the human rights abuses of PWID and to provide HIV-positive PWID with access to ART.

Table 4. Systemic factors associated with access: findings from selected studies (2000-2011)

Source	Country	Study design	Sample size	Systemic factors		
				Policies and social control	Detention	Health care system
Amirkhanian et al. (2011) [52]	Russia	Cross-sectional (2008-2009)	492	<i>No access associated with <u>Policies that lead to stigma against drug users</u>. Number of discriminatory experiences (AOR 1.06, CI: 1.10-1.12)</i>		
Andersen et al. (2000) [55]	USA	Cohort study (1996-1997)	2776			<i>Access associated with <u>Responsiveness of health care system to needs</u>: Length of time to appointment at usual care (cf same day) 2-6 days AOR 0.55 (p <0.01) >14 days AOR 0.66(p <0.01).</i>
APN+ (2011) [56]	6 in SE Asia	Mixed (Cross-sectional and Qualitative) (2008)	945 survey 27 in focus group			<i>No access associated with: <u>Limited availability</u> of ART (23.8%) <u>Health system not free -Financial barriers</u> associated with health care due to lack of free treatment for OI, CD4 counts etc <u>Responsiveness of health care and waiting time</u>: system discriminates against drug users and keeps waiting</i>

				Systemic factors		
Bobrova et al (2007) [59]	21 countries in CE Europe and Central Asia	Cross-sectional	55	<i>No access associated with:</i> <u>No national treatment guidelines for prescribing ART</u> and if existed none specific for provision of ART to PWID.		<i>No access associated with:</i> <u>Limited availability</u> of ART and low capacity to provide ART due to regulations about who able to prescribe ART. <u>Structure of health system:</u> vertical rather than integrated care : ART, drug use, and treatment for co-infections not at same place. Also lack of infrastructure and staff in AIDS centres to monitor disease and deliver treatment <u>Cost of ARV is high</u>
Celentano et al. (2001) [20]	USA	Prospective cohort study (1996-1999)	528			<i>Access associated with</i> <u>Access to and use of MMT</u> For men: (ARH 1.78 (CI: 1.14-2.76). For women: (ARH 0.48, CI 0.22-1.01)
Chakeapani et al. (2008)(66)	India	Qualitative	23	<i>No access associated with:</i> <u>Illicit drug policies and police interference in HIV programmes:</u> Targeting drug users to fill police “quotas” drives users underground and away from art services.	<i>No access associated with:</i> <u>Incarceration</u> Lack of HIV treatment services for drug users in prison	<i>No access associated with:</i> <u>Lack of effective linkages between drug treatment, harm reduction and ART services for PWID (vertical rather than integrated care:</u> each with user fees, transport costs, and poorly coordinated. <u>Limited access to drug treatment (costs and few services available)</u> so limited opportunities to stop drug use and get on ART

				Systemic factors		
Clarke et al (2003) [68]	Dublin, Ireland	Cross-sectional (2000)	150			<i>Access associated with</i> <u>Access to and use of MMT</u> MMT associated with uptake of ART (p= 0.005)
De Joncheere et al (2009)[69]	Latvia	Qualitative	12	<i>No access associated with:</i> <u>Illicit drug policies and police interference in HIV</u>		<i>No access associated with:</i> <u>Poorly coordinated health care services</u> (vertical rather than integrated care (eg HIV, TB and drug services provided by separate services. <u>Only one ART provider in country-</u> geographic access issues <u>ART availability-</u> problems with the continued supply of ART
de Melo et al (2006) [70]	Brazil	Retrospective cohort study (AIDS registry) (1986-2002)	170			<i>Access associated with:</i> <u>Health system factors:</u> Access to testing and monitoring. IDU less chance of viral load tests compared to NIDU (1.0 vs 4, p <0.01), less Cd4 monitoring (3 vs 5, p<0.01. and longer time between first visit and first viral load request (56.7 vs 19.3 months) p <0.03. This lack of monitoring impacts on access and use of ART.
Dzhalbieva et al (2009) [71]	Krygyzstan	Qualitative (2007-2008)	73	<i>No access associated with</i> Police harassment and forced testing – drives people underground so avoid health services		<i>No access associated with</i> Lack of HIV testing Inconsistent availability of free ART Stigma and discrimination towards drug users in health system Lack of comprehensive services- far to travel to services, sometimes denied care or need to pay for health services because use drugs

				Systemic factors		
Eramova et al (2010) [72]	Lithuania	Qualitative	14			<p><i>No access associated with:</i></p> <p><u>Stigma and Limited trust in health care</u> system as health services share information with police and place users on drug registries. Lack of confidentiality of medical information. Leads to avoidance of health care providers</p> <p><u>Costs:</u> copayments of HIV-related services such as Cd4 counts and cost of treatment for OI</p>
Human Rights Watch/TTAG (2007) [75]	Thailand	Qualitative	43	<p><i>No access associated with</i></p> <p><u>Policy of criminal sanctions:</u> Drug users are under police surveillance and fear being beaten or sent to detention centres for forced rehabilitation. Driven underground and do not access healthcare services.</p>	<p><i>No access associated with</i></p> <p><u>Detention in compulsory treatment facilities</u></p> <p>Limited access to testing or ART in compulsory detention centres.</p>	<p><i>No access associated with</i></p> <p><u>Stigma and Limited trust in health care</u> system as health services share information with police. Lack of confidentiality of medical information. Leads to avoidance of health care providers</p>

				Systemic factors	
Human Rights Watch (2006) [76]	Ukraine	Qualitative (2005)	101	<i>No access associated with <u>Policy of criminal sanctions towards drug users</u>. Blurring of medico-legal boundaries- health providers hand drug users to police. Fear they will be registered as drug users if seek treatment and then subject to police harassment and violence and also lose civic rights</i>	<p><i>No access associated with <u>Structure of health care system</u></i> Vertical rather than integrated system of care. HIV services do not provide treatment for OI or drug abuse- must go elsewhere first before accessing ART. TB centres refuse to treat people who are HIV positive. Costly and lengthy process to access care</p> <p><u>Health care costs</u>: Although ART is free, health care facilities levy official fees for public health services and doctors charge informal user fees, especially for drug users.</p> <p><u>Low trust in health system</u> due to <u>stigma</u> and blurring of medico-legal boundaries and limited confidentiality</p>
Human Rights Watch (2010) [77]	China	Qualitative (2009)	33	<i>No access associated with <u>Detention in compulsory rehabilitation centres</u>. People are tested but are not told results and only able to access ART once leave facility.</i>	
Knowlton et al. (2010) [81]	USA	Prospective cohort study (2001-2005)	807		<i>Access associated with: <u>Access to and regular use of HIV primary care services</u> (monitoring) more 4 visit to HIV primary care service in past 6 months (AOR 1.77;CI: 1.35-2.32)</i>

				Systemic factors		
Maher et al. (2007) [91]	Vietnam	Qualitative (2006)	Not reported	<i>No Access associated with:</i> <u>Policing</u> and “war on drugs”- police harassment and detention leads to failure to access ART. Afraid to seek health services as police target drug users at these health and harm reduction facilities.	<i>No Access associated with:</i> Detention centres- get tested for HIV but not get results or access to ART.	<i>No Access associated with:</i> <u>Limited access to HIV testing & counseling</u> and CD ⁴ test so not know when HIV positive and need ART. <u>Structure of health system:</u> requires co-financing ART is free but free Art supply is unreliable. Charges for treatment for OI and CD ⁴ and other monitoring tests. <u>Stigma and Lack of trust in health system</u> because of blurring of medico-legal boundaries (hand over to police and being detained in treatment) and because health providers discriminate and mistreat drug users
Open Society Institute (2009) [96]	Azerbaijan Russia, Georgia Ukraine	Mixed methods (2007-2008) Qualitative interviews and cross-sectional survey	701 (376 in survey)	<i>No Access associated with:</i> <u>Drug policy that focuses on legal sanctions and policing.</u> Blurring of medical and police system: Medico-police raids with forced testing- undermines belief/trust in health system and reduces incentives to seek treatment. Users fear being handed over to police as drug users if seek health services.		<i>No Access associated with:</i> <u>Limited access to HIV testing & counseling</u> so not know when HIV positive and need ART. <u>Structure of health system:</u> requires co-financing via levies or doctors’ informal fees. Charge fees to deal with HIV positive drug users. <u>Stigma and Lack of trust in health system</u> because of blurring of medico-legal boundaries (hand over to police) and because health providers discriminate and mistreat drug users
Palepu et al. (2004) [98]	USA	Prospective cohort study (1997-2001)	349			<i>Access associated with:</i> <u>Access to and use of substance abuse treatment</u> (AOR: 1.70 CI: 1.03-2.83)

				Systemic factors		
Rodriguez-Arenas et al. (2006) [27]	Spain	Prospective cohort study (1997-2003)	4643			<p><i>Access associated with:</i></p> <p><u>Prior experience of ART and knowledge of the treatment system:</u></p> <p>Treatment naïve patient, HAART uptake lower among IDU compared to other exposure groups (AHR 0.67; CI: 0.57-0.79). For previously treated, no difference between IDU and other exposure groups (AHR 1.07 CI: 0.83-1.37)</p>
Rompalo et al. (2001) [105]	USA	Cross-sectional (1993-1995)	579			<p><i>Access associated with</i></p> <p><u>Perception of active drug user</u></p> <p>Former IDU no more likely than current IDU to receive ART at integrated HIV & drug service site: (AOR 1.01, CI: 0.4- 2.53).</p> <p>Former IDU more likely than current drug users to receive treatment at HIV only care site (AOR 1.92; CI: 0.96-3.87).</p>
Rusakova et al (2008) [107]	Russia	Mixed methods	577			<p><i>No access associated with</i></p> <p><u>Structure of health system:</u> Vertical system so no integrated care. Requires treatment of OI and drug use before starting ART but refuse to treat TB if HIV positive.</p> <p><u>Limited availability of ART</u> (23.5% and 16.1%)</p> <p><u>Low level of trust in health care system</u> and ineffective drug services</p>
Sambamoorthi et al (2000) [109]	USA	Retrospective cohort study (1988-1996)	2600			<p><i>Access associated with</i></p> <p><u>Access to and use of MMT:</u></p> <p>(AOR 2.13 (1.45-3.21) compared to those not in MMT and using drugs.</p>

				Systemic factors		
Uhlmann et al (2010) [115]	Canada	Prospective cohort study (1996-2008)	231			<i>Access associated with</i> <u>Access to and use of MMT</u> : initiate ART at a higher rate than those not on MMT (ARH 1.62-CI 1.15-2.28).
Weber et al. (2009) [121]	Switzerland	Prospective Cohort study (1997-2006)	8660			<i>Access associated with</i> <u>Access to and use of DMT</u> : Individuals in DMT without injecting drug use (AOR 1.18 CI: 1.06-1.31) Individuals in DMT with injecting drug use (AOR 0.79 CI: 0.71-0.89) Current IDU (AOR 0.80 CI 0.67-0.96) significantly less likely to be on ART.
Wood, Hogg et al. (2005) [125]	Canada	Prospective cohort study (1996-2003)	234			<i>Access associated with</i> <u>Access to and use of MMT</u> : elevated rate of initiating ART (ARH 2.10; CI: 1.28-3.46).
Wood Kerr Zhang et al. (2008) [126]	Canada	Prospective cohort study (1996-2003)	460			<i>Access associated with</i> CD ⁴ monitoring so not know when to begin ART. 27.4% never had CD ⁴ test and only 4.9% had once every 4 months as per guideline. <u>Use of MMT</u> (AOR 1.66, CI 1.42-1.94) associated with CD ⁴ count monitoring.

RH = relative hazard, ARH adjusted relative hazard; CI= 95%confidence interval

OR = odds ratio; AOR odds ratio adjusted for confounders and covariates

3.3. Barriers and facilitators to ART adherence for PWID

Tables 5-7 summarise the key factors associated with adherence to ART regimes among PWID. These factors are categorized into patient-level (Table 5), disease and treatment-related (Table 6) and systemic (Table 7) barriers and facilitators to optimal adherence. As there were large variations in the types of methods used to assess adherence (and definitions of adherence) across the included studies, we were unable to conduct a meta-analysis to pool the results of the included studies. Consequently, the following subsections provide a narrative synthesis of the key factors associated with adherence.

3.3.1. Patient-level barriers and facilitators to ART adherence

Patient-level barriers and facilitators to ART adherence were noted in 42 studies (Table 5). These barriers and facilitators were grouped into socio-demographic, psychological and social-structural factors associated with adherence.

Socio-demographic factors associated with adherence

Fourteen studies noted socio-demographic barriers and facilitators to ART adherence for PWID (52, 57, 64, 67, 78, 80, 92, 94, 99-100, 107, 113-115; Table 5). These included age, gender, ethnicity and education. After adjusting for the influence of other covariates, age was significantly (albeit weakly) associated with adherence in only five studies (52, 57, 99-100, 113). Four of these studies (52, 57, 99-100) reported that being older was associated with greater likelihood of adhering to ART regimes and one study (113) noting that PWID under the age of 24 were at more risk for suboptimal adherence than older persons. Similarly, after adjusting for the influence of confounders, length of education was (weakly) associated with ART adherence in only one study (57). This study found that PWID with more than a high school education had increased odds of adhering to ART compared to PWID who had not completed high school.

In contrast, gender and ethnicity were strongly associated with ART adherence among PWID. After covariate adjustment, gender was significantly associated with ART adherence

in eight cohort studies (56, 67, 80, 92, 94, 113-115). In these studies, men who inject drugs had significantly higher rates of adherence compared to women. Several cohort studies (64, 67, 78, 94) also reported that ethnicity was associated with adherence to ART after controlling for the influence of potential confounders. Three (67, 78, 94) of these studies found that belonging to an ethnic minority (such as being African American or Hispanic) was significantly associated with lower rates of adherence. In contrast, one study (63) found that among men who have sex with men and inject methamphetamine, belonging to an ethnic minority other than African American or Hispanic was associated with greater probability of adherence to ART. Further, PWID who belong to several vulnerable population groups (i.e. are women and belong to an ethnic minority) seem most at risk for poor adherence to ART. For example, one study (67) found that the odds of not adhering to ART regimens increased when gender, education and ethnicity were examined simultaneously.

One reason for these gender and ethnic disparities in adherence to ART among PWID may be that marginalized populations such as women and ethnic minorities have fewer financial resources that facilitate continuous engagement in HIV care compared with less vulnerable populations. Where these financial resources are absent, adherence is significantly worse for vulnerable populations, especially women (55, 142). However, suboptimal adherences to ART for women and ethnic minorities is not entirely attributable to financial and economic barriers as similar findings were found in settings where there is universal access to free HIV care (113). Another factor that may contribute to suboptimal adherence among women is that women who inject drugs may have greater levels of social instability and be more marginalized than men. Some studies have reported that women who inject drugs are more involved in street survival activities (such as sex work) than their male counterparts and as a result of this greater social instability and marginalization, their engagement with HIV services is more precarious than that of men (113, 143). Similarly another study (74) found that women who inject drugs had greater social instability and social stress than their male counterparts and this had a deleterious effect on engagement in and adherence to HIV care.

Regardless of the reasons for these findings, it is clear that gender and ethnic disparities in adherence to ART exist for PWID, with women and people belonging to ethnic minorities at greater risk for suboptimal adherence. Increased efforts are required to reduce these disparities in adherence which quite probably have deleterious effects on HIV outcomes among these vulnerable populations. This will necessitate more research into the specific barriers to adherence that women and ethnic minorities who inject drugs face. Future studies that identify these gender and ethnicity-specific barriers will be useful for the development of targeted interventions to improve adherence for high risk groups of PWID.

Psychological factors associated with adherence

Psychological barriers and facilitators to ART adherence for PWID were identified by 40 studies (36, 40, 52, 54, 57-58, 60-61, 63-65, 67, 74, 78, 80, 92, 94, 95, 97-104, 106-108, 110-115, 117-118, 120-1, 124; Table 5). These psychological factors include cognitive processes, the presence of co-occurring mental illness, and substance use history and severity.

Current drug use and problem severity

After adjusting for the influence of other variables, the most frequently reported psychological factor associated with ART adherence among PWID was the current use of alcohol and other drugs. Twenty-six studies (52, 54, 58, 65, 67, 74, 78, 94-95, 97, 98-102, 106-107, 110, 112-3, 115, 118, 120, 121, 124) found that current substance use was strongly associated with reduced likelihood of adhering to ART and one study (78) found that active drug use was associated with a lower probability of restarting HAART once treatment had been interrupted compared to individuals who had never used drugs or who reported a prior history of IDU. Having a prior history of IDU was not associated with poor adherence in any of the included studies. Rather, in three studies (52, 95, 121) individuals with a prior history of IDU were no more likely to not adhere to ART than individuals who had never injected drugs.

The risk of non-adherence to ART appears greater when drug problems are severe; as indicated by daily or more than daily injection of heroin or cocaine (80, 101, 110, 113, 115), multiple substance use problems (102, 118), opioid dependence (95), and problematic alcohol use in conjunction with IDU (58, 67, 97, 106, 112). In support of this, one prospective cohort study (67) found a dose-response relationship between the amounts of alcohol used in conjunction with illicit drug use: as the amount of alcohol consumed increased for current injection drug users, the likelihood of ART adherence decreased.

There several plausible explanations for how active drug use impacts on adherence to ART. One possibility is that the social instability often associated with periods of active drug use may make following medication regimes difficult (116). Related to this, social instability associated with drug use may impact on the degree to which people are engaged with HIV services, which is a necessary precondition for adherence (31). While social instability does account for some of the variance in adherence rates among PWID, the deleterious effect of active drug use and drug problem severity on ART adherence persists even after significant covariate adjustment (58, 60, 65, 74, 78, 95, 102; Table 5). Another possible explanation for poor adherence may lie in the process of acquiring and effects of using drugs. To illustrate, participants in qualitative studies (94, 120) described how the process of acquiring, using and recovering from the effects of drugs separated them physically and psychologically from their ART. While using drugs, the drug itself assumed primacy and taking ART become of secondary importance. In addition, drug intoxication lead to forgetting to take medication.

These findings clearly show that risks for suboptimal adherence to ART are greatest for people who currently inject drugs (rather than former IDU) with high levels of drug problem severity. Instead of denying access to ART for people who are currently using drugs (because of adherence concerns), better strategies are needed to ensure that PWID remain engaged in HIV care in spite of their drug use. One promising strategy is to help PWID reduce their drug problem severity through the use of opiate substitution therapy (OST) such as methadone or buprenorphine. While the association between the use of OST

and adherence to ART will be discussed later, it is useful to note that OST attenuates the impact of active drug use on ART adherence (through reducing the frequency of opiate use, the frequency of IDU, and the severity of drug problems). For example, a large cohort study found that people who were in drug maintenance treatment and continued to inject had less chance of non-adherence than PWID and were not in drug maintenance treatment (106). In addition, another cohort study found that changes in alcohol and drug use over time were associated with improvements in adherence (97). Taken together these findings suggest that reductions in drug use severity are associated with better adherence and that PWID do not necessarily need to be abstinent from drugs to achieve acceptable levels of adherence to ART.

Co-occurring mental health problems

A further psychological factor associated with adherence was the presence of (untreated) co-occurring mental health problems. Anxiety was associated with adherence in only one study (63), with greater symptoms of anxiety linked to lower odds of adherence. Of the five studies that identified depression as a correlate of adherence (57, 65, 98, 114, 117) all reported that as depression severity increased the likelihood of adherence decreased. However there were some contradictory findings. For example, a large cohort study (60) found that while depression was a risk factor for non-adherence in univariate analyses, when the influence of other variables was controlled for depression was only a risk factor for non-adherence among former injection drug users and not current drug users. Another (58) found no association between depression and adherence among current PWID. It may be that current drug use masks the experience and reporting of depressive symptoms for some PWID.

While the mechanisms by which depression affects adherence are multi-fold, some qualitative studies (94, 120) noted that co-occurring depression among PWID may impact on adherence through increasing social isolation, affecting cognition (remembering to take medication) and diminishing motivation to continue with ART. Together these findings highlight that untreated co-occurring mental health problems are significant risk factors for

poor adherence to ART among PWID. There is some evidence that treatment for co-occurring depression helps improve adherence to ART not only through reducing depression severity but also through improving engagement in health services (144). For example, one study in this review (114) found that PWID with depression who were engaged in mental health treatment had better rates of adherence than PWID without depression. As a result, greater effort should be made to screen PWID for co-occurring mental health conditions and to improve access to mental health services for PWID.

Cognition and self-efficacy

After covariate adjustment, several studies found that adherence self-efficacy (as indicated by ART outcome expectations and adherence efficacy expectations) was associated with adherence (Table 5). Outcome expectancies were associated with adherence in seven of the included studies (36, 40, 57, 78, 94, 103, 120, Table 5). Two studies (57, 78) noted that people with more positive outcome expectancies (such as beliefs that ART will provide health benefits) had better adherence than PWID with less positive expectancies. In contrast, five studies (36, 40, 94, 103, 120) reported that negative outcome expectancies (such as beliefs that ART will not work, interferes with drug use, affects methadone efficacy) were negatively associated with adherence. In addition, adherence efficacy expectations (or confidence in one's ability to adhere to ART) were associated with adherence in four studies (36,40, 57, 78). Higher scores on this variable were associated with a greater likelihood of adherence. Self regulatory efficacy (or belief in one's ability to manage the side effects of HAART or reduce drug use), a further indicator of adherence self efficacy, was associated with adherence in two studies (36, 40). While adherence self efficacy was not a particularly powerful predictor of adherence among PWID (being weakly to moderately associated with adherence), findings from this review still suggest that where adherence self-efficacy is low, interventions to improve self-efficacy may facilitate better adherence. For instance, other studies have found that a good patient-provider relationship and a strong support network with other people living with HIV may bolster adherence self-efficacy and addresses concerns about potential side-effects (78). Although the role of the patient-provider relationship in adherence among PWID is discussed later

on, it is important to note here that Efforts to improve patient-provider interactions in clinical care may yield benefits for self-efficacy and ART outcome expectancies adherence.

Other cognitive factors associated with adherence were cognitive impairment and forgetting; with three studies (94, 112, 118) reporting associations between cognitive impairment and non-adherence among PWID. In addition, two other psychological factors were associated with adherence in this review. First, fear of stigma and discrimination was associated with poor adherence in four studies (94, 108, 111, 120). These studies all noted how fear of stigma lead to PWID hiding their HIV status and their use of ARV medication. This contributed to missed doses, especially in social settings. In contrast, acceptance of one's HIV status and a positive attitude to health was identified as a facilitator to adherence among PWID in five studies (64, 94, 104, 108, 112). These findings highlight the importance of social support as a means of reducing fears about social exclusion. The following section provides a detailed discussion about social support and other social structural influences on adherence among PWID.

Social -structural factors associated with adherence

Eighteen studies reported social- structural barriers and facilitators to ART adherence (58, 60, 61, 65, 74, 78, 93-95, 102-104, 108, 111-112, 116-117, 120; Table 5). These include social support, indicators of social stability (such as stable housing and income), and social exclusion.

Social exclusion

Three studies noted that social isolation, exclusion, and discrimination because of one's status as a PWID living with HIV are barriers to adherence (104, 108, 111). According to these qualitative studies, social exclusion acts as a barrier to adherence as people may avoid taking ART in social settings to prevent their HIV status from being disclosed. This denies PWID the opportunity to receive adherence support from social networks (108). People belonging to other marginalized groups are at greater risk for social exclusion because of their HIV or drug use status. For example, one study (102) noted that migrants,

refugees or individuals displaced via deportation were at increased risk for poor ART adherence. This is probably because migrants and refugees often lack extensive social support networks and tend to be marginalized from broader society and health services. In addition, the effects of social exclusion are often exacerbated for women who inject drugs or for PWID belonging to ethnic minority groups (143).

Social instability

After controlling for the influence of other variables on ART adherence, 13 studies (58, 60, 74, 78, 93-5, 102, 95, 108, 112, 113, 120) identified social instability as a risk factor for poor adherence. Specifically, this review found emerging evidence of a relationship between housing stability and adherence. Four studies found that unstable housing was significantly and strongly associated with greater risk for suboptimal adherence to ART among PWID (58, 92, 93, 120; Table 5). These findings are not altogether surprising given research among other HIV positive populations indicating that housing instability is a barrier to HAART adherence (135). This is probably because unstable housing is associated with multiple life difficulties; with at least one study in this review (120) noted that addressing these multiple life problems (e.g. securing shelter and food) sometimes takes greater priority than regular engagement with HIV care or taking medications. Other features related to unstable living conditions also are likely to impact on PWID's ability to adhere to HAART medication regimens. Crowded living arrangements, lack of security and privacy to take ART, food insecurity which impacts on ability to take ART, absence of cooking and food storage facilities, as well as substandard sanitary facilities all potentially impact on ability to adhere to ART regimens (44). Whatever the reasons, the findings of a relationship between unstable housing and poor HAART adherence are worrying as PWID living with HIV/AIDS are often economically disadvantaged and challenged by homelessness or unstable housing (135-6).

While homelessness and unstable living environments pose a risk for poor adherence, it is important to note that wide variations in adherence have been observed among unstably housed populations (145). In addition, one study in this review (117) found no

relationship between housing status and adherence to ART among PWID. While the failure to detect a significant association between these variables may be a result of the study's small sample size (n= 57) and its lack of power to detect differences between groups, this study suggests that when given adequate support unstably housed PWID are capable of achieving similar ART adherence rates to stably-housed persons. This suggests that homeless or unstably housed PWID living with HIV may benefit from comprehensive adherence support programmes. Further research is needed to better understand how housing stability interacts with other risk factors to influence ART adherence among PWID.

Another indicator of social instability is deprivation (as evidenced by food insecurity, low income and limited employment) which also contributes to poor adherence to ART among PWID. Five studies found that social deprivation was associated with reduced odds of ART adherence (74, 95, 102, 108, 120) even after covariate adjustment. In one study (74) eating less than two meals per day was significantly associated with greater odds of ART non-adherence. This is not surprising given earlier findings that in situations of food insecurity patients may take their ART medications inconsistently as many medications need to be taken after a meal (137). Similarly, two studies (95, 102) found that PWID with a low income and who were unemployed faced greater risks of ART discontinuation compared to those with better incomes and stable employment. In contexts where there is limited access to free HIV care, financial instability may impact on the patient's ability to continue with HIV treatment and remain engaged in health services. For example, two qualitative studies (108, 120) reported that financial concerns and low or under employment impacted on adherence, primarily because the person was unable to afford the costs associated with HIV care and also because they were more concerned about meeting their immediate survival needs rather than following a medication schedule (120). Despite the support for the relationship between social instability and poor ART adherence, one study (60) found that social instability was correlated with poor ART adherence only among people who injected drugs in the past (and not among current IDU). This anomalous finding is probably due to the fact that all PWID reported high levels of social instability resulting in limited variability in the social stability measure used by the study(60).

The absence of a daily routine and life structure was another indicator of social instability associated with poor adherence to ART among PWID in five studies (78, 94, 112, 116, 120). According to findings from qualitative studies, having a daily routine and structure provides PWID with reminders to take medication and limits forgetting. In contrast, frequent changes to daily routine (for example, when people sleep at different places several times a week or do not keep regular hours) may separate a person from their medications for long periods of time (112, 116) and result in short-term treatment disruptions. These findings suggest that interventions that work to create more structure in the lives of PWID may help improve adherence within this population.

Whatever the reasons for these findings, it is clear that interventions are needed to improve HAART adherence among PWID with high levels of social instability. At a systemic level, improving access to social housing for PWID may provide some social stability that could facilitate engagement with health services. At an individual-level, facilitating better social support for PWID who are living with HIV might buffer against the negative effects of social instability on ART adherence. Five studies in this review identified the provision of social support as a facilitator of adherence for PWID (58, 61, 65, 94, 103) especially when this support included reminders to take ART and specific medication adherence support measures (61, 94, 103). Further research on the potential buffering effect of social support on social structural barriers to HAART adherence among PWID may point to interventions that mitigate the impact of social instability on adherence (146).

Table 5. Patient level-factors associated with adherence: findings from selected studies (2000-2011)

Source	Country	Study design	Sample size	Social structural	Psychological (including cognitive)	Socio-demographic
Aloisi et al. (2002) [52]	Italy	Prospective cohort study(1997-2000)	366		<p><i>Non-adherence associated with:</i> <u>Current injecting drug use</u> (AOR 3.47; CI: 1.40–8.58)</p> <p><u>Past injecting drug use</u>: (AOR 1.24, CI: 0.65–2.38)</p> <p><u>Non-injecting drug use</u> (AOR: 4.23, CI: 1.85–9.67)</p>	<i>Non-adherence associated with:</i> <u>Age</u> (in 10 year increments) (AOR 0.65; CI 0.42–0.98)
Amirkhanian et al. (2011) [54]	Russia	Cross-sectional (2008-2009)	492		<i>Non-adherence associated with:</i> Past 3 month use of <u>heroin</u> (AOR: 7.03; CI 1.59-31.10)	
Arnsten et al (2007) [57]	USA	RCT (2001-2003)	636		<p>95% Adherence associated with <u>health beliefs</u>: “do not believe hiv meds eat methadone” (AOR: 1.53, CI:1.00 to 2.36) “sense of responsibility for protecting others from HIV” (AOR 1.42, CI: 1.04-1.93)</p> <p>Positive <u>outcome expectancies</u> for taking meds (AOR: 2.04; CI:1.12 to 3.70)</p> <p><u>Self efficacy</u> (for taking ART as prescribed) AOR: 2.13, CI:1.55 to 2.92)</p> <p><u>Depressive symptoms</u> (AOR: 0.74, CI: 0.58 to 0.94)</p>	<p>95% Adherence associated with: being <u>male</u> (AOR: 1.28, CI: 0.83 to 2.00);</p> <p><u>age > 40</u> (AOR 1.22, CI: 0.79 to 1.89);</p> <p>high school <u>education</u> or greater (AOR: 1.57 (1.03 to 2.41)</p>

Source	Country	Study design	Sample size	Social structural	Psychological (including cognitive)	Socio-demographic
Berg et al. (2004) [58]	USA	Prospective Cohort study (1998-2001)	113	95% Adherence associated with <u>Stable housing</u> ($\beta = 16$; CI: 5.3 to 26.7) <u>Belonging to an HIV support group</u> ($\beta = 25.2$; CI:12.3 to 38.2).	95% Adherence associated with <u>Active drug use</u> : crack/cocaine use ($\beta = -18.3$, CI:-31.2 to -5.4). Gender x alcohol use ($\beta : -23.9$ CI: -47.3 to -0.5) <u>Depression</u> not associated ($\beta = 4.05$, CI: 5.82- 0.06).	
Bouhnik et al. (2002) [60]	France	Prospective cohort study (1997-1999)	210	<i>Non-Adherence (less than 90%) associated with high social instability</i> (AOR 2.85 CI: 1.08-7.48) for ex-IDU only- not current opiate users.	<i>Non-Adherence associated with Depression</i> for ex-IDU but not current opiate users (AOR 2.94 CI: 1.65-5.25)	
Broadhead et al. (2002) [61]	USA	Qualitative (2001)	15	<i>Adherence associated with Peer support</i> from other drug users can assist with adherence (provide reminders to take ART, provide health information)		
Campos et al. (2008) [63]	Brazil	Cross sectional (2001-2002)	293		<i>Non-Adherence associated with Severe anxiety</i> (ARH = 1.87, CI: 1.14-3.06).	
Carrico, et al (2010) [64]	USA	Cross-sectional	122		<i>Adherence (95%) associated with Positive affect</i> (AOR = 1.63, CI = 1.00-2.65).	<i>Adherence (95%) associated with Ethnic minority</i> other than African American or Hispanic (AOR 4.00, CI:1.09-14.70)
Carrieri et al. (2003) [65]	France	Prospective cohort study (1995-1999)	96	<i>Non-Adherence (<95%) associated with Living in stable relationship</i> (AOR 0.4; CI: 0.2-1.0).	<i>Non-Adherence (<95%) associated with Current Drug injection</i> (AOR: 3.3; CI: 1.0-10.3). <u>Depressed mood</u> (AOR: 2.5, CI: 1.0-6.0).	

Source	Country	Study design	Sample size	Social structural	Psychological (including cognitive)	Socio-demographic
Chander et al. (2006) [67]	USA	Prospective cohort study (1998-2003)	1711		<p><i>Adherence (95%) associated with <u>Active drug use</u> (AOR: 0.55, CI:0.44-0.68)</i></p> <p><i><u>Dose response relationship with alcohol:</u></i></p> <p>Drug use and no alcohol (AOR 0.50, CI: 0.37-0.68)</p> <p>Drug use and moderate alcohol (AOR 0.40, CI: 0.30-0.54)</p> <p>Drug use and hazardous alcohol (AOR 0.32, CI: 0.20-0.51).</p>	<p><i>Adherence associated with Being <u>male</u> (AOR 1.25, CI:1.00-1.56).</i></p> <p><i><u>Ethnicity:</u> African American (AOR: 0.54, CI: 0.4-0.73)</i></p>
Gebo et al. (2003) [74]	USA	Cross-sectional (1999-2000)	196	<p><i>Non-Adherence associated with <u>Social instability and deprivation:</u></i></p> <p>Eating less than 2 meals per day (AOR 17.54, CI: 1.92-160.40)</p>	<p><i>Non-Adherence associated with <u>Current illicit drug use</u> (AOR 4.18, CI: 1.68-10.75)</i></p>	
Johnson, et al (2003) [78]	USA	Cross-sectional (2000-2002)	2765	<p><i>Non-Adherence associated with: <u>Housing stability</u></i></p> <p>Being Homeless (past year) AOR: 1.38, CI: 1.02-1.85)</p> <p>Unstable routine "It is hard to fit my medications into my daily life" (AOR 1.40, CI:1.24-1.57)</p>	<p><i>Non-Adherence associated with <u>Injection drug use</u> (past year) (AOR: 1.91, CI: 1.36-2.68)</i></p> <p><i><u>Positive outcome expectation:</u> (AOR 0.82, CI:0.72-0.93)</i></p> <p><i><u>Adherence self-efficacy</u> AOR 0.97, CI:0.97-0.98)</i></p>	<p><i>Non-Adherence associated with <u>Ethnicity:</u> African American (AOR 1.62, CI: 1.32-1.97)</i></p>
Kavasery et al (2009) [80]	USA	Prospective cohort study (1996-2006)	335		<p><i>Non-Adherence associated with <u>>daily injection drug use</u> (ARH 1.43, CI:1.02 to 1.98)</i></p> <p><i><u>Active injection drug use</u> associated with a lower probability of restarting HAART (ARH, 0.69; CI: 0.49 to 0.97).</i></p>	<p><i>Non-Adherence (treatment interruption) associated with <u>Gender:</u> Female (ARH 1.36, CI: 1.02 to 1.82)</i></p>

Source	Country	Study design	Sample size	Social structural	Psychological (including cognitive)	Socio-demographic
Kerr et al. (2004) [36]	Canada	Prospective cohort study (2000-2001)	108		<p><i>Adherence (95%) associated with <u>Efficacy expectations</u> (AOR 1.8, CI: 1.0-3.1)</i></p> <p><i><u>Negative Outcome expectations</u> (AOR 0.8, CI: 0.7-0.9)</i></p>	
Kerr et al. (2005) [40]	Canada	Prospective cohort study (2000-2001)	160		<p><i>Non-Adherence (<95%) associated with <u>Self-regulatory efficacy</u> (AOR 0.86; CI: 0.7-0.9).</i></p> <p><i><u>Efficacy expectations</u> (manage side effects) (AOR 0.70, CI: 0.5-0.9)</i></p> <p><i><u>Negative Outcome expectation</u> (AOR 1.41; CI: 1.2-1.6)</i></p>	
Milloy et al (2011) [92]	Canada	Prospective cohort study (1996-2009)	490			<i>Non-Adherence (<95%) associated with <u>Gender</u> : Female AOR 2.11, CI:1.50-2.97)</i>
Milloy et al (2011) [93]	Canada	Prospective cohort (1996-2009)	247	<i>Non-Adherence (<95%) associated with Homelessness (AOR 0.65, CI 0.36-0.60)</i>		

Source	Country	Study design	Sample size	Social structural	Psychological (including cognitive)	Socio-demographic
Mimiaga et al. (2010) [94]	Ukraine	Qualitative	16	<p><u>Adherence associated with Social support</u> (and reminders) from family and friends</p> <p><u>Unstable lives</u>(lack of routine leads to forgetting)</p>	<p><u>Non-adherence associated with: Opioid dependence</u> (ART is less a priority than getting next fix)</p> <p><u>Negative outcome expectations of ART</u></p> <p><u>Cognitive difficulties</u> (forgetting)</p> <p><u>Co-occurring mental health problems</u> (Depression leads to lack of motivation)</p> <p><u>Fear of stigma</u>-avoid taking pills in front of others, miss doses</p> <p>Adherence associated with <u>acceptance of status</u>, desire for health</p>	
Morris et al (2007) [95]	USA	Prospective cohort study MACS 1998—2003 WIHS 1994-2002 ALIVE 1988-1994	2266	<p><u>Non-Adherence (discontinuation) associated with Poverty</u>: Legal Income <\$10 000 per year (ARH: 1.44, CI: 1.2-1.78)</p> <p><u>Employment</u> (ARH 0.81, CI: 0.67-0.98)</p>	<p><u>Non-Adherence (discontinuation) associated with History of IDU</u> (ARH 1.24, CI: 1.03-1.48)</p> <p>When stratified by <u>current drug use</u>: Current IDU risk of discontinuation (ARH 1.65 CI: 1.23-2.22) Ex-IDU : (ARH 1.16, CI 0.96-1.41)</p>	<p><u>Non-Adherence (discontinuation) associated with Ethnicity</u> Black (ARH: 1.84, CI: 1.47-2.29) Hispanic (ARH 1.96, CI: 1.5-2.57)</p>
Orejudo et al (2009) [97]	Spain	Prospective cohort study (2003-2004)	100		<p><u>Adherence (one-week compliance) associated with Alcohol and Drug use</u> Changes in alcohol intake ($r = .142$), opiate use ($r = .134$) and cocaine use ($r = .132$)</p>	

Source	Country	Study design	Sample size	Social structural	Psychological (including cognitive)	Socio-demographic
Palepu et al (2004) [98]	USA	Prospective cohort study (1997-2001)	349		<i>Adherence (95%) associated with <u>Drug and alcohol use</u> in past 30 days (AOR 0.17, CI: 0.11-0.28)</i> <i><u>Depression</u> (AOR 0.48 CI:0.32-0.78)</i>	
Palepu et al (2004a) [99]	Canada	Prospective cohort (1997-2002)	1746		<i>Non- Adherence (<95%) associated with <u>Injected drugs</u> (AOR 1.49, CI: 1.17-1.90) (adjust clinical characteristics)</i>	<i>Non- Adherence (<95%) associated with Age (AOR 0.81, CI:0.72-0.91) Gender male (AOR 0.50, CI: 0.38-0.65)</i>
Palepu et al (2006) [100]	Canada	Prospective cohort study (1996-2003)	278		<i>Adherence (95%) associated with <u>Heroin use</u> (AOR 0.57 CI: 0.42-0.79)</i>	<i>Adherence (95%) associated with Age (per 10 year increment) (AOR 1.62, CI: 1.27-2.07)</i>
Palepu et al (2011) [101]	Canada	Prospective cohort study (1996-2008)	543		<i>Adherence (95%) associated with <u>Frequent (> daily)</u> heroin injection (AOR 0.47 CI: 0.36-0.60)</i>	
Peretti-Watel (2006) [102]	France	Cross-sectional (2003)	2932	<i>Non-adherence (<95%) associated with <u>Social instability</u>: financial difficulties associated lack of adherence (AOR 1.40 CI 1.03-1.91), being a migrant (AOR 1.51 CI 1.21-1.88)</i>	<i>Non-adherence (<95%) associated with <u>Multiple addictions</u> (all with heroin IDU) vs low levels of drinking and smoking (AOR 2.51 CI: 1.18-5.32)</i>	

Source	Country	Study design	Sample size	Social structural	Psychological (including cognitive)	Socio-demographic
Piekarska-Mankiewicz & Cholewinska (2009) [103]	Poland	Case-control (2008)	60	Adherence (95%) associated with <u>Emotional Support</u> of friends and family (60%)	Non-Adherence (95%) associated with <u>Negative outcome expectancies</u> (Belief ART interferes with methadone 7%)	
Roberson et al. (2009) [104]	USA	Qualitative (2004-2005)	12	Adherence negatively associated with <u>Social isolation & discrimination</u> due to stigma (hide meds/status and miss doses).	Adherence associated with <u>Acceptance of HIV status and taking health seriously</u>	
Roux et al (2008) [106]	France	Prospective cohort study (1995-2000)	276		Non-Adherence (<95%) associated with <u>Current Injection use</u> : Compared to abstinent, -MMT and injected (AOR 2.2, CI 1.1-4.5), Buprenorphine and injected (AOR 2.3, CI 1.2-4.4). No DMT and injected (AOR 3.3, CI 1.4-8.1) <u>Depression</u> (AOR 1.4, CI: 1.1-1.9) <u>Alcohol consumption</u> (30 unit increments per month) (AOR 1.19, CI 1.1-1.28)	
Rusakova et al (2008) [107]	Russia	Mixed methods	577		Non- Adherence associated with <u>Current Drug Abuse</u>	Non-adherence associated with Younger people with low education

Source	Country	Study design	Sample size	Social structural	Psychological (including cognitive)	Socio-demographic
Sabin et al. (2008)[108]	China	Qualitative (2005-2006)	36	<p><i>Non Adherence associated with <u>Social isolation</u> due to double stigma of being HIV and IDU and lack of social support for ART adherence and use.</i></p> <p><i><u>Social instability</u> because of stigma- low or under employment</i></p>	<p><i>Non- Adherence associated with <u>Mental health problems</u>- lead to poor motivation and social isolation- psychological burden</i></p> <p><i><u>Failure to disclose status</u> (to support adherence) and fear of disclosure due to stigma</i></p>	
Shannon et al (2005) [110]	Canada	Prospective cohort study (2002-2004)	184		<p><i>Non -Adherence (<95%) associated with <u>Drug use</u>: frequent heroin injection (AOR 2.64, CI: 1.60-4.02)</i></p>	
Small et al (2009) [111]	Canada	Qualitative (2006-2007)	12	<p><i>Non- Adherence associated with <u>Social dynamics</u> of stigma and discrimination (isolation and deny scarce resources) towards HIV positive drug users by other inmates-</i></p>	<p><i>Non- Adherence associated with <u>Fear of stigma and discrimination</u> leads to <u>lack of disclosure</u> about status and reluctance to take ART in front of others. Contributes to less than optimal adherence.</i></p>	
Stein et al (2000) [112]	USA	Cross-sectional (1997-1998)	42	<p><i>Non- Adherence associated with <u>Lack of structured lifestyle</u>: being away from home 18 (43.9%); Busy with other things 22 (53.7%), daily routine changed 10 (24.4%)</i></p>	<p><i>Non- Adherence associated with <u>Drug use</u>: IDU while receiving MMT (p <0.05)</i></p> <p><i>Alcohol abuse while receiving MMT (p <0.05)</i></p> <p><i><u>Health beliefs</u>: Misperceptions about importance of scheduled doses (p <0.05)</i></p> <p><i><u>Cognition</u>: forgetting 23 (56.1%)</i></p>	

Source	Country	Study design	Sample size	Social structural	Psychological (including cognitive)	Socio-demographic
Tapp et al. (2011)[113]	Canada	Prospective cohort study (1996-2008)	545		<i>Adherence (95%) associated with <u>Frequent drug use</u>: Daily heroin injection (AOR 0.56, CI: 0.43-0.73) Daily cocaine injection (AOR 0.58, CI 0.47-0.72)</i>	<i>Adherence (95%) associated with <u>Gender</u>: Female (AOR 0.70 CI: 0.53-0.93) <u>Age</u> Younger <24: (AOR 0.27, CI: 0.13-0.57)</i>
Turner et al. (2001) [114]	USA	Prospective cohort study (1996-1997)	2267		<i>Adherence associated with <u>Depression</u> (because of receipt of care) p<0.003</i>	<i>Adherence associated with <u>Gender</u>: 18% of women adherent compared with 25% of men (p<0.001)</i>
Uhlmann et al (2010) [115]	Canada	Prospective cohort study (1996-2008)	231		<i>Adherence(95%) associated with <u>Drug use</u> Daily heroin use significantly associated poorer adherence (AOR 0.60 CI: 0.44-0.82)</i>	<i>Adherence(95%) associated with <u>Gender</u> Female: (AOR 0.63,CI: 0.4-1.00)</i>
Wagner & Ryan (2004) [116]	USA	Cross-sectional (2003)	51	<i>Adherence(95%) associated with <u>Social stability</u>: Daily routine activities scale account for 36% of variance (F (1, 44) = 36, p<0.001. Lifestyle structure add 9% to variance (F change = 8.9; P<0.01)</i>		
Waldrop-Valverde et al. (2005) [117]	USA	Cross-sectional	58	<i>Non-adherence associated with <u>Housing status</u> not related to adherence (AOR 1.81 CI: 0.49-6.6)</i>	<i>Non-adherence associated with <u>Greater depression</u> (AOR 0.92 CI 0.86-0.99)</i>	
Waldrop-Valverde et al. (2008) [118]	USA	Cross-sectional	57		<i>Non-adherence associated with <u>Low literacy and cognitive impairment</u> (AOR 9.45, CI: 1.49-60.17) <u>Current multiple drug use</u> IDU and Cocaine use in last week (AOR 5.89, CI: 1.50-23.25)</i>	

Source	Country	Study design	Sample size	Social structural	Psychological (including cognitive)	Socio-demographic
Ware et al. (2005) [120]	USA	Qualitative (2005)	52	<i>Non-adherence associated with <u>Social instability</u>: Multiple life difficulties (financial, housing, other demands, access to MMT) may take greater priority than scheduled meds. Drug use impact on routine of regular medicine use.</i>	<i>Non-adherence associated with <u>Drug use</u>: process of acquiring, using and recovering from use physically and psychologically separates people from ART</i> <i><u>Negative outcome expectations</u>: Low confidence in providers' ability to treat HIV in people with drug problems, concern about drug-ART interactions</i> <i><u>Co-occurring depression</u> also leads to lapses</i> <i><u>Fear of stigma and discrimination</u>- so not take ART in social situations when using drugs</i>	
Weber et al. (2009) [121]	Switzerland	Prospective Cohort study (1997-2006)	8660		<i>Non-adherence (ART interruption) associated with <u>Continued drug use</u> DMT and IDU (AOR 1.52 CI: 1.31-1.77); Current IDU with no DMT (AOR 1.53 CI: 1.19-1.97) compared to ex-IDU</i>	
Wood, Montaner et al. (2004) [124]	Canada	Prospective cohort study (1996-2000)	1422		<i>Non-adherence (rate of HAART discontinuation) associated with <u>Current drug use</u>: IDU associated with more rapid HAART discontinuation (ARH 1.4 , CI: 1.2-1.7)</i>	

RH = relative hazard, ARH adjusted relative hazard; CI= 95%confidence interval

OR = odds ratio; AOR odds ratio adjusted for confounders and covariates

3.3.2. Disease-level barriers and facilitators to ART adherence

Disease-level barriers and facilitators to ART adherence were noted in eight studies (36, 78, 80, 92, 100, 103, 110, 113; Table 6). Most of these studies identified HIV severity as a barrier to adherence, with lower CD4 + counts (103, 110, 113) and higher HIV RNA viral loads (80, 92, 113) associated with a greater likelihood of non-adherence even after controlling for the influence of other covariates. Patients with high viral loads and low CD4+ counts may feel too sick to take their ART and/or may not be able to cope with the side effects of ART. This was a self-reported reason for non-adherence in one study in this review (58). Similarly, another study (78) found a greater likelihood of non-adherence as problematic HIV symptoms increased. Findings from this review suggest that if HIV symptoms are effectively managed through ART, this can facilitate ART adherence. HIV viral load suppression was a significant facilitator to adherence in one study (110) where PWID who achieved viral suppression had 66% reduced odds of non-adherence compared to PWID without viral suppression. Similarly, another study (103) noted that improvements in CD4 + counts and reductions in viral load were motivators for adherence. While these findings suggest that HAART adherence is related to the observed benefits of these medicines, it is important to note that the strength of the associations between CD4+ counts, HIV-1 RNA levels and HAART adherence for PWID was significantly diminished when other potential barriers to adherence were examined. Although need for HAART is an important determinant of HAART adherence among PWID, findings from this review suggest that other barriers impinge on whether this need translates into adherence.

3.3.3. Treatment-level barriers and facilitators to ART adherence

Treatment-related barriers and facilitators to ART adherence were noted in 18 studies (36, 40, 58, 71, 75-6, 78, 94, 99, 102-4, 106-7, 110-111, 119-120; Table 6). These included medication regime factors and factors associated with the patient-provider relationship.

Medication regime factors associated with adherence

Eight studies reported medication regime barriers to ART adherence for PWID (36, 40, 58, 78, 94, 102-4, 106; Table 6). In these studies, the presence of side-effects was the most

common medication-related barrier to ART adherence. Seven studies noted that the odds of non-adherence increased as the number of adverse side-effects increased (36, 58, 78, 94, 102-3, 106). In contrast, one study (78) found that when side-effects are well managed, there is reduced likelihood of non-adherence to ART regimes. A further medication-related barrier associated with poor ART adherence is the complexity of the ART dosing schedule (78, 94). One study (78) noted that the risk of non-adherence grows with every increase in the number of daily medication doses. Similarly, a qualitative study conducted in the Ukraine (94) noted that complex dosing schedules that require multiple medications to be taken at prescribed times in a strict order and sometimes include food restrictions are challenging to PWID, especially if they have high levels of social instability. Good patient-provider relationships, in which patients are adequately informed about the side effects of HAART, are given tools to manage side effects and are given a say in treatment decisions may help mitigate some of these medication-related barriers to adherence. The following section describes how such patient-provider relationships impact on adherence for PWID.

Patient-provider relationship and adherence

Eleven studies noted characteristics of the patient-provider relationship associated with ART adherence for PWID (71, 75-6, 99, 103-4, 107, 110-111, 119-120; Table 6). Four studies reported that good patient-provider relationships (characterised by clear communication, confidence in the providers' ability to treat HIV, patient-centred communication, and a supportive and caring relationship) facilitate better adherence and mitigate some of the other patient and treatment-related barriers to adherence (103-4, 111, 119). Good patient-provider interactions may affect adherence by improving the patient's knowledge of treatment options and by enhancing self efficacy to adhere to HAART regimens (45). The engagement of PWID with health providers may be especially important to their HAART use, given that many PWID are disadvantaged and may be distrustful of the medical system (147).

In contrast, relationships with health care providers characterised by low confidence in the health provider's ability to manage HIV among PWID (99, 111) and ill treatment (71, 75-76,

107, 110) are barriers to adherence, largely because such relationships discourage PWID from continuing with HIV treatment. While additional clinical training for physicians delivering ART to PWID may help improve health providers' interactions with PWID (2), a singular focus on improving health providers' practices masks some of the systemic factors that underpin the mistreatment of PWID by health providers in some countries. Almost all the studies (71, 75-76, 107) that identified poor patient-provider relationships as a barrier to adherence were conducted in countries where there is institutionalised stigma towards PWID. In countries where stigma towards PWID is endemic, health care providers often mistreat and discriminate against HIV-positive PWID by not providing confidential care, making them wait for or refusing services (71, 75-76, 107). PWID also tend to have little say in and are ill-informed about their treatment plans (76, 107). As a result, PWID in these contexts have little trust in health care providers and this acts as a disincentive for continued use of HIV services (75-6, 107). In contexts where institutionalised stigma shapes how health care providers respond to PWID, emphasis needs to be placed on addressing the systemic factors that impinge on the quality of the patient-provider relationship. These systemic influences on adherence are described more fully below.

Table 6. Disease and Treatment-related factors associated with adherence: findings from selected studies (2000-2011)

Source	Country	Study design	Sample size	Treatment characteristics		Disease characteristics
				Patient-provider relationship	Medication regime	
Berg et al. (2004) [58]	USA	Prospective Cohort study (1998-2001)	113		<i>Adherence associated with <u>Significant medication side effects</u> ($\beta = -22.5$, CI: -34.2 to -10.9)</i>	
Dzhalbieva et al (2009) [71]	Krygyzstan	Qualitative (2007-2008)	73	<i>Non-adherence associated with <u>Poor relationship</u> with health care provider and ill treatment because drug user</i>		
Human rights Watch/TTAG (2007) [75]	Thailand	Qualitative	43	<i>Non-Adherence associated with <u>Poor relationship between providers and patients</u>: stigma and discrimination leads to disruptions in treatment</i>		
Human Rights Watch (2006) [76]	Ukraine	Qualitative (2005)	101	<i>Non-Adherence associated with <u>Relationship between patient and provider</u>: Poor treatment by medical staff reduces motivation to continue ART</i>		
Johnson, et al (2003) [78]	USA	Cross-sectional (2000-2002)	2765		<i>Non-adherence associated with: <u>Complexity of Medication regime</u>: Number of doses per day (AOR 1.32 CI 1.07-1.63)</i> <i><u>Management of ART side effects</u> (AOR 0.87, CI: 0.80-0.95)</i>	<i>Non-adherence associated with: <u>Total HIV symptom bother</u> (AOR 1.01, CI:1.00-1.02)</i>

				Treatment characteristics		
Kavasery et al (2009)[80]	USA	Prospective cohort study (1996-2006)	335			<p><i>Non-adherence associated with:</i></p> <p><u>Disease severity:</u> HIV RNA copies/100 ml (400-10 000) (AOR 1.89, CI: 1.30 to 2.73).</p> <p>HIV RNA copies/100 ml >10 000 (AOR 2.12, CI: 1.51 to 2.96).</p>
Kerr et al. (2004) [36]	Canada	Prospective cohort study (2000-2001)	108		<i>Non-adherence (missing doses) associated with:</i> Side effects (17%),	<i>Non-adherence (missing doses) associated with:</i> Being too sick (17%)
Kerr et al. (2005) [40]	Canada	Prospective cohort study (2000-2001)	160		<i>Non-adherence (discontinuation) associated with:</i> Side effects (41%)	
Milloy et al (2011) [92]	Canada	Prospective cohort study (1996-2009)	490			<i>Non-adherence (<95%) associated with:</i> <u>Disease severity:</u> HIV RNA viral load (AOR 5.41, CI: 4.73-6.20)
Mimiaga et al. (2010) [94]	Ukraine	Qualitative	16		<p><i>Non-adherence associated with:</i></p> <p><u>Complexity of treatment regimes:</u> few treatment options available. Available options have complex dosing schedules and food restrictions which is challenging for IDU with unstable lives.</p> <p><u>Medication side effects</u> as major barrier</p>	
Palepu et al (2004a) [99]	Canada	Prospective cohort (1997-2002)	1746	<i>Non-adherence (<95%) associated with:</i> <u>physician HIV experience</u> (median years) (AOR 0.97, CI: 0.96-0.98)		

				Treatment characteristics		
Palepu et al (2006) [100]	Canada	Prospective cohort study (1996-2003)	278			<i>Adherence (95%) associated with <u>Disease severity</u> Baseline CD4 count (AOR 0.9 CI: 0.83-0.99).</i>
Peretti-Watel (2006) [102]	France	Cross-sectional (2003)	2932		<i>Adherence (95%) associated with Perceived adverse <u>side effects</u>(AOR 0.63, CI 0.52-0.77)</i>	
Piekarska-Mankiewicz & Cholewinska (2009) [103]	Poland	Case-control (2008)	60	<i>Adherence associated with Physician approach : friendly and responsive</i>	<i>Non-adherence associated with Adverse <u>side effects</u> (60%)</i>	<i>Adherence associated with <u>Observed benefits of ART</u> (reduced viral load improved CD4)- 83% motivating factor.</i>
Roberson et al. (2009) [104]	USA	Qualitative (2004-2005)	12	<i>Adherence associated with <u>Helpful and supportive relationship</u> with health care provider relationship</i>		
Roux et al (2008) [106]	France	Prospective cohort study (1995-2000)	276		<i>Non-Adherence (<95%) associated with Number of self-reported <u>side effects</u> (AOR 1.07 CI 1.0-1.12).</i>	
Rusakova et al (2008) [107]	Russia	Mixed methods	577	<i>Non-adherence (discontinuation) associated with: Provider/Physician decisions to stop ART (patients had no say in treatment plan) 50% in St Petersburg and 31% in Orenburg</i>		
Shannon et al (2005) [110]	Canada	Prospective cohort study (2002-2004)	184	<i>Non-adherence (<95%) associated with: Poor treatment by health professional (AOR 1.70, CI:1.23-3.04)</i>		<i>Non-adherence (<95%) associated with: <u>Disease severity</u>: CD4 <200 (AOR 2.51, CI: 1.91-3.23) Viral load suppression (AOR 0.34, CI: 0.20-0.51).</i>

				Treatment characteristics		
Small et al (2009) [111]	Canada	Qualitative (2006-2007)	12	<i>Adherence associated with <u>Effective communication</u> with health care providers</i> <i><u>Good relationship</u> with health care providers.</i>		
Tapp et al. (2011) [113]	Canada	Prospective cohort study (1996-2008)	545			<i>Adherence (95%) associated with baseline viral load (per log 10 copies/ml) AOR 0.81 (CI: 0.68-0.97) baseline CD4 count (per 100 cells/mm) AOR 0.89 (0.84-0.94)</i>
Wang et al. (2010) [119]	China	RCT (2007-2008)	116	<i>Adherence associated with <u>Supportive relationships</u> with health providers (Nurse home visits and education) p<0.0001)</i>		
Ware et al. (2005) [120]	USA	Qualitative (2005)	52	<i>Nonadherence associated with <u>Low confidence in providers'</u> ability to treat HIV among drug users</i>		

RH = relative hazard, ARH adjusted relative hazard; CI= 95% confidence interval

OR = odds ratio; AOR odds ratio adjusted for confounders and covariates

3.3.4. Systemic barriers and facilitators to ART adherence

Systemic barriers and facilitators to ART adherence were noted in 26 studies (36, 60, 71, 75-77, 80, 91-2, 94, 98-101, 103-108, 110-111, 113-5, 120-1; Table 7). These barriers and facilitators relate to factors associated with the health care system, with detention, and with law enforcement policies.

Characteristics of the health care system associated with adherence

Health care system barriers and facilitators to ART adherence for PWID were identified by 20 studies (60, 71, 75-6, 91-2, 94, 99-101, 103-4, 106-8, 110, 113-5, 121; Table 7).

Access to drug maintenance treatment and other health services

Access to and the use of drug maintenance treatment for people who inject opiates was the most frequently reported health system facilitator for optimal ART adherence; with 12 studies noting the positive impact of opioid substitution treatment (OST) on adherence (60, 71, 92, 94, 99-101, 106, 110, 113, 115, 121). Specifically, seven cohort studies (92, 99-100, 106, 110, 113, 115, 121) noted that people who access and use OST have significantly greater odds of achieving optimal ART adherence compared to PWID and do not use OST. This effect persisted even after significant covariate adjustment. In addition, three studies (60, 101, 106) noted that the likelihood of individuals on OST not adhering to their ART regime was no greater than individuals who had never injected drugs. A possible explanation for the positive relationship between OST and adherence is that OST helps PWID reduce their drug problem severity to levels that allow for adequate HAART adherence (113). Two qualitative studies support this contention (71, 94). In both of these studies, participants noted that the use of OST helped reduce the time they spent acquiring and using drugs which gave them more time to concentrate on their health and stick to their ART regimes.

In addition, reducing drug use through the use of OST may give PWID opportunities to address other barriers to adherence. There is some evidence that long-term OST use may facilitate improvements in social stability and economic status (148-9) which this review

has identified as facilitators to HAART adherence. There is also evidence that social support networks (another facilitator to adherence) are likely to improve with the long-term use of OST (150). In addition, OST use results in regular contact with substance abuse service providers and the health care system which may provides opportunities for medication reminders and adherence counseling.

Regardless of how OST facilitates ART adherence among PWID, these findings clearly point to the need to expand access to and the coverage of OST programmes as a means of improving ART adherence. This is especially important for countries where HIV infections are largely attributable to IDU and where there is low or no access to OST (18, 84). In many countries where there are IDU-related HIV epidemics (especially in Eastern Europe and South-East Asia), enforcement-focused drug policies preclude the provision or expansion of OST and the prohibitive regulation of narcotics imposes barriers to the administration of OST (151). This problem persists despite evidence that MMT can be implemented effectively in a wide variety of settings, including developing and transitional countries (152). While some of the countries in these regions do have pilot OST programmes, the coverage of these programmes is limited and the future unclear due to funding uncertainty (153-4). The importance of addressing limited access to OST is highlighted from the findings of a qualitative study conducted in a country where OST is only available in pilot programmes. This study noted that limited access to OST was a significant barrier to achieving optimal adherence (60). Failure to scale up these pilot programmes could result in missed opportunities to improve HAART adherence among PWID and consequently control the spread of HIV.

In terms of access to other health services, only one of the included studies (114) examined whether access to psychiatric services acted as a facilitator to ART adherence for people with co-occurring depression and drug use. This study, conducted in the USA, found that access to psychiatric care acted as an adherence facilitator for women with co-occurring depression but not for men. On the contrary, men with co-occurring depression had improved adherence if they regularly attended drug dependence treatment services, but

not women. One possible reason for this unusual finding is that the structure of drug dependence treatment services in the US may not be women friendly, with women possibly preferring to use services in other health sectors to address their problems.

Organisation of the health care system

Several studies show that the organisation of health care systems constitutes a major barrier to the continuity of HIV treatment and care for PWID (76, 91, 94,103-4). These studies indicate that health systems in many countries do not facilitate the provision of comprehensive services for PWID. For instance, several countries (e.g. Russia, Ukraine) still have highly centralized health care systems in which specialty services are vertically organized. These silos of care hinder the provision of comprehensive care for PWID who need to travel between various specialty facilities to meet their service needs. This is not only time consuming but also leads to out of pocket travel expenses which act as a disincentive for continuing ART (76, 94, 103). This is cause for concern as HIV-positive PWID often have complex service needs that span multiple health specialties including HIV specialty care, addiction treatment, psychiatric care and hepatology, as well as obstetrics and gynaecology for women (155).

Other features of health systems also act as barriers to ART adherence among PWID. Five studies noted that health care costs hinder adherence. Even in countries where there is free ART, there are often other costs associated with HIV management such as the costs of viral load and CD4+ counts and the costs of treatment for opportunistic infections (76, 91, 94, 107-8). This is a barrier to ART adherence because people may experience ART interruptions because they cannot afford the costs associated with viral load and CD4+ count tests (76, 91, 94). Related to this, the availability of free ARV medication is not always constant in developing and transitional countries, with stock out-ages and medication shortages frequently occurring. This leads to treatment interruptions that can last for several weeks (91, 94). Studies show that although ART is freely provided in some countries, medication for the management of side effects (e.g. pain) is not freely available. This may lead to poor adherence in an effort to reduce the side-effects of ART (76, 107-8).

In addition, there are other costs associated with public health service use in many developing and transitional countries. These costs contribute to treatment interruptions when PWID cannot afford health care. Some studies (76, 94) have highlighted how countries with poorly financed health systems sometimes charge user fees which limit the regular use of health services for people of restricted means. In addition, doctors in these health systems may charge “informal” fees to patients. These “informal” fees vary in amount according to the type of service needed and the characteristics of the patient; with PWID sometimes being charged higher fees because of stigma (76, 94). PWID are also required to pay more for confidential medical services and to prevent being registered as a drug user. This relates to the endemic stigma that PWID face within the health care system which in itself contributes to poor adherence.

Six studies reported that stigma and discrimination within the health care system is a major barrier to HAART adherence for PWID (60, 75-6, 91, 94, 107). These mainly qualitative studies were conducted in countries (such as Russia, Ukraine, Vietnam) where drug policies have a law enforcement focus and strongly sanction PWID. This policy framework shapes how health systems within these countries respond to PWID. All of these studies noted that HIV positive PWID are commonly discriminated against in the health care system. This discrimination takes the form of ill-treatment (and denial of confidential care); refusal to treat PWID; and treatment delays, with PWID being made to wait very long times for services. In addition, in many of these countries, health care providers work closely with the police and alert the police to patients who actively use drugs. Together these factors contribute to PWID having little trust or confidence in health care services. This acts as a further disincentive for the continued use of ART among PWID. Taken together, these findings clearly point to the need for health system interventions that address health care financing barriers, ensure the availability of free HIV monitoring and ART for those in need, and that remove institutionalized stigma and discrimination towards PWID. As health care systems are shaped by countries’ policy and legislative frameworks, interventions to improve health systems responses to HIV among PWID should also address barriers to adherence that occur within these frameworks.

Drug policies, legislation and adherence to ART

There are only a few studies that explore how drug policies that prioritise law enforcement over public health impede continued engagement in HIV services and adherence to HAART among PWID (60, 75-77, 91, 94). Studies note that in countries with these law enforcement- focused drug policies, PWID are often subject to police harassment. For example, studies note that police often arrest and detain known drug users for short periods to assist with drug-related cases or to fulfill arrest quotas. These short-term detentions often separate PWID from their ART (60, 75-77, 91, 94). In addition, four studies mention that police often search people who are known to use drugs and during these searches confiscate all medications, including ART (60, 76, 91, 94). This loss of medication leads to treatment interruptions. Studies also suggest that there is a blurring of medico-legal boundaries in many countries with conservative drug policies. Specifically, health providers work closely with the police and are known to call the police or place people on national drug user registries when someone mentions they use drugs. People on these national drug registries then run the risk of continued police monitoring and harassment. Also doctors accompany police on drug raids and conduct compulsory HIV testing on people who use drugs. Several studies report that this blurring of medico-legal boundaries reduces trust in the health care system, promotes the social exclusion of PWID, and as such hinders continued ART use among PWID (60, 75, 91, 94). Together findings from this review show that national drug strategies that are predominantly law-enforcement focused hinder the use of health services and therefore ART adherence among PWID. In addition, law-enforcement focused policies also lead to high levels of detention and incarceration among PWID which poses its own set of challenges for ART adherence.

Detention and adherence

Detention-related barriers and facilitators to HAART adherence among PWID were identified by thirteen studies (36, 60, 75-77, 80, 91-2, 94, 98-9, 104, 111, 120; Table 7). These studies examined various forms of detention including detention in compulsory treatment centres, short term detention through policing activities for drug-related offences, pre-trial detention, and incarceration in prison. Irrespective of the type, detention was

almost always associated with interruptions in the use of ART or ART discontinuation. ART gets interrupted at various points in the detention process. First, there is a risk of interruption when people enter detention. Four of the studies included in this review reported that being detained by the police for drug-related offences and pre-trial detention lead to missed medication doses and short term interruptions in care (36, 60, 76, 94, 111), especially as there is often no access to medication in short-term detention facilities.

Second, the prison system itself is a risk factor for poor adherence. Nine studies (36, 75, 77, 80, 92, 94, 98, 111, 120) identified being incarcerated in prison as significant risk factor for non-adherence, even after controlling for the influence of potential confounding factors. In fact, one recent cohort study (98) found a dose-response relationship between the number of times a person had been incarcerated and the risk of non-adherence: for every increase in the number of times a person had been incarcerated, the likelihood of ART adherence worsened. A number of factors seem to contribute to the negative effect of incarceration on adherence. In many countries, there is limited availability of ART in detention settings, which may lead to treatment disruptions or discontinuation (71, 77, 94). Even in countries where ART is available in prison environments, the structure of the prison system may hamper ART adherence. Several studies noted that frequent transfers between or within prisons separates people from their medication and as it often takes time to replace these medications this results in treatment interruptions (71, 75, 77, 104, 111). Other studies noted lengthy delays in obtaining new prescriptions once old prescriptions had run out which also results in treatment interruptions (104, 111). Additionally, poor relationships between prisoners and prison health providers and high levels of HIV-related stigma within prisons may also discourage PWID from disclosing their HIV status while incarcerated (111), leading to difficulties in obtaining continued care. However for a small proportion of people who actively use drugs and struggle to achieve optimal adherence on the “outside”, the structure of prison may actually facilitate adherence with one study noting that for a subset of participants, adherence was more likely in prison than on release from incarceration (104). Third, for PWID treatment interruptions can occur on release from detention. As detention settings separate PWID from their usual health provider this

may lead to delays in re-engaging in care once released from incarceration (98). In addition, several qualitative studies have noted that many prison settings make little effort to help HIV-positive prisoners re-engage with their health providers to ensure continuity of care upon release (111, 120). Related to this, in some countries (especially those with law-enforcement oriented drug policies), incarceration leads to a loss of identify documents. Without these essential documents, they are unable to access continued HIV (or other health) services on release from prison (71).

Apart from incarceration in prison, other forms of detention also lead to treatment discontinuation. In countries that run compulsory drug “rehabilitation” facilities, detention in these facilities is associated with ART discontinuation (75, 77, 91). Studies have noted that PWID have difficulties ensuring continuity of ART on entry into these detention facilities and also on release into the community (75, 77, 91). There is also limited opportunity for the treatment of opportunistic infections in these compulsory treatment facilities (75). It is estimated that the vast majority of PWID interred in these facilities return to active drug use on release from compulsory treatment (156) which in itself is a risk for HAART discontinuation.

As the overwhelming majority of PWID are detained by the police or incarcerated at least once in their lifetime (44), it is important to ensure that detention settings are conducive to HAART adherence. Findings from this review suggest that structural interventions are required to improve ART delivery in detention settings. There is emerging evidence that where HAART is freely available in well-resourced detention settings, the highly structured environment of prison can facilitate adherence for some PWID (104, 156). There have been several successful models of ART delivery for incarcerated PWID. Models that seem particularly effective are directly observed ART delivery and the provision of OST in conjunction with ART. These models of service delivery are discussed in the next section.

Table 7. Systemic factors associated with adherence: findings from selected studies (2000-2011)

Source	Country	Study design	Sample size	Systemic factors		
				Law enforcement policies	Detention	Health care system barriers
Bouhnik et al. (2002) [60]	France	Prospective cohort study (1997-1999)	210			<i>Non- Adherence (<95%) associated with:</i> Those not on OST more likely to be nonadherent than IDU on DMT (AOR 4.45 CI: 2.14-9.24)
Dzhalbieva et al (2009) [71]	Krygyzstan	Qualitative (2007-2008)	73	<i>Non- Adherence associated with Police harassment of current and ex-drug users and rights violations.</i>	<i>Non- Adherence associated with <u>Police detentions and arrests</u> for possession lead to treatment interruption</i> <i><u>Incarceration</u> for drug possession- no HIV prevention and treatment programmes available in female prisons Limited health care services available and no MMT</i> <i>Incarceration leads to loss of identity documents- on release takes time to get these documents. Without documents cannot access health services.</i>	<i>Non- Adherence associated with <u>Limited access to and use of OST</u>, especially among women - pilot programmes only</i> <i><u>Limited access to drug treatment</u>- most only provide detoxification services.</i> <i><u>High costs</u> associated with anonymous detoxification (where police are not notified)</i> <i><u>Stigma and discrimination by health care providers</u>- ill treatment or refusing to treat drug users</i>
Human rights Watch/TTAG (2007)[75]	Thailand	Qualitative	43	<i>Non- Adherence associated with <u>Police harassment</u> of drug users because of war on drugs policy results in treatment interruptions. Drug users reluctant to use health care services.</i>	<i>Non- Adherence associated with <u>Detention and incarceration</u> in compulsory treatment or prison. Difficulties in ensuring continuity of ART on entry and on release from detention. Treatment interruptions occur if transferred between facilities. Limited treatment for Opportunistic infections in detention facilities.</i>	<i>Non- Adherence associated with:</i> <i><u>Stigma and discrimination</u> towards HIV positive and drug users in health care system: delays in care, disruption to continuity of care, lengthy waits. Does not encourage adherence</i>

Human Rights Watch (2006) [76]	Ukraine	Qualitative (2005)	101	<i>Non- Adherence associated with <u>Police harassment</u> of HIV positive drug users- confiscate ART and claim they are narcotics. Leads to treatment interruptions.</i>	<i>Non- Adherence associated with <u>Detention and incarceration</u> as part of policing/social control and <u>war on drugs policy</u>:- short term detention of known drug users- lead to disrupted care and no access to ART while detained</i>	<i>Non- Adherence associated with <u>Health care costs</u>: formal and informal fees levied on all services- especially if HIV positive drug user. Makes continuity of care and treatment for OI difficult. <u>Lack of comprehensive, integrated care</u>: Lack of treatment for OI. Will only give art once OI treated. Treatment disruptions if OI <u>Lengthy waits for care</u> and distance to travel- barrier to adherence <u>Ill-treatment within system</u> because of stigma to drug users and HIV positive- lead to discontinuation of ART</i>
Human Rights Watch (2010) [77]	China	Qualitative (2010)	33		<i>Non- Adherence associated with <u>Detention and incarceration</u> in compulsory treatment or prison. Difficulties in ensuring continuity of ART on entry and on release from detention. Treatment interruptions occur if transferred</i>	
Kavasery et al (2009) [80]	USA	Prospective cohort study (1996-2006)	335		<i>Longer periods (> 6months) of Non-adherence associated with: <u>Incarceration</u>: (AOR, 2.80; CI: 0.97 to 8.12)</i>	
Kerr et al. (2005) [36]	Canada	Prospective cohort study (2000-2001)	160		<i>Non-adherence associated with: <u>Recent Incarceration</u>: AOR 4.84 (CI: 1.2-18.7)</i>	

Maher et al. (2007) [91]	Vietnam	Qualitative (2006)	Not reported	<i>Non-adherence associated with: <u>Policing</u> and “war on drugs”- police harassment and detention leads to disruptions in care</i>	<i>Non-adherence associated with: <u>Detention</u> in “rehabilitation centre”- lead to interruption in care- no or low access to ART</i>	<i>Non-adherence associated with: <u>Stigma and discrimination</u> within health care system if drug user. <u>Limited free health care</u> user pays for care (not meds but OI treatment, additional CD4 and other tests) <u>Limited access to free medicines</u> (availability) leads to disruptions (health care system, limited testing, low access to medicines</i>
Milloy et al (2011) [92]	Canada	Prospective cohort study (1996-2009)	490		<i>Non-adherence (<95%) associated with: <u>Incarceration:</u> 1-2 events (AOR 1.49, CI 1.06-2.12); 3-5 events (AOR 2.48, CI: 1.66-3.71); >5 events (AOR 3.11, CI: 1.93-5.03).</i>	<i>Non-adherence (<95%) not associated with <u>Access to and use of MMT</u> (AOR 0.47, CI: 0.36-0.62)</i>

Mimiaga et al. (2010) [94]	Ukraine	Qualitative	16	<i>Non-Adherence associated with <u>Police harassment</u> of HIV positive current and former drug users- confiscate ART and claim they are narcotics. Leads to treatment interruptions. arrest and detain without access to meds)</i>	<i>Non-Adherence associated with <u>Detention and incarceration</u></i> Short term detention of current and former drug users by police due to social control. Arrest and detain drug users and during detention have no access to medication.	<i>Non-Adherence associated with <u>HIV stigma and discrimination</u></i> by health providers when sought treatment – refusal to treat or lengthy delays in treatment leads to lack of continuity of care Failure to disclose HIV positive when hospitalized due to stigma- leads to short-term interruptions in care. <u>Wait time</u> often associated with being treated for HIV <u>OST helps with adherence-</u> have more time to care for self as not sourcing street drugs. <u>Vertical system</u> where referred out for other health care needs lead to out of pocket expenses (travel, treatment), time consuming and impacts on motivation to continue HIV treatment
Palepu et al (2004a) [98]	Canada	Prospective cohort (1997-2002)	1746		<i>Non-adherence (<95%) associated with <u>Incarceration</u></i> (AOR 2.40, CI: 1.54-3.75)	
Palepu et al (2006) [99]	Canada	Prospective cohort study (1996-2003)	278			<i>Adherence (95%) associated with: <u>Access to and use of MMT</u></i> (AOR 1.56, CI: 1.16-2.00)
Palepu et al (2011) [100]	Canada	Prospective cohort study (1996-2008)	543			<i>Adherence (95%) associated with: <u>Access to and use of MMT</u></i> (AOR 2.33 CI: 1.86-2.92)

Peretti-Watel (2006) [101]	France	Cross-sectional (2003)	2932			<i>Non-adherence (<95%) not associated with:</i> <u>Access to and use of DMT</u> : Patient on DMT (AOR 1.08, CI 0.71-1.65)
Piekarska-Mankiewicz & Cholewinska (2009) [103]	Poland	Case-control (2008)	60			<i>Adherence associated with</i> <u>Accessibility of medical care</u> (47%) <u>Long distance to health care system</u> is a barrier to adherence (10%)
Roberson et al. (2009) [104]	USA	Qualitative (2004-2005)	12		<i>Non-adherence associated with incarceration:</i> Logistics of movement in prison-transfers to hospitals or other parts of prison impact on adherence as sometimes takes time to get ART during transfer, charts are lost, replacing scripts takes time. Prison routine can facilitate adherence as highly structured - especially if drug user had chaotic lives. Some report better adherence while in prison (medication calls as reminders, reliable refills)	<i>Non-adherence associated with</i> <u>Prison health service provision</u> : long queues and waits for meds so miss doses
Roux et al (2008) [106]	France	Prospective cohort study (1995-2000)	276			<i>Non-adherence (<95%) not associated with:</i> <u>Access to and use of DMT</u> : MMT or BT and no injection (AOR 1.0 CI 0.5-1.8, and AOR 1.0, CI 0.6-1.6 respectively).

Rusakova et al (2008) [107]	Russia	Mixed methods	577			<i>Non-adherence associated with <u>Stigma and discrimination in health care system</u> towards drug users: sometimes refuse to treat or lengthy delays in getting care- results in interruptions to care. <u>Availability of required drugs</u> sometimes results in unplanned cessation of ART (27.3% St Petersburg, less than 5% in Orenburg) and short term treatment interruptions</i>
Sabin et al. (2008) [108]	China	Qualitative (2005-2006)	36			<i>Non-adherence associated with <u>Health care costs</u>: ART is free but worry about future costs and costs of other aspects of care such as OI, treatment for side effects, transport to services, CD4 tests.</i>
Shannon et al (2005) [110]	Canada	Prospective cohort study (2002-2004)	184			<i>Non-Adherence (<95%) associated with <u>Access to and use of MMT</u> (AOR 0.53,CI: 0.36-0.87)</i>

Small et al (2009) [111]	Canada	Qualitative (2006-2007)	12		<p><i>Non-adherence associated with:</i> <u>Incarceration:</u> Leads to interruption or delays in getting meds especially when entering the system and awaiting trial (holding cells). There is no medication or access to health care there.</p> <p>Multiple transfers within prison system lead to short term interruptions and care only resumed when person arrives at institution.</p> <p>Also delays in obtaining new script, delay in procuring and dispensing meds (not according to schedule), delay in obtaining specialist care- often takes months.</p>	
Tapp et al. (2011) [103]	Canada	Prospective cohort study (1996-2008)	545			<p><i>Adherence (95%) associated with:</i> <u>Access to and use of MMT</u>(AOR 2.35, CI: 1.88-2.94)</p>
Turner et al. (2001) [114]	USA	Prospective cohort study (1996-1997)	2267			<p><i>Adherence associated with:</i> <u>Access to psychiatric care, if have co-occurring depression</u> (AOR 1.49, CI: 1.04-2.15), especially for women (AOR 1.92 CI: 1-3.68) but not men (AOR 1.26, CI 0.81-1.98).</p> <p><u>Access to drug treatment</u> (AOR 1.44, CI 1.12-1.87), especially for men with (AOR 1.65 CI 1.19-2.28) or without co-occurring depression (AOR 1.26, CI 1.02-1.17) but not for women</p>

Uhlmann et al (2010) [115]	Canada	Prospective cohort study (1996-2008)	231			<i>Adherence associated with: <u>Access to and use of MMT</u> (AOR 1.49, CI. 1.07-2.08)</i>
Ware et al. (2005) [120]	USA	Qualitative (2005)	52		<i>Non- Adherence associated with Disrupted use of ART when <u>institutionalised</u> in drug treatment, incarcerated, or in hospital</i>	
Weber et al. (2009) [121]	Switzerland	Prospective Cohort study (1997-2006)	8660			<i>Non-adherence associated with: <u>Access to and use of DMT</u> not associated with treatment interruptions (if no injection drug use)</i>

RH = relative hazard, ARH = adjusted relative hazard; CI= 95% confidence interval

OR = odds ratio; AOR = odds ratio adjusted for confounders and covariates

4. Factors associated with the delivery of ART to PWID

Providing optimal care to PWID living with HIV is a challenge given the multiple barriers to accessing and adhering to ART that PWID experience. Even in countries with universal access to free ART, PWID have disproportionately low rates of access and adherence to ART in comparison to other people living with HIV (8-9, 23, 25, 36, 40, 45). For many PWID, the organisation of the health system is a major obstacle to accessing and continuing to use HAART (44). Even for people living with HIV/AIDS (PLWHA) without a history of drug use, health system factors impact on the effective use of HAART. For example, in the United States a number of policy factors and a fragmented health care delivery system have restricted engagement in HIV care for PLWHA; especially in rural areas where there is inadequate access to medical services and high levels of HIV-related stigma (157). The impact of health system factors on the optimum delivery of HAART is even more apparent in countries in Southern Africa that have generalised HIV epidemics in conjunction with weak health systems. In these countries, inadequate supply of skilled and motivated health workers, and cultures of service delivery that limit the creation of person-centred therapeutic partnerships are some of the factors that obstruct HAART delivery (131, 157). Given the important role that health systems play in facilitating or hindering access and adherence to HAART, it is important to examine ways in which health systems can be strengthened to improve HAART delivery to PWID. This section reviews the literature on models of HIV service delivery for PWID and health system factors associated with improved HAART use among PWID.

4.1. Models of HIV service delivery for PWID

PWID living with HIV often have multiple health and social needs that include the need for addiction, HIV, obstetrics and gynaecology (for women), STI, hepatology, mental health, tuberculosis (TB), and housing services (8). To facilitate the effective use of HAART and optimize health outcomes among PWID, functional health systems are required that allow for the provision of comprehensive services that span these diverse service needs (44). Good communication, collaboration and co-ordination of care across health service

providers is key for providing comprehensive health services to PWID, regardless of how the health system is structured (158-9).

Historically, there have been two main models of comprehensive service delivery to PWID. The first is a *distributive or off-site referral* model. In this model, PWID are not offered a comprehensive range of services at a single service site but are linked to other needed services (offered by off-site service providers) via systems of referral and linkages. The second model of comprehensive care is that of *co-located services or the on-site* model. In this on-site model, comprehensive services in the form of primary health (including primary HIV) and substance abuse services, and sometimes additional services (such as mental health services and ancillary social services) are provided at a single service site (158-160). Each type of service delivery models has inherent strengths and limitations.

4.1.1. Advantages and disadvantages of the distributive model

With the distributive model, no rearrangement of the existing health care delivery system is required to facilitate access to comprehensive services for PWID. As distributive models use the existing infrastructure and resources present in the health system, and forge linkages between these resources, they do not hold any additional costs for the health system. An example of where the distributive model works relatively well is Georgia. By 2004, this country had achieved universal access to free ART. In addition, access to ART for PWID is relatively good with 60% of the 752 patients enrolled in ART between 2004-2009 being PWID (161). Georgia's health system is still centralized with the ART programme co-ordinated by the Infectious Diseases, AIDS and Clinical Immunology Research Centre (IDACIRC) in Tbilisi and addiction and TB services being provided elsewhere. However, TB treatment is free and there is good collaboration between the HIV/AIDS and TB services (161).

While this system of service provision works well when there are strong linkages and service agreements between different types of health service providers (158), this model does not function when the linkages between services are weak. Apart from this, many

countries that use a distributive approach to the provision of comprehensive care leave it up to the PWID to navigate the pathways to additional services. These referral pathways are extremely difficult to navigate, with each service having its own barriers to access (71, 75-77, 94). For example, the Russian Federation and Ukraine have centralised health systems with vertical programming comprising of specialised and distinct services for HIV/AIDS, STIs, psychiatric care and drug dependence treatment (44, 162).

Compartmentalized health systems such as these are cumbersome for PWID living with HIV and other co-morbid conditions to navigate as they are required to register at multiple specialty clinics to get their numerous health needs met (44, 45). As specialists have limited training in other disciplines and seldom communicate or collaborate around patient matters, it is left to the PWID to surmount the geographic gaps between clinical systems (9, 45, 162). In addition, each specialty service has its own set of eligibility criteria; with active drug use often making PWID ineligible for particular types of services such as TB (71, 76, 94). Apart from these barriers that require navigation, there are also costs associated with the use of multiple services. Together these factors limit the uptake of referrals to comprehensive services (including HIV services) among PWID (71, 76, 94, 158, 162). These findings suggest that the use of distributive models of service delivery in health systems that have weak linkages between services and that expects PWID to navigate off-site systems of care is not sufficient to ensure that PWID receive the services they need (158).

Several interventions have been proposed to strengthen these distributive models (Table 8). Studies have noted that community-based case management and transportation assistance are important ancillary services that facilitate the uptake of off-site referrals for PWID (158, 161-168). Studies show that case management helps PWID to navigate fragmented health systems (162, 167). There is also emerging evidence that strength-based case management in conjunction with transport assistance improves the uptake of drug services among PWID. For example, a randomised trial among needle exchange programme (NEP) clients found that community-based case management in conjunction with the provision of transport was significantly associated with increased entry into drug

dependence treatment (166). A recent systematic review also found that the use of motivational interventions and cognitive behavioural counseling in case management facilitates OST uptake among out-of-treatment PWID (168).

Over the last few years, patient navigation has emerged as a promising strategy to facilitate access to HIV care among marginalised populations, including PWID (157, 169). Patient navigators are often peers from similar cultural and socio-economic backgrounds providing distinct, but complementary services to those provided by case managers and other supportive service providers (157). Navigators mostly assist PWID to access services by helping them overcome logistic barriers to care and also by helping PWID develop behavioural skills to improve self-care and effective communication (via supportive peer counseling) that may improve their relationships with health service providers (157, 169-70; Table 8). The latter is an important factor not only for access but also for continued engagement in HIV care among PWID (171). A study from California using a peer-based outreach intervention found that while the use of peer counselors helped improve the uptake of HIV services for PWID, uptakes of referrals for social services and housing were greater than referral uptakes for HIV medical care among PWID living with HIV (172). However, having these survival needs met may improve social stability among vulnerable PWID which in itself is an important facilitator the effective use of HAART (143, 171). If peer workers or case managers are able to provide PWID with services that address their social stability and survival needs, this may be important first step towards engaging PWID in HIV care (171-2).

Table 8. Health system interventions to facilitate the effective use of HAART: findings from selected studies (2000-2011)

Source	Country	Setting	Type of intervention	Study design	Sample	Measures	Results
Rothman et al, 2007	USA	Drug treatment facilities in NY State	Co-location of HIV primary care within drug treatment programmes	Longitudinal study: 1. (1990 to 2002) 2. (1992 to 1999)	1. 168,340 HIV tests 2. 20,948 clients	1. HIV testing rates 2. HIV quality of care	1. 52,562 HIV tests on IDUs 2. Quality either matched or outperformed that provided by more conventional health care settings
Wood et al, 2006	Canada	Vancouver, DTES	Targeted HIV testing & counselling & receipt of HIV test results within 8 months	Prospective cohort (1996 to 2003)	105 IDUs unaware of their HIV status	Time to first ART use	Increased rate of ART uptake among IDUs previously unaware of their HIV status
Stopka et al, 2007	USA	5 California local health jurisdictions	Integration of HIV & HCV C&T targeting IDUs	Pre vs post intervention (Feb to Jun 2003)	1645 IDUs (baseline) 1305 IDUs (intervention)	1. HIV testing rates 2. HIV disclosure rates	1. Increased HIV C&T rates (27.1% vs. 8.4%) 2. Increased HIV disclosure rates (54.3% vs. 71.8%)
Roux et al, 2011	France	17 out-patient hospital services delivering HIV & HCV care	HCV treatment	Prospective cohort (Jan 2006 to Dec 2008)	593 HIV/HCV co-infected	ART adherence	HCV treatment is positively associated with ART adherence among HIV/HCV co-infected individuals (80% vs. 68%)
Weber et al, 2009	Switzerland	7 HIV out-patient clinics, private physicians & regional hospitals	OST	Prospective cohort (1997 to 2006)	8660 HIV+ (2569 IDUs)	Uptake & outcome of ART	OST & cessation of injection improved uptake & outcome of ART
Tran et al, 2011	Vietnam	6 standalone MMT clinics (3 in Hai Phong & 3 in Ho Chi Minh)	MMT	Cohort study (Jan to Oct 2009)	370 HIV+ IDUs	HRQL	MMT improved HRQL among IDUs living with HIV

Source	Country	Setting	Type of intervention	Study design	Sample	Measures	Results
Achmad et al, 2009	Indonesia	Hospital, Bandung, West Java	Integration of HIV testing & ART into MMT	Cohort study (May 2006 to Jan 2009)	223 IDUs on MMT	Uptake of HIV testing & ART	Providing HIV testing & treatment increased uptake of HIV testing & initiation of ART among MMT clients
Lucas et al, 2010	USA	HIV clinic, Baltimore, Maryland	Clinic-based BUP/NX vs. case management & referral to opioid treatment programme	Single-centre 12-month RCT (Nov 2005 to April 2009)	93 opioid-dependent HIV+	Participation in & outcomes for both opioid & HIV treatment	Clinic-based BUP/NX increased participation in opioid agonist therapy & HIV primary care visits
Altice et al, 2011	USA	10 geographically dispersed HIV clinical sites	Integration of BUP/NX into HIV clinical care	Observational study (3, 6, 9 & 12 months) (2004 to 2009)	295 opioid-dependent HIV+	Receipt & outcome of ART	BUP/NX increased ART initiation rate & CD4 counts
Palepu et al, 2006	Canada	Vancouver	MMT among HIV/HCV co-infected	Cohort study (1996 to 2003)	278 HIV+ IDUs (276 also HCV+)	HAART adherence & HIV treatment outcomes	MMT improved adherence to HAART & HIV treatment outcomes among HIV/HCV co-infected IDUs
Uhlmann et al, 2010	Canada	Vancouver, DTES	MMT	Prospective cohort (1996 to 2008)	231 ART naïve HIV+ IDUS	Time to first ART use & subsequent adherence	MMT increased ART initiation rate & adherence among ART naïve IDUs living with HIV
Altice et al, 2007	USA	Mobile health clinic, New Haven, Connecticut	DAART vs. SAT	6-month RCT (2001 to 2006)	141 HIV+ heroin &/or cocaine users	HAART adherence & virological outcomes	DAART significantly improved virological outcomes vs. SAT, but only modest improvements in adherence were observed

Source	Country	Setting	Type of intervention	Study design	Sample	Measures	Results
Tyndall et al, 2007	Canada	Two community health clinics, Vancouver, DTES	Two comprehensive DOT programmes (MAT & POP)	Retrospective study (1998 to 2004)	297 HIV+ IDUs	HAART adherence	Comprehensive DOT achieved 84.5% adherence rate during observation
Parashar et al, 2011	Canada	Community health centre, Vancouver, DTES	MAT programme	Cross-sectional (Jul 2007 to Jan 2010)	212 HIV+ unstably housed (44% current IDUs)	ART adherence	MAT attendees 4.76x more likely to be ≥95% adherent than non-attendees
Clarke et al, 2002	Ireland	Hospital-based methadone clinic	DOT	Prospective cohort (1998 to 1999)	39 HIV+ IDUs on methadone	HIV treatment outcomes	DOT (HAART+methadone) improved HIV treatment outcomes
Conway et al, 2004	Canada	Multi-disciplinary health care clinic, Vancouver, DTES	DOT	Prospective cohort (Jun 1997 to Oct 2001)	54 HIV/HCV co-infected IDUs on methadone	HIV treatment outcomes	DOT (HAART+methadone) improved HIV treatment outcomes
Lucas et al, 2006	USA	3 urban methadone clinics, Baltimore, Maryland	DAART vs. SAT	Prospective cohort (Apr 2001 to Mar 2005)	82 HIV+ IDUs on methadone	HIV treatment outcomes	Methadone clinic-based DAART improved virological & immunological outcomes vs. SAT
Berg et al, 2011	USA	12 methadone clinics with on-site HIV care, Bronx, New York	STAR*DOT vs. SAT	6-month RCT (Jun 2004 to Aug 2007)	77 HIV+ drug users on methadone	ART adherence	STAR*DOT improved adherence rate vs. SAT (86% vs. 56% by week 24)
Wang et al, 2010	China	Hunan Province	Nurse-delivered home visits + telephone calls	8-month RCT (Jul 2007 to Apr 2008)	116 HIV+ active or past heroin users	ART adherence & QoL	Intervention improved ART adherence & QOL

4.1.2. Advantages of the co-located model

The main advantage of the co-located or on-site referral model is that several services are provided at the same site (e.g. drug dependence treatment, harm reduction and HIV care services). By co-locating multiple services at a single service site, many of the geographic, bureaucratic and attitudinal barriers that inhibit PWID from seeking HIV care are overcome (158). First, the patient does not need to travel between service sites. Besides providing greater and more convenient access to needed medical and behavioural services, this model of service delivery also limits financial barriers to accessing health services (152). Second, this model encourages better communication, collaboration and co-ordination of care between different service providers and their agencies when developing treatment plans for PWID (158, 173). This facilitates better case management of each client and also provides opportunities to treat, in an integrated manner, the multiple co-occurring conditions that PWID often experience. Third, for PWID who are marginalized from the mainstream health system, co-location of HIV care within drug dependence treatment, harm reduction, and/ or social housing services is likely to prove more acceptable than services offered within the mainstream health system. This may facilitate the earlier initiation of HIV treatment (158,174).

In addition, co-located services may address some of the provider and regulatory barriers that PWID experience in mainstream health care. This is probably because service providers within co-located services targeting PWID are less biased towards PWID than service providers located within mainstream HIV services with limited experience or training in working with PWID (159, 173). At least one study included in this review found that HIV service providers located within drug dependence treatment services are more likely to provide PWID with HAART than service providers located within mainstream HIV services (65). Apart from the obvious benefits of co-located services for PWID, there are also benefits to agencies serving PWID. Within the co-located model, there is the potential to reduce the overhead costs associated with service provision through housing multiple agencies at the same site which allows some of the administrative costs associated with running these agencies to be shared (173).

There are several examples of local areas and model sites which offer co-located services. An example of the latter is the integrated primary health care model used by Kirketon Road Centre (KRC) in the Kings Cross area of Sydney, Australia (175). KRC operates a comprehensive medical, counseling, social welfare and outreach service that targets PWID among other high risk populations. It offers services such as needle and syringe programmes (NSPs), STI services, social services (housing and legal) and referral to drug dependence treatment (175). The site offers both fixed site and mobile services with a bus equipped to function as a mobile health clinic and staffed by a team of nurses and counselors (175).

4.1.3. Evidence for the impact of co-located services on the use of HAART

While the provision of co-located services is often a research recommendation (e.g. 163-165), there have been few documented evaluations of this model of HIV service delivery for PWID. Findings from the systematic review on factors associated with successful HAART delivery provide evidence that co-located services facilitates better uptake of and adherence to HAART among PWID (see Table 8). This section summarises some of this evidence.

Integrating HIV testing and substance abuse treatment

HIV testing and counseling (HCT) and the timely receipt of results is a prerequisite for linking PWID to HIV treatment and care (157). There is some evidence that integrating HCT and other primary care services into drug dependence treatment facilitates the initiation of HAART. An analysis of a co-located model of HIV primary care services offered within drug abuse treatment programmes in New York State between 1990 and 2002 found that this integrated model of care was effective at increasing HCT rates and in facilitating initiation of HAART among PWID living with HIV (159). To date, 17 drug dependence programmes provide co-located HIV primary care and drug treatment services in over 50 sites in the State of New York (173). Similarly, the Barriers to Antiretroviral Therapy (BART) cohort (1996 to 2003), a prospective study from Vancouver, Canada

demonstrated that the early receipt of HIV test results facilitated ART uptake among PWID living with HIV who were previously unaware of their status (122). This finding suggests that PWID living with HIV might benefit from targeted HCT initiatives that encourage the receipt of HIV test results and make linkages to further HIV services (122). Harm reduction services (such as NSP and OST services) where PWID often gather are obvious sites into which these HCT initiatives can be integrated.

There is also some evidence that integrating HCT into hepatitis C (HCV) counseling and testing services may improve the uptake of HCT among PWID. A 2003 study, targeting PWID from five local health jurisdictions in California, found that integrating HIV and HCV counselling and testing (C&T) services significantly increased HCT rates among PWID compared to when HCT services were offered alone (27.1% versus 8.4%; 176). PWID who received integrated HIV and HCV testing were also more likely to return for their results than people who received HCT only (71.8% vs 54.3%; 176).

Integrating HCV and HIV treatment

Even though many physicians remain reluctant to initiate HCV treatment in HIV and HCV co-infected PWID on HAART for fear that adherence to both treatments will be compromised (177), there is some evidence that integrated HCV and HIV treatment may improve adherence. A French multi-centre prospective cohort study (conducted between 2006 and 2008) of PWID co-infected with HIV and HCV found that initiating HCV treatment was positively associated with adherence to HAART (80% adherence) compared to those PWID who did not receive HCV treatment (68% adherence; 177).

Integrating harm reduction services with HAART delivery

There is also some evidence that integrating HIV treatment into harm reduction services (such as NSPs and safer injection facilities) can improve the uptake of HAART among PWID. For example, a qualitative study of Vancouver's first safe injection facility (Insite) found that the facility's integrated model of care which combined peer support, safer injection facilities, and on-site access to primary health care was effective in facilitating the uptake of

HIV services among vulnerable PWID (178). Similarly, findings from an evaluation of the Dr Peter Centre (DPC), an HIV care facility in Vancouver that implemented a supervised injection programme for PWID, found that integrating a supervised injection facility within an HIV care facility improved access to and the delivery of comprehensive HIV care for PWID (37).

Co-locating OST and HIV treatment

Earlier sections of this report outline the considerable body of evidence which indicates that OST use plays a significant role in promoting access and adherence to ART for PWID (see for example 92, 99-100, 106, 110, 113,115, 121). It is likely that OST brings about a level of social stabilisation that allows for ART initiation and adherence (5, 121).

Interestingly, a recent longitudinal study of the first MMT cohort (January to October 2009) in Vietnam showed that MMT improved the health related quality of life (HRQL) among PWID living with HIV. These improvements in quality of life very likely play a role in enhancing adherence to HIV care among PWID (179). Given the evidence that OST helps facilitate the effective use of HAART among PWID, it makes sense to try and ensure that HIV positive PWID are linked with OST services.

Emerging evidence suggests that the provision of co-located HIV and OST services is more effective for promoting ART use among PWID than services provided via a distributive model. A small study from Bandung, Indonesia conducted between May 2006 and January 2009 showed that integrating HIV testing and treatment into a hospital based methadone programme was associated with increased uptake of HIV testing and initiation of ART among a cohort of PWIDs enrolled in MMT (180). Similarly, a recent 12-month randomised trial of the integration of buprenorphine into HIV services in Baltimore, USA found that persons allocated to co-located HIV and buprenorphine treatment had significantly better participation in opioid treatment programmes, reduced opioid use, and more HIV primary care visits than participants allocated to intensive case management with off-site referral to OST (181). More recently, results from a large US multi-site, observational study found that initiating buprenorphine in HIV clinical care settings was significantly associated with

earlier ART initiation and improved CD4+ counts than individuals in OST care alone (182). Together these studies demonstrate the value of providing co-located HIV and OST services for PWID.

Directly observed therapy (DOT) as a strategy for enhancing adherence in co-located HIV and drug services

There is some evidence that dispensing ART together with OST services may facilitate the direct observation (DOT) of ART use –a potentially useful tool for facilitating adherence among PWID (34,118). DOT has been widely used to improve medication adherence, clinical outcomes and to reduce the incidence of drug resistance for TB (183-4). The use of DOT to enhance ART adherence among PWID is beginning to yield promising results. For example, the Community Health Care Van project (CHCV), a mobile health clinic established in 1993 and linked to the New Haven Needle Exchange Programme in New Haven, Connecticut, integrated the provision of NSP, OST and ART services (185). Findings from this 6-month randomised controlled trial which used directly administered antiretroviral therapy (DAART) as the intervention, showed that DAART was significantly more likely to improve adherence and virological outcomes than self-administered therapy (SAT) (186). Furthermore, a retrospective analysis of clinic records (1998 to 2004) from two community health clinics located in Vancouver, Canada demonstrated that the provision of HAART within comprehensive multi-disciplinary DOT programmes achieved adherence rates of 84.5% among programme participants who all had a history of IDU or currently injected drugs (187). The high rates of adherence in these programmes were probably not only due to the use of DOT but also to the presence of co-located health and social welfare services that addressed various barriers to adherence (such as housing, addiction treatment and social services; 187).

DOT and other adherence support programmes seem particularly useful for enhancing adherence to HAART among PWID faced with multiple barriers to achieving adherence such as severe drug problems, other co-occurring health problems, and high levels of social instability. A recent (2007-2010) cross-sectional study conducted among unstably housed

persons living with HIV (of which 44% were PWID) found that participants attending the DOT programme were almost five times more likely to be optimally adherent (>95%) than non-attendees (188). In addition, OST services that allow for frequent and ongoing contact with PWID living with HIV are strategically placed for the provision of adherence support programmes such as DOT or DAART on a long-term basis (189). Several studies support this contention. An early prospective study (1998-1999) among a small cohort of PWID attending a hospital-based methadone clinic in Ireland demonstrated that combining HAART and methadone intake via DOT significantly improved HIV treatment outcomes among a mixed cohort of ART naïve and experienced PWID (190). Similarly, a prospective study (1997-2001) from Vancouver, Canada showed that a DOT programme of co-administered methadone and HAART improved HIV treatment outcomes among a small cohort of HIV/HCV co-infected PWID (191). Another prospective study conducted among an urban cohort in Baltimore, Maryland found that DAART given in conjunction with methadone improved virological and immunological outcomes when compared with a cohort that self-administered HAART (192). More recently, a randomised controlled trial, known as Support for Treatment Adherence Research through Directly Observed Therapy (STAR*DOT), conducted between June 2004 and August 2007 at 12 methadone clinics with on-site HIV care in New York found that the adherence rate among PWID receiving the STAR*DOT intervention was significantly higher than among those participants who were self-administering ART (193). By week 24, the mean adherence rate among those receiving the STAR*DOT intervention was 86% compared to 56% among those self-administering ART ($p < 0.0001$) (193). These encouraging findings point to the positive impact that DOT strategies can have on HIV adherence rates among vulnerable groups, especially when provided in co-located HIV and drug dependence treatment services.

However, while directly observed ART administration may be sustainable in the long-term among PWID who receive daily doses of methadone, it does place a significant burden on PWID who have to incur travel costs on a daily basis to receive their ART. It may be more feasible to use this adherence enhancement tool in the short term to achieve optimal adherence during the first 6 months of HAART use or to use DOT during periods of social

instability. Thereafter, adherence to self-administered HAART can be strengthened by supportive interventions. For example, a randomised trial (July 2007 to April 2008) from Hunan Province, China showed that nurse-delivered home visits in conjunction with telephone calls (that provide information about ART medication and adherence, skills to facilitate adherence, reinforce motivation, mobilise family support, and provide referral to OST if needed) were more effective for improving adherence to ART and quality of life among a small group of active or past heroin users living with HIV than standard care (119).

4.1.4. Disadvantages of co-located services

Co-located services do not necessarily translate into the provision of integrated care (174). For successful service integration to occur, an inter-disciplinary team together with an integrated treatment plan needs to be established for each PWID. Multidisciplinary treatment teams can occur in distributive and co-located service models –it is not the location of the service that is important but rather the extent to which service providers are able to collaborate in the development of a holistic treatment plan for PWID (174, 194). Potential benefits of a single treatment plan under the supervision of a single health care team include improved quality of care, opportunities for cross-training health care providers and a better chance of capturing adverse drug events (159, 174).

Despite the potential benefits of co-located services for PWID and while many countries ascribe to the co-location of services in theory; in practice this on-site referral model is not widely implemented. Some of the inherent limitations of this approach have restricted the extent to which it has been implemented. Resource and financial constraints for example limit the extent to which co-located services are offered. Many countries with poorly financed health systems cannot afford to provide specialty services targeted at PWID (194). Financial constraints may limit the extent to which agencies offering co-located services provide comprehensive care. Harm reduction agencies are often poorly funded and may lack the infrastructure to provide the full range of on-site health and social services needed to address PWID's needs. Due to the cost of services, access to some additional services

will still be provided via off-site referral. This may reduce the acceptability of these services to PWID. Apart from this, having multiple service agencies located at the same site and/or service providers from different professional cultures can be challenging (173).

4.2. Choice of service delivery model

In practice, a country's choice of HIV service delivery model is influenced by a range of factors including health system financing, policies towards PWID, the size of the population of PWID, and the extent to which the HIV epidemic is concentrated among PWID (Figure 4). For example, countries (or even regions) with high levels of HIV among PWID, with drug policies focused on reducing the public health harms associated with drug use, and relatively well-financed health systems may veer towards providing specialist, co-located services for PWID (e.g. Canada, 195). In contrast, it may not make fiscal sense for countries with generalized HIV epidemics, small proportions of PWID (e.g. countries in sub-Saharan Africa and Central America), and poorly resourced health systems to provide co-located HIV and other services targeted at PWID only. These countries are more likely to veer towards providing comprehensive HIV services using the distributive model. Even in countries with HIV epidemics that are largely concentrated among PWID, the structure of the health system influences how HIV services are delivered to PWID. Countries with highly centralized health systems in which there is little decentralized primary health care provided (such as Russia and the other former Soviet republics) are unlikely to ascribe to models of co-located service delivery. Similarly countries with enforcement-oriented drug policies and high levels of stigma towards PWID may be reluctant to provide specialty services for PWID.

4.2.1. Country case examples of co-located versus distributive models of care

It is difficult to classify countries according to whether they use a co-located or distributive model of service delivery for PWID as many countries provide a mix of these models. Many countries with policies that support the principle of co-located service provision in reality only provide these services in a limited way. The exception to use this is countries where factors like systemic barriers within the health system preclude the provision of co-located

services. Even in several of these countries, there are some donor-funded pilot projects that offer co-located HIV and other services for PWID. We provide some country case examples of different mixes of distributive and co-located service delivery for PWID living with HIV. All of the countries presented have HIV epidemics concentrated among PWID (1).

Figure 4: Factors associated with distributive or co-located models of care

Examples: Country/region	Drug Policy - enforcement focused	Centralised health system	Well financed health system	HIV concentrated among PWID	High prevalence of PWID	Veer to co- located or distributive services
Australia	N	N	Y	Y	Y	Co-located
Canada (BC)	N	N	Y	Y	Y	Co-located
Malaysia	Y	Y	N	Y	Y	Distributive
Russia	Y	Y	N	Y	Y	Distributive
South Africa	N	N	N	N	N	Distributive
Ukraine	Y	Y	N	Y	Y	Distributive

Ukraine: A mainly distributive model

By the end of 2007, the Ukraine had the highest prevalence of HIV in Europe; with an estimated 395,000 adults infected with HIV (representing 1.63% of the population; 196). Of these PLWHA, an estimated 41.4% of adults are PWID (196). While recent data suggest that the HIV epidemic may be stabilizing, the majority of new infections are still concentrated among PWID and their sexual partners (197). HIV service delivery to PWID

Box 1: Crimean Republican Narcological Dispensary, Simferopol

This integrated care (IC) site has provided OST since 2004: buprenorphine from 2004, followed by methadone from 2008 (199). On noticing that many of their TB and HIV patients were PWID, local TB and AIDS doctors began to co-operate with the narcological dispensary (200). In this IC site, there is not a dedicated case manager, but there is a strong referral system between the narcology, AIDS and TB clinics with weekly multidisciplinary team meetings held at the Narcological Dispensary and regular cross-recruitment of patients (199). Mental health care is provided by in-house psychiatrists at the Narcological Dispensary (199). In addition, the AIDS Centre places a doctor at the IC site at least once a week and offers hepatitis and STI testing and care off-site (199). The main challenges faced are the lack of adequate funding for the IC programme and the way in which Ukraine's health care system still requires patients to leave the site in order to access key services (199).

is further complicated by the fact that the Ukraine has major TB and multi-drug resistant-TB (MDR-TB) epidemics which seem more common among people living with HIV and PWID (197-8).

Since independence in 1991, the Ukraine has been trying to reform a highly centralised health system. In this system, specialty services were vertically organized and there was little opportunity for communication, collaboration or cross-training (198). Currently HIV and TB programmes still function as separate vertical programmes, often lacking proper co-ordination, collaboration and integration of services (200). Specifically, HIV diagnosis and treatment is primarily the domain of state-owned AIDS centres, the intensive phase of TB treatment is available only if hospitalised in a state-owned TB facility, and drug dependence treatment is almost exclusively available at state-owned narcology clinics (9, 45, 197). The system relies largely on a distributive service model in which PWID need to visit various sites to get their multiple health needs met. As services for PWID are not provided in an integrated manner and there is no central authority responsible for organising and implementing integrated services for PWID living with HIV (200), it is left up to the individual to navigate these different systems of care (45, 197).

Despite this, there have been some major reforms to the health system in Ukraine (largely led by civil society organizations (CSOs), with harm reduction services now available for PWID (although coverage is still not ideal). Specifically, NSPs and OST for PWID are now available (45, 200-1). While OST provision occurs mainly at state-owned narcology clinics and community-based treatment centres, there are a number of pilot sites where OST is co-located and or integrated with HIV services and/or TB care (200-1).

Box 2: Kriviy Rig City Narcological Dispensary

The site of this IC programme is situated on the grounds of a large psychiatric hospital (199). Methadone services commenced in 2008 paving the way for the IC programme which is supported by funding from the Clinton Foundation (199). The IC programme links OST clients to HIV care and treatment, counselling, TB and other services (199). Although some key services (e.g. dispensing of HIV and TB medications) are still provided off-site, all care is co-ordinated by the IC programme's multi-disciplinary team which comprises a full-time narcologist, nursing staff, psychologist and social worker (199). The AIDS and TB specialists are available at the site once a week (199). Unfortunately, the AIDS and TB centres are quite far from the narcological dispensary and as yet, do not provide OST for in-patient treatment, but there are plans in the near future for them to do so (199). Access to other professionals, including a lawyer and a gynaecologist are provided by the local harm reduction organisation (199).

Some examples of these integrated care sites included the Crimean Republican Narcological Dispensary (Box 1), Kriviy Rig City Narcological Dispensary (Box 2) and Dnipropetrovsk City AIDS Centre (Box 3).

Box 3: Dnipropetrovsk City AIDS Centre

This site, also supported by funding from the Clinton Foundation, is located within the City AIDS Centre (199). It is well-resourced with good infrastructure and provides on-site HIV, narcological, gynaecological, case management and social support, on demand (199). A TB specialist and psychologist are available once a week and a psychiatrist is available once a month. TB medications are dispensed together with OST, allowing for enhanced DOT. IC clients in need of OST are fast-tracked through the system as most are already registered with the local narcological dispensary and have completed the required HIV and TB diagnostic work (199). Since the IC programme began, improvements in the quality of care, patient retention, ART adherence, virological outcomes and quality of life have been observed (199). Nonetheless, sustainable funding is a concern and clients still face discrimination when referred to outside institutions to access additional services. Also, AIDS Centre staff have reported police interference (199).

Despite positive shifts towards providing more comprehensive services to PWID, coverage is poor and there are many systemic barriers to accessing services. Only 2% of PWID in the Ukraine have access to OST (18) and similarly the Ministry of Health reported

that only 6044 patients were receiving OST by February 2011 (of a population estimated to be around 330 000; 200). Similarly roughly 2% of PWID living with HIV receive ART (18). Reports indicate that clinicians are reluctant to provide ART to PWID due to misguided perceptions that levels of adherence would be low and lead to the development of antiretroviral resistance (201-2). Access to ART is further compounded by the high cost of ART and since January 2011 disruptions in the supply of ARVs has further restricted access to treatment and undoubtedly has a negative impact on adherence levels (200).

Unfortunately, any progress Ukraine has made with regards to access to HIV and harm reduction services for PWID threatens to be undermined by police raids on drug dependence treatment clinics which commenced in 2010 (203) as well as regulations that continue to allow PWID to be placed on official registers that are used to exclude them from certain occupations, and subjects them to police harassment (9, 45, 160). This discourages PWID from accessing harm reduction and other medical services (200). Without the removal of these regulatory constraints and formation of a strong national co-ordinating structure, it's unlikely that Ukraine will succeed in implementing an integrated national response to the HIV epidemic among PWID (200).

Indonesia: a mainly distributive model

Indonesia has an HIV epidemic that is concentrated among PWID. In spite of a national HIV prevalence rate of only 0.22% among adults in 2008, data from 2006 and 2007 estimated much higher HIV prevalence rates among PWID of 42.5% and 52.4%, respectively (204-5). Historically this country has focused on law enforcement approaches to dealing with drug use and therefore there have been few drug dependence treatment or other public health services available for PWID. However, recent years have seen some reforms and considerable effort been placed into developing a more integrated, comprehensive and systematic response to the HIV epidemic than had been seen previously (204). This reforms lead to the introduction of a national harm reduction programme in 2003 and the implementation of universal access to free ART in 2004 (204, 206). This harm reduction programme is relatively comprehensive and includes behavioural change counselling, distribution of condoms, STI services, HCT, HIV care, NSPs, drug addiction treatment including OST and community outreach programmes (204).

Box 4: Kios Atmajaya, Jakarta

Commencing in 2002, this is a comprehensive HIV programme managed by Atmajaya Catholic University in Jakarta (207). The field station serves as a hub to a large population of PWID in 7 sub-districts. Case management activities started in 2003, initially using outreach to identify clients in need of additional assistance. Case managers are responsible for assessing the needs of PWID living with HIV, developing a client-focused action plan and helping them access services, both in the community and in government institutions. Types of services include the provision of free medical services at the field station, referral to detoxification and OST, referral to community health centres or if seriously ill, government hospitals, and if needed, assistance with obtaining access to the government's free medical scheme (207).

Apart from this national programme, there are several organizations that work to facilitate access to comprehensive harm reduction and ART services for PWID (see Box 4). For example, the Indonesia HIV/AIDS Care and Prevention Project (IHPCP) has

been instrumental in promoting and supporting NSPs, methadone programmes and access to ARVs for PWID (205). In addition, Indonesia is at the forefront of harm reduction work in prisons in South East Asia. Indonesia has a national strategy to address HIV prevention, care and treatment in prisons, particularly among PWID (204, 206, 208). Prison-based programmes are implemented in collaboration with NGOs (204) and Box 5 presents an

example of such a programme. Prisoners, however still have difficulty in accessing condoms and sterile needles and syringes (204).

Indonesia also has been able to scale up its response to HIV as it manufactures generic ART locally which keeps the costs of the medications down (206). In

Box 5: Kerobokan prison, Bali

This prison adopted ten of the twelve activities that make up the comprehensive harm reduction package in Indonesia (204). The two excluded components are sterile needle supply and safe disposal. The first methadone patients were recruited in August 2005 and by September 2008 there were 39 patients on methadone in the prison. A number of stakeholders are involved in supporting the programme and include the HIV Cooperation Programme for Indonesia (HCPI) (follow-on programme to IHPCP), Sanglah Hospital as the referral hospital, two local community health centres and a number of NGOs (204).

addition, access is facilitated through free health care provision that includes the cost of HIV tests, and TB drugs (204). Despite having free access to ART since 2006, most people living with HIV are still saddled with the financial burden of having to pay for HIV-related health services (such as medical consultations, laboratory tests for CD4 counts and drugs other than ARVs (e.g. methadone; 204, 209). Other major obstacles have been the limited availability and continuity of ART supplies and the shortage of health workers with the necessary skills to administer ART (204).

While there has been a growth in the number of sites offering HCT, ART, and NSP and OST programmes to PWID (205), coverage is still poor and there are many systemic barriers to accessing available services. By 2008, the number of PWID receiving ART relative to the estimated number of PWID living with HIV was 6 per 100 (18, 204). More than likely the associated costs of ART use and engagement in HIV services together with the continued criminalisation of drug use have deterred PWID from utilising the available health care services and harm reduction programmes (205-6, 209). For example, the National Narcotics Board responsible for the delivery of the national harm reduction programme is attached to the National Police (206). This more than likely reduces the appeal of the programme for PWID and increases distrust in harm reduction services. In addition, legal and regulatory constraints (such as laws that still prohibit the use of narcotics) act as barriers to the provision of care (204). These findings suggest that the uptake of

comprehensive HIV services for PWID will improve if these legal and regulatory barriers are addressed.

British Columbia, Canada: co-located service delivery

British Columbia (B.C.) is a large, diverse province in Western Canada that has a publicly funded, universally accessible health care system without user fees (195). HIV incidence among PWID in Vancouver began to rise dramatically in 1992, reaching a peak of 18 per 100 person-years in 1997; one of the highest reported in the developed world (210). By 2006, HIV prevalence among PWID in Vancouver was estimated to be 17% (211). While initially centred among PWID in Vancouver's Downtown Eastside (DTES), HIV rapidly spread to other communities of IDU (205). Since mid-2007, a decrease in HIV incidence among PWID has been observed across B.C. (15). These decreases are believed to be attributed to the increased uptake of HAART among PWID, changes in drug use patterns (e.g. less injecting) and participation in harm reduction programmes including OST (15). Recent estimates of HIV prevalence among PWID in the province range from 13% to 22% (15). It is therefore not surprising that PWID have been, and still are, considered to be a priority population for HIV prevention, treatment, and care in B.C. (15, 195).

In B.C., the provincial response to the HIV epidemic among PWID has been comprehensive and sustained. The response has included: distribution of harm reduction supplies such as sterile needles/syringes and condoms to PWID; outreach services (e.g. street nurse programmes, peer-based outreach) to engage people in care, research studies

Box 7: Service Delivery in Prince George

In Prince George, a town in northern B.C., co-ordinated, client-centred services are offered through integrated case management based on community and service partnerships. Harm reduction and nursing services are provided. On-site services include HIV, HCV and TB testing, STI testing and treatment, wound care, immunisations, PAP and pregnancy testing. In addition, there is a mobile service that provides nurse-delivered primary care and referrals to additional services (195).

Box 6: Victoria AIDS Resource and Community Service Society (VARCS)

VARCS is a non-profit organisation that provides support to people living with HIV and their caregivers. With funding from the Vancouver Island Health Authority, VARCS operates a mobile needle exchange service and responds to calls from homes. Besides one paid staff and one volunteer on a full time basis, a street outreach nurse provides weekly assistance (195). The services provided include wound care, vein management, HIV, HCV, TB, STI testing, immunisations, pregnancy tests, harm reduction education, and referrals to a variety of health services including ART (195).

for tracking the epidemic and risk behaviours among PWID; innovations such as supervised injection programmes (e.g. Insite, Dr. Peter Centre) and research trials

of prescribed opioids; expansion of and better integration of mental health and substance use services, including OST; provision of HIV primary and specialty care to PWID, including the provision of HAART; directly observed treatment programmes for HAART; initiatives to increase HIV, HCV, STI and TB testing; and initiatives to reduce poverty and homelessness (178, 195). Many of these services have been provided in an integrated way either through the provision of co-located services (see Box 6 and 7) or intensive case management (see Box 8).

Box 8: WISH Drop-In Centre

Women's Information and Safe Haven (WISH) has been operating a drop-in centre exclusively for female sex workers in Vancouver since 1987. WISH has a strong referral network with agencies that provide harm reduction, drug treatment and social services. The centre is open from 18h00 to 23h00 six nights a week (Sunday to Friday), nurses provide primary health care services twice a week and acupuncture, herbal therapy and counselling services are available once a week. In partnership with Providing Alternatives Counselling and Education (PACE) Society, WISH operates a peer-led mobile outreach programme that provides services to women working on the street from 22h30 to 05h30 seven nights a week (213). An 18-month evaluation of MAP (2006 to 2008) found that women who used the service were significantly more likely to use detoxification and residential drug treatment services compared to women who did not use the service (213). Another smaller pilot study (January 2007 to January 2008) found that a peer-driven intervention (PDI) may have positively impacted on adherence to HAART (214). The PDI consisted of four key elements: weekly peer support meetings, capacity training for women to become health advocates for one another, a peer outreach service, and on-site nursing care (214).

Recent efforts include the Seek and Treat for Optimal Prevention of HIV/ AIDS (STOP HIV/AIDS) Project. This is a four-year initiative (2010 to 2013) to expand access to HIV testing, treatment and support among hard-to-reach and vulnerable populations in Vancouver's DTES and Prince George (212).

Taken together, findings from this province in Canada show that where there is a drug policy that supports public health interventions for PWID, combined with good integration of care between services targeting PWID (whether co-located or not), few systemic barriers to accessing these services, and adequate service coverage, rates of new HIV infection among PWID can be successfully minimised.

4.2.2. Towards the greater integration of health services for PWID

Even though evidence supporting the provision of integration services for PWID delivered at the same site is accumulating, it is still too early to recommend just how many services and how much integration is necessary to achieve optimal HAART delivery for PWID. In

some cases, the co-location of comprehensive services may not be necessary for successful service integration to occur. In the interim, it may be preferable for existing service delivery models to maintain the focus of their service provision and gradually introduce more diversified and integrated services rather than aggressively pursue within programme integration.

As recently recommended by Volkow & Montaner, a strategy of “virtual integration” is probably the more practical approach to pursue considering the current weak and fragmented state of many of the world's health care systems (194). In this model, there is a virtual multidisciplinary team which develops an integrated treatment plan for each patient that addresses his/her service needs in various domains. Although these services remain available at different sites, the treatment team smoothes the path of accessing these services for each individual (via case management and transport assistance; 194). Yet this proposed strategy of virtual health service integration will only be possible if there is increased synergy between public, private and voluntary service providers operating within a legal and policy environment that is conducive to the expansion of affordable HIV and harm reduction services for PWID (163, 202).

5. Limitations to the review

This review was subject to several limitations. First, a large number of documents were reviewed by a small research team in a short period of time: although every effort was made to be thorough and include all relevant source materials, some information may have been overlooked. To limit this, the search strategy employed by this review and the draft report were reviewed by the Reference Group and other experts so that gaps in the literature could be identified. Another limitation is that the literature (and therefore this review) is dominated by research findings from high income countries, with greater research capacity than low and middle income countries. We attempted to limit this publication bias by extensively searching the grey literature from civil society organisations, international funding agencies, government websites and conference proceedings for relevant documents from low and middle income countries and we also

requested unpublished material from experts in the field. However, these grey literature reports were difficult to access and despite our best efforts we may have inadvertently excluded an important document from this review, especially if this document was not easily accessible electronically. Given this limitation, greater effort needs to be made to make these kinds of materials readily available electronically. A third limitation relates to the quality of the studies included in the review. There were large variations in the types of methods used to assess access to and adherence to HAART among PWID, as a result we were unable to conduct a meta-analysis to pool the results of the included studies. Similarly, it was sometimes difficult to compare study findings as studies gave varying definitions of access and adherence and some did not report the cut-off scores they used to define adherence versus non-adherence (although most used 90 to 95% adherence as a cut-off). This limitation highlights the importance of improving country-level research capacity to examine access and adherence to HAART among PWID.

6. Conclusion and recommendations

Despite improvements in the global availability of HAART for PWID, findings from this systematic review clearly show that PWID still experience numerous barriers that delay the initiation of HAART and reduce the likelihood of optimal adherence to these life saving medications. These barriers need to be addressed urgently as the effective use of HAART not only extends and improves the quality of life of PWID but also averts new infections among PWID and their sexual partners (8, 13-15, 46, 86-9). Findings from this review suggest that interventions to improve HAART uptake and adherence among PWID have to be comprehensive and multi-pronged. These interventions should focus on addressing patient-level barriers as well as systemic barriers that hamper the efficient delivery of HAART to PWID and entrench disparities in HIV outcomes among PWID relative to other people living with HIV. Based on these findings, we recommend that the following steps are taken to improve HAART use among PWID.

6.1. Recommendations for improving the effective use of HAART among PWID

6.1.1. Gender and ethnic disparities in access and adherence to HAART among PWID must be addressed urgently.

Given clear findings of gender and ethnic disparities in the use of HAART among PWID, greater effort needs to be placed into engaging women and ethnic minorities who inject drugs into harm reduction and HIV primary care; either through sustained outreach services to these marginalized groups or through the development of interventions that address the gender-and ethnicity-specific barriers that PWID face when attempting to engage in HIV care. However, in order to develop these targeted interventions, more research into the specific barriers that women and ethnic minorities who inject drugs face when using HIV services is required. In the mean time, interventions that focus on empowering vulnerable groups of PWID on how to access health services may yield some benefits. There is emerging evidence that peer-based services are useful in this regard (171). Another avenue to pursue is to provide at least some women-only health and community-based harm reduction services. These services may appeal to women who are more engaged in street survival activities (213-4).

6.1.2. Countries should introduce and where available scale up the provision of OST for PWID

Among studies included in this review, access to and the use of OST was the most important facilitator of the effective use of ART among PWID (e.g. 99-101, 113-115, 140-1). Not only does OST use reduce the risk of HIV transmission due to reductions in risky drug use, but OST also increases rates of ART initiation among treatment naïve PWID. Findings suggest that OST use improves ART adherence levels, by reducing drug use severity and improving the social stability of PWID (99-101). In addition, adherence is supported when OST is administered in conjunction with ART. Consequently, greater effort needs to be put into connecting PWID with and retaining them in OST services.

Yet, OST is often not available, provided in a suboptimal manner, or illegal in countries where there are IDU-related HIV epidemics [9, 18, 84]. In regions where the HIV epidemic is concentrated among PWID, efforts to control the HIV epidemic would be improved by increasing access to OST for PWID, removing barriers that prevent people from using OST services, and ensuring adequate coverage of these services for PWID (18, 84). In countries where methadone and other forms of OST are illegal, introducing and scaling up OST will require high-level political intervention and ongoing pressure from national and international advocacy agencies.

6.1.3. Improving the social stability of PWID may increase ART initiation and adherence rates among PWID

Our findings show that high levels of instability (due to homelessness, unstable housing and food insecurity) hamper access and adherence to HAART among PWID. Consequently, programmes and policies that aim to improve the social stability of PWID are needed. At a provider-level, this will require system integration skills and connecting patients with other medical, psychiatric and housing services to optimize care for this vulnerable population. Some promising interventions that appear to improve the social stability of PWID include OST and other drug dependence treatment services. In addition, the provision of auxiliary social services (such as food kitchens and social housing projects) to improve social stability may also be a useful bridge to HIV care for vulnerable PWID (178). These services can be used as a site for the provision of integrated HIV services including testing, counseling and HAART delivery. Such services may be more appealing to unstably housed PWID than HIV services located in conventional primary care facilities.

6.1.4. Improving the effective use of ART among PWID by facilitating access to mental health services

Evidence from this review suggests that depression and other untreated mental illness is a barrier to the effective use of HAART among PWID and access to treatment for these conditions significantly improves uptake and adherence to HAART. Based on these findings, we recommend that access to mental health services for PWID with co-occurring

mental health problems needs to be improved. As such, screening for mental health problems should occur at all services (especially harm reduction, OST and HCV services) frequented by PWID. For PWID with co-occurring mental disorders, access to psychiatric treatment also needs to be facilitated, either onsite or via appropriate linkages to care and active case management.

6.1.5. Better relationships between PWID and HIV service providers could facilitate continued engagement in HIV treatment

There is considerable evidence from this review that relationships between health providers and PWID are often of poor quality and characterized by mutual distrust. Findings from this review show how such poor patient-provider relationships discourage PWID from seeking and remaining in HIV care. However, findings also suggest that where patient-provider relationships are good, providers are able to facilitate adherence self-efficacy and thereby retention in care. Given the potentially positive impact that health providers have on ART adherence among PWID, we recommend that considerable effort needs to be placed into improving the quality of patient-provider relationships in all country contexts. Some recommendations for improving relationships between health providers and PWID include providing health providers with training in patient-centred communication skills, training regarding PWID, and adherence improvement strategies for this population. Peer mentoring also can equip PWID with communication skills that help them relate better to health care providers. While these individual-focused strategies may be useful in some contexts, they probably will not be effective in countries where there is institutionalized stigma and discrimination towards PWID within the health system. In such contexts, more systemic interventions are required to facilitate patient-provider relationships that support the use of HAART among PWID.

6.1.6. Reducing the social exclusion of PWID as a means of improving engagement in HIV and other health services

Findings from this review indicate that policies and practices which promote the social exclusion of PWID from mainstream society separate PWID from HIV care and has a

deleterious effect on the initiation and continued use of ART for this vulnerable population. In order to improve the use of ART among this vulnerable population, the legal and regulatory frameworks that promote the social exclusion of and stigma towards PWID in many countries must be reformed. Similarly health system factors that entrench the social exclusion of PWID must be reviewed. Unless these systemic barriers that drive the social marginalization and exclusion of PWID are addressed, it is unlikely that interventions to improve the social connectedness of PWID will be successful. Once these systemic barriers have been removed, social support interventions (such as the use of peer support networks) may be useful for reducing the social marginalization of PWID and encouraging engagement in HIV treatment (166-7, 170, 213-4).

6.1.7. Reforming enforcement-oriented drug policies is essential for promoting access to and adherence to ART among PWID

Evidence from this review suggests that enforcement-oriented drug policies that lead to police harassment of PWID, place PWID on drug registries which limit their social rights, and lead to institutionalized stigma towards and social exclusion of PWID are major barriers to HAART use among PWID. Attempts to improve access to and the use of ART among PWID should include concerted political efforts to change drug policies and laws that stigmatise vulnerable and marginalized populations and separate them from needed health services. Changing these laws will require political will, pressure from advocacy agencies, as well as pressure from international donors and politicians. Without these policy and legislative changes, health disparities between PWID and other HIV infected populations in these settings will increase as PWID will remain reluctant to use HIV, harm reduction, OST and other drug dependence treatment services.

6.1.8. To facilitate better access to ART for PWID, health care system barriers to HIV service use must be removed

Findings from this review show how factors within health care systems limit the use of ART by PWID. It is clear that in countries where there is institutionalised stigma within health systems towards PWID, this results in delayed or denied access to HAART. In such contexts

health care reforms are urgently needed. Civil society organizations as well as international agencies must bring pressure to bear on countries where PWID are denied access to HAART within the health system or are subject to discrimination, long wait times or additional user fees as a result of their status as a PWID. In addition, in countries where health systems require patients to co-finance their HIV treatment, efforts need to be made to remove the costs associated with HIV testing and monitoring, the treatment for opportunistic infections and HAART-related side-effects, and routine medical examinations. The availability of free ART should be secured and reforms put in place to prevent delays in obtaining medications and stock outages.

6.1.9. To ensure the effective use of HAART among PWID better integration of HIV and drug dependence services are needed

Evidence from this review suggests that access and adherence to HAART among PWID is facilitated by well-integrated HIV, harm reduction and drug dependence treatment services. Despite this finding, evidence suggests that many of these essential services for PWID remain compartmentalized with little service integration occurring. Service compartmentalization is a significant barrier to accessing needed services for PWID who experience geographic, cost, and eligibility barriers at each service point. Consequently we recommend that health services work towards greater integration of essential services for PWID. While the provision of co-located services remains an ideal for improving access to comprehensive care for PWID, large scale co-location of services remains difficult in countries with weak and fragmented health systems. In such cases, adopting a strategy of virtual integration is a practical approach to ensuring better integrated service delivery for PWID (194). Strong political will, well-designed information systems, universal electronic health records, multiple points of access and patient involvement across the continuum of care are needed for virtual integration to work (157).

6.1.10. To support the effective use of ART among PWID, detention-related barriers to HIV care must be removed

Evidence from this review indicates that all forms of detention pose significant risks for delayed, denied or interrupted use of HAART among PWID, with a dose-response relationship reported between number of incarceration events and poor adherence. In many countries, access to ART is still limited in detention facilities, especially in pre-trial detention but also in prisons and compulsory drug “rehabilitation” facilities. For PWID already on ART, treatment gets interrupted when they enter detention but also when they are transferred from one detention facility to another and/or when they are released (due to limited continuity of care). These detention-related barriers to ART use are important to address as the overwhelming majority of PWID are detained by the police or incarcerated at least once in their lifetime (44). We recommend that detention of PWID in compulsory drug “rehabilitation” facilities without access to HIV prevention and treatment is ended. Enforcement-oriented drug policies that allow short-term detention at the hands of law enforcement or lengthy periods of pre-trial detention (with no access to ART or medical services) also need to be changed. Civil society organizations should put pressure on governments to act when detained PWID are denied their rights to a speedy trial and access to health services and can also assist detained PWID by providing them with access to legal services. For those PWID who are incarcerated, prison health services and in particular HIV and TB services should be closely linked to public health services. Finally, community health care providers and civil society organizations should work with prison facilities to ensure continued access to ART for HIV-positive prisoners within the constraints of the prison setting.

6.1.11. Adherence-enhancing interventions should be used to facilitate the effective use of ART among vulnerable groups of PWID

Adherence-enhancing interventions (such as the use of DAART) should be used to achieve optimal adherence for PWID when first starting HAART and during periods of high instability. DAART is particularly effective when integrated into other services used daily by vulnerable PWID such as OST programmes, NSP and safe injection facilities.

6.2. Concluding remarks

While the provision of optimal care for PWID remains a challenge due to the multiple barriers that hamper HAART use in this marginalized population, nonetheless this report shows that many of these barriers are mutable. Addressing these barriers is of critical importance as failure to do so may limit the promise that HAART holds in terms of improving health-outcomes for HIV-infected PWID as well as for controlling the spread of HIV (5, 8-9, 15-17). However tackling these barriers and expanding HAART access to all PWID who meet eligibility criteria will require each country to develop a sustained and intensive strategy to identify HIV-infected PWID, help them stabilise their lives, and facilitate sustained engagement in appropriate health care and support in a voluntary and consensual framework (29). In countries with enforcement rather than public health oriented drug policies, the first step would be to reform these policies. Other systemic challenges such as stigma and discrimination, inadequate health care resourcing and weak health systems, and insufficient mental health, drug dependence treatment, and harm reduction services need to be addressed for this initiative to work. In all countries, such an initiative will require commitment and collaboration from the public and private sectors (including civil society organizations).

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