What do HIV-positive drug users' experience tell us about their antiretroviral medications taking? An international integrated literature review

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Running head: Adherence to antiretroviral medications

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Conflict of interest: None

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Abstract

Background and aims: HIV-positive drug users' poor adherence to antiretroviral regimens can pose a significant and negative impact on individual and global health. This review aims to identify knowledge gaps and inconsistencies within the current evidence base and to measure HIV-positive drug users' adherence rates and the factors that influence their adherence.

Methods: A search of quantitative and qualitative studies in relation to HIV-positive drug users' adherence to antiretroviral treatment was performed using five databases: Applied Social Sciences Index and Abstract (ASSIA), Cumulative Index to Nursing and Allied Health Literature (CINAHL), Medline, Embase and PsycINFO (Ovid interface). Relevant studies were retrieved based on the inclusion and exclusion criteria stated in the review. Findings were compared, contrasted, and synthesised to provide a coherent account of HIV-positive drug users' adherence rates and the factors that influence their adherence.

Results: The proportion of HIV-positive drug users who achieved ≥ 95% adherence across the studies varied widely, from 19.3%-83.9%. Adherence rates changed over the course of HIV treatment. The factors that influenced adherence were reported as follows: stigmatisation, motivation, active drug use, accessibility and conditionality of HIV and addiction care, side effects and complexity of treatment regimens, forgetfulness and non-incorporation of dosing times into daily schedules.

Conclusions: HIV-positive drug users' medication-taking is a dynamic social process that requires health professionals to assess adherence to HIV treatment on a regular basis.

Keywords: Adherence, HIV-positive drug users, antiretroviral treatment, international literature review

Introduction

The literature on Human Immunodeficiency Virus (HIV)-positive individuals' adherence to Highly Active Antiretroviral Therapy (HAART) reveals the importance of strict adherence for maximum therapeutic impact. A cut-off of 95% or better adherence has been studied as the appropriate threshold for clinical efficacy, and this finding is consistent throughout empirical research and government publications [1-5]. Individuals with poor adherence to long-term HAART compromise the effectiveness of the treatment and pose a threat to the public, including incomplete viral suppression, increased HIV transmission, development of drug resistance, and limitation of treatment options [2, 6-7].

Despite the importance of adherence to HAART, there is a growing body of literature that recognises that among the general HIV population, HIV-positive drug users have lower adherence rates compared to other HIV groups [3, 8-15]. In light of this evidence in the existing literature, it is becoming extremely difficult to ignore the existence of the importance of understanding HIV-positive drug users' adherence behaviour.

Adherence refers to "*the extent to which patients' behaviours matches agreed recommendations from the prescriber* [2: p.12]" This term is adopted more by many as an alternative to compliance, because adherence involves 'patient's agreement' to doctor's recommendations [2]. To date, a systematic understanding of HIV-positive drug users' adherence to HAART is still lacking. Only two systematic reviews have been done to investigate the rates of adherence to HAART among HIV-positive drug users and its influencing factors [10,16].

Feelemyer et al. [16] conducted a systematic review of 15 empirical studies aiming to examine the levels of adherence to HAART among people with active injection drug use or with a history of injection drug use in transitional/low/middle income countries. The results of this review showed that the adherence levels ranged from 33%-97%, and the overall mean weighted adherence among all studies was 71.9%. However, several issues were identified in this review article. Firstly, most of the included studies did not focus on HIV-positive drug users but the general HIV population. Secondly, twelve out of fifteen studies did not aim to measure adherence rates, and some of those did not have such data. Of the 15 studies, it was found that only one study appeared to be related to HIV-positive drug users' adherence to HAART. Therefore, the level of adherence to HAART among drug users remains unclear in the current evidence base.

Malta and her associates' systematic review of 41 quantitative studies aimed to assess the adherence to HAART among HIV-positive drug users and its facilitators and barriers [10]. The results showed that active substance use, depression and low social support were associated with poor adherence. On the other hand, receiving care in structured settings (e.g. directly observed treatment) and drug addiction treatment were associated with higher adherence. The results of this review provide insight into the influencing factors of HIV-positive drug users' adherence to HAART. There is one major limitation in this review [10], which is the exclusion of relevant qualitative studies. The inclusion of relevant qualitative studies can help to gain a deeper understanding of underlying issues in relation to HIV-positive drug users' adherence to HAART.

Taken together, while some research has identified drug users as a less adherent group, uncertainty remains as to why this HIV subgroup is less adherent compared

to other HIV populations. Therefore, this review aims to critically review international quantitative and qualitative literature relating to HIV-positive drug users' adherence to HAART. Through a review of the relevant literature, it can provide a comprehensive understanding of HIV-positive drug users' adherence to HAART and its underlying issues, and identify any knowledge gaps and inconsistencies within the current evidence base.

Methods

Through the process of a literature search, it was revealed that all included quantitative studies used a non-experimental design with various adherence assessment approaches and standards to investigate drug users' adherence levels. As a result, pooling a meta-analysis or meta-regression of separate studies to estimate the overall adherence rate and identify its significant influencing factors across studies becomes less meaningful. In an attempt to synthesise the quantitative and qualitative studies, an integrated literature review was, therefore, carried out to systematically categorise and thematically analyse the selected studies based on their characteristics and findings [17]. Meta-ethnography was used to compare conceptual data from the included qualitative studies to identify and develop overarching themes [18].

Search strategy

A search was performed using the databases of the Applied Social Sciences Index and Abstract (ASSIA), Cumulative Index to Nursing and Allied Health Literature (CINAHL), Medline, Embase and PsycINFO (Ovid interface). The keywords used in the search were 'antiretroviral' OR 'HAART' AND 'adherence' OR 'adher*' OR

‘compliance’ OR ‘non-adherence’ OR ’non-compliance’ OR ‘concordance’ AND ‘HIV’ OR ‘AIDS’ AND ‘drug use’ OR ‘intravenous drug use’ OR ‘injecting drug use’.

Inclusion and exclusion criteria

Inclusion criteria:

1. Studies that involved HIV-positive drug users
2. Study sample is at the age of 18 or older
3. Published in English or Traditional Chinese
4. Empirical studies that focus on adherence to HAART
5. Qualitative, quantitative, and mixed-methods studies, and dissertations (grey literature)
6. With full text
7. Studies from 2000 to July 2018

Exclusion Criteria:

1. Studies that did not involve HIV-positive drug users
2. Study sample is less than18 years old
3. Simplified Chinese
4. Unclear study methodology
5. Studies that did not focus on adherence to HAART

Articles published in traditional Chinese and dissertations set in the inclusion criteria are to maximise the chance of finding empirical studies and to reduce publication bias. In terms of the language selection, literature written in English and the first author’s original language, traditional Chinese, was included in the search.

Reporting study selection

Figure 1 shows the PRISMA diagram for the search that led to the final included studies in this review. This literature search included studies from 2000 to July, 2018. The literature searched was restricted to dates from 2000 onwards due to combined HAART regimens accelerated during the early 2000s, called HAART era, and the

overwhelming amount of quantitative literature relating to adherence to HAART. Through the search strategy, 3968 articles were generated from the databases. Based on the inclusion and exclusion criteria, 3848 articles were excluded during the title screening stage, leaving 120 studies. After removal of the articles that did not meet the criteria, abstract and full-text screening eliminated further 74 articles. Five articles were hand-searched and included, leaving 51 articles for inclusion in this review. At abstract and full-text screening stage, numerous quantitative studies in relation to HIV-positive drug users' adherence to HAART were identified as opposed to qualitative studies. The study selection process and the rationale for exclusion are shown in **Figure 1**. Summary of selected studies is presented in **Table 1 and 2**.

Results

Characteristics of the included studies

Of the retrieved quantitative studies (n=40), 13 were from Canada, 20 from the United States of America (USA), 4 from France, 1 from the Netherlands, 1 from India and 1 from Vietnam (**Table 1**). Of the 13 articles from Canada, 11 were from the same prospective and ongoing research project in Vancouver. The 4 articles from France were also derived from the same prospective research project. In total, 26 articles were prospective studies (the follow-up period, ranging from 1 month to 91 months), 12 cross-sectional, and 1 secondary data analysis. There were 27 studies involving HIV-positive drug users (either illicit drug users or injecting drug users); 1 involving methadone maintained patients; 7 studies involving HIV-positive substance users with a clear sample description of what constitutes substance users; 5 studies involving HIV-positive individuals divided into subgroups (active drug users, past

drug users, and non-drug users). All of the included quantitative studies recruited sample through convenient and/or snowball sampling.

The retrieved quantitative studies predominantly focused on levels of adherence, and its influencing factors, however, these studies defined adherence in a variety of ways and used different measurement tools. Most studies measured participants' levels of adherence to HAART through self-report (continuous variable: doses taken/total prescribed doses during certain period of time, or ordinal variable: self-rating adherence level), pharmacy dispensation record (the number of days patients received HAART refills/the total number of days of medical follow-up), or electronic monitoring system (Medication Events Monitoring System caps, MEMS caps). Three studies focused on drug users' discontinuation of HAART. Four measured the mean adherence rate across study participants. Of the studies measuring drug users' adherence with a continuous scale, 19 studies defined adherence as taking ≥95% prescribed doses, 2 defined adherence as taking ≥90% prescribed doses, 4 defined adherence as taking 100% prescribed doses, and 2 defined it as taking ≥ 80% prescribed doses..

In terms of qualitative studies, 11 were retrieved for this review (**Table 2**). There were a paucity of qualitative research focusing on HIV-positive drug users' experiences of adherence to HAART at the literature screening stage. All the qualitative studies that involved HIV-positive drug users' experiences of taking HAART were included in this review. Although some included studies had not gone much further than describing and summarising what participants said, participants' statements presented in the studies still allows readers to see the voice of HIV-positive drug users regarding their HAART taking. In other words, the quality of these qualitative studies was assessed according to the degree to which authors

represented the views of their participants [19]. Of the 11 qualitative studies, 2 were from Canada, 3 from the USA, 1 from Spain, 2 from Russia, 1 from Ukraine, 1 from India, and 1 from the Netherlands. Of the included studies, 4 studies used thematic analysis, 2 used framework analysis, 1 used content analysis, 1 conducted ethnographic interviews, 2 followed Strauss and Corbin's codification process [20], and 1 followed Glaser and Strauss's analytic approach [21].

In the following sections, the quantitative findings related to adherence rates is firstly introduced, followed by the synthesis of quantitative and qualitative findings pertaining to the factors that influence adherence.

An estimate of adherence levels among HIV-positive drug users

Ten studies involving only drug users and defining adherence as taking ≥95% prescribed doses revealed that drug users who had ≥95% adherence ranged from 19.3% to 85.9% [22-31]. However, this result largely represented the USA and Canada, because 7 out of the 10 studies were from Canada [23-29], and 3 were from the USA [22, 30, 31]. Two studies from France, involving IDUs and using 80% as the cut-off point for adherence, showed that 65.2% of 164 IDUs in Moatti's study [32] and 70% of 210 IDUs in Bouhnik's study [33] had ≥ 80% adherence. One cross-sectional study by Arnsten et al. [34] measured 636 HIV-positive drug users' adherence rate with use of 90% as the cut-off point for good adherence, showing that 75% of them had ≥ 90% adherence. Two studies from the USA, involving HIV-positive substance abusers (illicit drugs and alcohol abusers) and using 100% as the cut-off point, showed that 46% of 1889 substance abusers in Tucker's cross-sectional study [35] and 55% of 1138 substance abusers in Mellins's cohort study [36] had 100% adherence. Two prospective studies by Kalichman et al. [37] and Ti et al. [38] measured the average adherence rate among 85 and 587 HIV-positive illicit

drug users in the USA and Canada respectively, which were reported to be approximately 50%. Compared to former drug users and non-drug users, active drug users were reported to be significantly associated with poorer adherence to HAART [22, 34, 39-46].

Drawing on the results, there was an indication that HIV-positive drug users had lower adherence rates. Nonetheless, a few included studies showed that HIV-positive drug users had high adherence rates. For example, one prospective study from Vietnam showed that 83% out of 100 HIV-positive drug users had perfect or very good adherence at some point (self-reported categorical scale) [43]. Another study from the USA reported that the mean adherence rates among low-income HIV-positive substance abusers ranged from 94.46%-97.97% [47]. The results are not consistent across the studies, and the aforementioned studies only measured HIV-positive drug users/substance abusers' adherence at some points. Thus, it cannot represent participants' overall adherence levels.

There are four included studies, Mann et al. from Canada [26], Waldrop-Valverde et al. [48], Hinkin et al. [42] from the USA and Lambers et al. [49] from the Netherlands, investigating the change in adherence levels.

The study from the Netherlands showed that 25% of 102 drug users became less adherent (was defined by the authors as < 95% adherence) at some points during the study period [49]. This indicates that adherence to HAART does not always stay at the same level. Congruently, three quantitative studies from Canada and India investigated HIV-positive IDUs' discontinuation of HAART [50-52]. These studies showed that 33.8% of 545 IDUs in Hadland's study [50] in Canada, 44% of 160 IDUs

in Kerr's study [51] in Canada, and 32.7% of 226 IDUs in Sharma's study [52] in India discontinued HAART during the follow-up period.

In terms of the trend of HIV-positive drug users' adherence levels over time, the prospective study from Mann et al. [26] looked into pharmacy dispensation records, and the results showed that the proportion of achieving ≥ 95% adherence among HIV-positive drug users increased over time, from 19.3% in 1996 to 65.9% in 2009. By contrast, a prospective study from Waldrop-Valverde et al. [48] investigated cocaine users' adherence levels using an electronic monitoring device, and the results showed that there was a significant drop in adherence from Month 1 to Month 6. The reduction in percentage dose adherence was from 76.7% at Month 1 to 66.5% at Month 6. The difference in the adherence rates over time was found to be due to personal factor in Waldrop-Valverde's study [48] and the advance of HAART in Mann's study [26]. Mann's study [26] investigated drug users' adherence levels over a longer period of time, from the early era of HAART to more recent era of HAART. The advance in HAART has changed the form of HAART regimens, contributing to increased adherence rates over that period of time [26]. As opposed to Mann's study [26], the follow-up period was shorter in Waldrop-Valverde's study [48], and the decrease in adherence rates among drug users was reported to be more associated with self-efficacy of taking HAART. In a longitudinal study by Hinkin et al. [42], it was revealed that both drug positive and drug negative groups had a decrease in adherence rates over time. The mean adherence rate had dropped from 77.4% to 68.4% in the drug negative group, whereas there was a significant decrease in the adherence rate among the drug positive group, from 70.1% to 51.3%. The trend of the adherence rate in the entire sample was from 74.4% for the first 2 months, to 68.5% for month 3, and down to 62.6% for month 5 and 6.

By and large, the results of the included quantitative studies demonstrated the adherence rates among HIV-positive drug users, and its dynamic process. However, it is not without limitations. Firstly, as most of the included studies used convenient sampling methods to recruit participants, the adherence rates cannot be representative of HIV-positive drug users [53]. Secondly, most of the included studies used self-report or pharmacy dispensation records to assess adherence rates. Self-report measure may bring social desirability bias or recall bias in research [54]. Nevertheless, it has been reported that drug users' self-report was correlated with patients' clinical outcomes, criminal records, and interviews, and it has been tested as a reliable method [55]. In terms of measuring adherence by using pharmacy dispensation records, issues arise as to whether patients who refill medications actually take them. This pharmacy record method has been reported by Palepu et al. [56] as unreliable because of the insignificant association between HIV-positive drug users' adherence level and HIV-1 RNA suppression. Taking this into account, measuring adherence levels with more than one method may enhance the accuracy of adherence assessment.

Factors influencing adherence to HAART

Having gained insight into HIV-positive drug users' adherence rates in the current evidence base, this section focuses on its influencing factors. A multitude of influencing factors have been identified and explored in the included qualitative studies (n=11). Of the 11 qualitative studies, 8 involved HIV-positive individuals who had a history of injecting drugs [57-63]. One involved HIV-positive active drug users (smoked/ injecting drug use) [64]. One involved IDUs who use methadone maintenance [65]. One involved HIV-positive individuals who had a history of using drugs and treatment interruption for 30 days [66]. The conceptual data from the

included qualitative studies were compared and contrasted, and were subsequently collated into themes, and then the themes was triangulated with relevant quantitative evidence in an attempt to gain a comprehensive account of HIV-positive drug users' experiences of taking HAART.

Throughout the process of comparing findings across the included studies, six themes were identified—

1) Stigmatisation in relation to HIV and illicit drug use

2) The motivation for taking HAART

3) Active drug use and HAART adherence

4) Accessibility and conditionality of HIV and addiction treatment

5) Side effects and complexity of HAART regimens

6) Forgetting and not fitting HAART regimen into schedule.

The six themes are discussed in the following sections.

Stigmatisation in relation to HIV and illicit drug use

Stigma was identified as one of the predominant themes. Seven studies reported that HIV-positive drug users/inmates had experienced stigmatisation and discrimination associated with HIV and illicit drug use [57,59,61-62,64-66]. Some experienced violence in the prison settings [62] and others were shunned and discriminated by family [57,64-66], police officers [59] and health professionals [61,65,67] due to their HIV status. In addition to HIV status, participants' engagement in the everyday violence associated with their drug dependence appeared to exacerbate their negative image portrayed by society [66].

Two major factors that led to families' and public stigmatisation and discrimination towards HIV-positive drug users emerged from participants' statements across the included qualitative studies — lack of knowledge relating to HIV, and images of 'HIV and illicit drug use' discredited by society. As with lack of knowledge, misconceptions about the transmission routes of HIV were revealed to bring public fear and lead to estrangement. For example, HIV-positive drug-using participants in Mimiaga's study [59] reported that police officers in Ukraine were afraid of them, and avoided physical contact from them or even things they had touched. As a result, their experiences of stigmatisation had influenced their willingness to access care.

Three qualitative studies from Ukraine (n=16), India (n=19), and Russia (n=42) revealed that health professionals held assumptions in relation to HIV-positive drug users' poor adherence and refused to treat them [57,59,61,67]. Aside from health professionals' negative assumptions of drug users, Pach et al.'s [60] (n=34) and Kiriazova et al.'s [67] qualitative studies (n=25) indicated that some drug users did not trust health professionals, either. This created the barrier to accessing HIV care. With a lack of engagement and trust in the health system, some drug users did not have adequate knowledge about HIV and HAART [57,60,64]. As a result, they were more likely to gain knowledge of HAART based on information circulating through social networks, and held negative assumptions and misinterpretation of HAART [57,60,64]. Congruently, Kelly's study [68] with the use of secondary data analysis (n=76) pointed out that having HIV-positive drug users in friend circles was associated with less adherence to HAART.

Experiences of stigmatisation from families has also been reported in Chakrapani's qualitative study [57] in India, where being HIV positive and using illicit drugs were perceived by IDUs' families to bring shame to the whole family. By holding negative

perceptions of HIV and illicit drugs, some were forced by their families to move out of their house, leading to homelessness [57]. As a consequence, financial instabilities (e.g. lack of money, food and housing), social stigmatisation, and disruptions in drug users' daily lives had affected their ability to follow treatment regimens [60,63,64,66]. Several quantitative studies also showed the significant association between homelessness and nonadherence [23,29,33,39,49].

The impact of stigmas related to HIV and illicit drug use not only impeded HIV-positive drug users' acquisition of support, but worsened their psychological distress, self-stigmatisation, and willingness to seek support [59,63,65,66]. With the feelings of denial, shame, and fear of stigmatisation, some tended to not disclose their HIV status, and were more likely to hide or not bring HAART medications with them [59,64,65]. In some cases, HIV-positive drug users articulated their low levels of motivation to live and take HAART [59,63,66].

In line with the findings derived from the qualitative studies, the included quantitative studies indicated that HIV-positive drug users' poor adherence to HAART was significantly associated with their psychological distress or depression [34,36,39,45,69]. In addition, two studies from the USA by Magidson et al. [47] and France by Moatti et al. [32] indicated that environmental punishment (perception of being exposed to punishing experience) and frequency of negative life events were related to poor adherence to HAART. Of particular concern, environmental punishment was the mediator between depression and poor adherence [47]. The results illustrated the influence of social environment on individuals' psychological well-being and subsequent HAART-taking behaviour.

In brief, it seemed that stigma related to HIV and illicit drug use could pose an impact on HIV-positive drug users' acquisition of support. Without the support available for them, it can further increase drug users' levels of perceived stigma and psychological distress. Social and self-stigmatisation was revealed to be linked to the lack of knowledge pertaining to HIV and illicit drug users, and the influence of social values.

Motivation for taking HAART

Despite the impact of stigma on HIV-positive drug users' HAART-taking behaviour, some HIV-positive drug users appeared to be motivated to take HAART. Two factors were identified to enhance HIV-positive drug users' motivation of taking HAART—acceptance of HIV status and acquisition of support from health professionals, family or friends [58,-60,63-65]. With the acquisition of support, it facilitated affected individuals' life stability and adherence to HAART by providing tangible support [59,60,64]. In addition, drug users having a stable job has been identified as a factor enhancing their sense of responsibility and level of motivation to adhere to HAART [64,70].

One qualitative study (n=23) by de la Hera et al. [58] pointed out that maintaining a good relationship between health professional and HIV-positive drug users enhanced drug users' knowledge related to HAART management. In turn, drug users with adequate knowledge were found to be more likely to be aware of their HAART-taking acts and managed HAART more consciously. Aside from external support, internally, drug users' self-acceptance and wanting to live longer were revealed to strengthen their will to adhere to HAART [59,64,65].

Drawing on the qualitative findings from the included studies, HIV-positive drug users' motivation to take HAART seemed to be influenced by the degree of support they got and their self-acceptance. As such, it had helped drug users grow belief and confidence in their capacity for taking HAART [58,65].

Active drug use and HAART adherence

The majority of the included quantitative studies indicated that illicit drug use significantly and negatively affected HIV-positive drug users' adherence to HAART [9,22-24, 33,36,39,41-43,45,47,52,69,71-73]. A longitudinal study conducted in New York by French et al. [22] investigated the impact of the change in substance abuse on participants' adherence to HAART. The result showed that participants who changed from no substance use at one interview to substance use at the follow-up interview were more likely to transition from adherence to non-adherence. However, this paper does not specify the patterns of drug use among the participants. It would enhance understanding if this study had included more details about the dynamics of drug use as to whether participants experienced relapse or just started using illicit drugs. The tendency to use drugs to cope with stress was reported in Arnsten's prospective study [39] to be significantly associated with non-adherence to HAART. This indicates that drugs could be used as a coping strategy by users to deal with stress, resulting in poor adherence.

Concerned about the impact of drug use on adherence, getting a fix was the heroin users' main focus [57-60,63,64]. The large amount of time active drug users spent on pursuing their next fix had affected their ability to access health care [59,60]. In addition, the large sum of money spent on heroin placed HIV-positive drug users in poor financial circumstances [63,64]. Drawing on the findings, both stigma and illicit drug use were revealed to collectively increase HIV-positive drug users' vulnerability

related to incarceration, employment, family relationships, mental health, and access to care, contributing to breakdowns in the continuity of HIV care [24,49,51,64,66].

Congruent with the qualitative research findings, Mellins et al. [36] and Tucker et al. [35] in their cross-sectional studies reported that HIV-positive drug users' non-adherence to HAART was associated with low attendance rates at a medical appointment and poor integration of the medication regimens into their lifestyle. Wittveen and Ameijden [63] in their ethnographic interviews noticed that the drug use patterns among drug-taking adherers ranged from using drugs once a day to using drugs once a month. Although Wittveen and Ameijden [63] did not further explain what enabled them to regularly use illicit drugs and take HAART medications, they pointed out that methadone had alleviated participants' withdrawal symptoms and stabilised their emotions, further enhancing their adherence to HAART. In line with this, numerous included quantitative studies also reported methadone maintenance treatment was significantly related to adherence to HAART among HIV-positive drug users [24,25,27,29,31,41,49,71,72,74]. These findings are incongruent with the results of a cross-sectional study with 133 methadone users by Shrestha and Copenhaver [75] which indicated that methadone users who continue using drugs were more likely to have suboptimal adherence and incomplete viral suppression.

In summary, it seemed that the addictive effects of illicit drugs could disrupt HIV-positive drug users' lifestyle and their ability to access HIV care, whereas methadone appeared to have the protective effect of alleviating their withdrawal symptoms and enhancing adherence. However, due to the prevalence of methadone users who continue injecting drugs [75], the impact of methadone use on affected individuals' drug-taking and adherence behaviour remains complex, which requires future research on their complex interplay.

Accessibility and conditionality of HIV and addiction treatment

Though HAART and addiction treatments play an important role in facilitating HIV-positive individuals' adherence to HAART, some drug users articulated the difficulty in accessing HIV and addiction care [52,57,60-62,66,67]. The accessibility of HIV and addiction care varied from country to country. Sharma's cross-sectional study [52] from India illustrated that the financial cost of HIV diagnostic testing, treatment of opportunistic infections, and transport significantly increased HIV-positive drug users' financial burden and impeded their access to HAART. In correctional systems, issues in relation to difficulty accessing HIV medications were reported in two qualitative studies by McNeil et al. [66] and Small et al. [62] in Canada. In the two studies, some participants complained about the unavailability of HIV medication between the times of arrest, trial, and arrival at the institution where they served their sentence, and upon release from custody [62,66]. As such, these structural factors increased the challenge of drug users' access to HIV care.

In addition to these structural factors, two qualitative studies from Russian and India revealed that HIV treatment conditionality was a great hindrance of access to HIV care among HIV-positive drug users [57,61]. In Chakrapani's [57] and Rhodes and Sarang's [61] studies, physicians' provision of HAART to HIV-positive drug users appeared to be contingent. Physicians provided HAART to affected individuals, only when affected individuals could show evidence that they were reliable, deserved taking HAART, and were able to be in control of their drug use. Such value judgement was upheld by physicians' concerns in an attempt to decrease drug resistance, maximise treatment outcomes, and adapt to economic constraints within healthcare [57,61]. As a result, it had led to delayed access to care, treatment

interruption, or disengagement from health care among HIV-positive drug users [57,61].

Such ways of treating HIV-positive drug users situated HAART as a relative priority in the hierarchy of immediate need where managing the 'problems' of illicit drug use came first. Moreover, this policy was revealed to be put in place due to physicians' doubts of drug users' capacity to adhere to HAART in the face of ongoing and untreated drug use [57,61]. In addition to the conditionality of access to HIV care, HIV-positive drug users' accounts, in the qualitative studies by Pach et al. [60] from the US (n=34 HIV+ IDUs), Chakrapani et al. [57] from India (n=19 HIV+ IDUs), and Rhodes and Sarang [61] from Russia (n=42 HIV+ IDUs), showed the inadequacy and ineffectiveness of addiction treatment, and a lack of effective linkage between HIV care and drug dependence treatment/needle syringe programme. In contrast to the findings from these studies, easy access to HAART was reported by HIV-positive drug users who had a good relationship with health professionals in a qualitative study by de la Hera et al. [58] from Spain (n=23 HIV+ IDUs). Drawing on the findings from the aforementioned studies, it seemed that the accessibility of HIV care can also be linked to the establishment of the trusting relationship between health professionals and HIV-positive drug users.

Although infrastructure within healthcare varies from country to country, the findings from the included studies pointed out that it still created a barrier to individuals' willingness to access care, especially for those who were in a financially disadvantaged situation. In addition, the distrusting relationship between healthcare providers and HIV-positive drug users could also widen the accessibility gap.

Side effects and complexity of HAART regimens

Side effects have been reported by several qualitative studies and one cross-sectional study as a barrier to adherence to HAART among HIV-positive drug users [52,59,60,63,67]. The commonly reported side effects were diarrhoea, fatigue, nausea, vomiting, and stomach-aches [52,59,60,63,67]. Some had treatment interruption due to the experience of side effects [52,59,60,63,67], and others did not receive HAART because of their misconception and concerns over the toxicity and danger of taking the treatment [60,66].

For HIV-positive drug users who started HAART in the early to mid-1990s or lived in a country where HAART options were limited (such as Ukraine), complexity of the treatment regimen was reported to influence their adherence to HAART [58-59,63,66]. A qualitative study by Mimiaga et al. [59] from Ukraine pointed out that several participants found it challenging to adhere to HAART due to high pill counts, the necessity of taking medications at specific times, and with food restrictions. Nonetheless, McNeil's study [66] from Canada indicated that the use of modern HAART has transformed the treatment regimens into a more simplified form, which had enhanced participants' adherence.

To sum up, the advance in HAART regimen globally has simplified the way that individuals take HAART regimens, and has decreased individuals' burden of taking HAART. Nonetheless, 'side effects' of HAART remained one of the major barriers to adherence to HAART in the included studies. Misconception and experience of side effects of HAART were found to exert an impact on receiving and/or continuing HAART among participants in the included studies.

Forgetting and not fitting HAART regimen into schedule

Fitting HAART regimen into daily schedules has been reported to bring challenges to adherence to HAART among drug users [59,63,76]. Though this theme emerged in the included qualitative studies, there was a lack of explanation and exploration in the studies as to in what situations or how HIV-positive drug users were more likely to forget doses and not incorporate HAART into life.

To avoid forgetfulness, some HIV-positive drug users, from Wittveen and Ameijden's [63], Mimiaga's [59], Ware's [64] qualitative studies, developed strategies to promoting adherence to treatment. The strategies included incorporating medication regimens into drug use routines, use of medication containers, phone alarms/alarm clocks, or stickers to remind their dosing schedules. Some took HIV medications with them all the time [59,63].

Discussion

Drawing on the quantitative results from the included studies, the proportion of HIV-positive drug users who achieved ≥ 95% adherence across the studies varies widely across and within countries, from 19.3%-83.9% [22-31]. This indicates that adherence rates tended to be inconsistent amongst the included studies. Drug users' adherence levels could drop and change over time [42,48,50-52]. Over the course of receiving HAART, many drug users had a history of discontinuing HAART at some points [50-52]. The average adherence rate was approximately 50% [37-38]. However, the advance in HAART, from complex regimens to simplified regimens, have enhanced the level of adherence among HIV-positive drug users [26]. This indicates that HIV-positive drug users' HAART-taking behaviour is an ongoing and dynamic social process where the patterns of their HAART-taking behaviour did not

remain the same but fluctuated over time. Although several attempts have been made to assess HIV-positive individuals' adherence levels by using self-reported questionnaires, pharmacy dispensing records or electronic monitoring devices, current assessment tools cannot capture the dynamic process of drug users' HAART-taking behaviour. In that sense, the question with regards whether HIV-positive drug users adhere to HAART cannot be simply answered as one or the other. Therefore, the review of qualitative studies played an important role in this paper to deeply understand and explore drug users' experiences of taking HAART

Among HIV-positive drug users, active drug use was reported to be significantly associated with poor adherence to HAART [22,34,39-46]. In particular, the impact of drug use on drug users' lifestyle and financial instability was found to be linked to their poor adherence to HAART [57-60,63,64]. Furthering the results from quantitative studies, the included qualitative studies showed that active drug use, specifically heroin, was found to affect participants' decision of prioritising needs. They tended to prioritise the need of getting fixed over enhancing health condition, resulting in decreasing their motivation of taking HAART. In response to stress, drug use was reported in Arnsten et al. [39] prospective study as a coping strategy among HIV-positive drug users. These findings imply the complex relationships between individuals' emotion, coping, and HAART-taking behaviour. As a result, active drug use had increased the challenge of initiating and sustaining HAART use among HIV-positive drug users. On the other hand, methadone treatment was reported to have a protective effect on enhancing adherence [24,25,27,29,31,41,63,71,72,74].

In addition to drug use, stigma related to HIV and illicit drug use was revealed in the included studies to greatly impede drug users' access to care and adherence to HAART [57,59,61,62,64,65]. In particular, the included qualitative studies from the

middle/low-income countries tended to report the negative impact of social stigma on HIV-positive drug users' adherence to HAART compared to those from high income countries. Public lack of knowledge and social values attached to HIV and drug use were found to shape one's assumptions and stigmatisation towards HIV-positive drug users. Drug users' experiences of stigmatisation from family, health professionals, and friends could undermine their psychological wellbeing and delay their access to HIV treatment. Participants' experiences of stigmatisation was shown to affect their psychological well-being, self-stigmatisation, and willingness to seek support and regularly receive HAART. By contrast, self-acceptance and acquisition of support were identified to enhance HIV-positive drug users' motivation of taking HAART.

Infrastructures within healthcare were another factor revealed in the included studies to impede participants' access to HIV and addiction treatment. Accessibility of care was particularly found, in the qualitative studies from Russia and India, to be linked to the economic constraints and value judgement towards drug users within the society [57,61]. As for HAART regimens, concerns over side effects were revealed to shape participants' preconception of HAART and decrease their willingness to take HAART. Not fitting HAART regimen into everyday life was reported to increase the chance of missing doses.

Together, based on the results from the included studies, there are several implications for practice, policy and future research. In practice, firstly, it is recommended that health professionals should assess HIV-positive drug users' adherence to HAART on a regular basis, given the dynamic and fluid process of drug users' adherence to HAART. Secondly, this paper recommends health professionals to provide care to HIV-positive drug users with respect, dignity, and non-judgemental

attitudes. Thirdly, it is suggested that HIV-positive drug users' psychological well-being, support system, and experience of HAART taking should be incorporated and emphasised in the care plan. The provision of coping strategies by health professionals and peer support groups, with regards the common issues experienced by drug users, can enable them to manage HAART taking more effectively. Fourthly, this review stresses the importance of linking HIV care with addiction care and prison settings. In doing so, it can help to retain HIV-positive drug users' access to HIV care and optimise their health outcomes.

For policy uptake, this review offers suggestive evidence for policy makers to create a supporting and inclusive environment for HIV-positive drug users to minimise social stigmatisation. Policy makers can take the initiative to increase the accessibility of HIV care in communities and prison settings, and bridge the gaps between HIV and addiction services. In addition, this paper suggests that national governments should ensure the rights of HIV-positive drug users are protected, thereby they can access health and social services without fear of discrimination or stigmatisation.

In terms of implications for future research, although quantitative research on HIV-positive drug users' adherence rates has been conducted extensively, there is a paucity of qualitative research focusing on HIV-positive drug users' experiences of HAART taking. This review suggests the need to gain insight into their experiences of taking HAART and further develop a model or framework that can enhance understanding their adherence behaviour. This can provide a guideline for policy makers and health professionals to assess HIV-positive drug users' adherence to HIV care, and further develop associated interventions.

While this review provides a comprehensive understanding of HIV-positive drug users' adherence rates across the studies and the influencing factors, there are limitations. Firstly, this review article did not conduct statistical tests. Due to different standards of optimal adherence rates and adherence assessment tools used by the included studies, this increased the difficulties of estimating HIV-positive drug users' adherence levels. Secondly, during the process of this systematic literature review, expert discussion panels were not involved in the reviewing process. Consequently, this may bring authors' biases into the analysis. Last but not least, all of the included studies assess HIV-positive drug users' adherence levels and experience of HAART taking through self-report. This might lead to overestimation of their adherence levels and introduction of socially-desirable answers when synthesising the evidence.

Conclusion

This is the first review article that includes both qualitative and quantitative research, and provides a more comprehensive and in-depth understanding of HIV-positive drug users' experience of HAART-taking. The results from this review can provide insight into the underlying issues that could potentially influence HIV-positive drug users' adherence to HAART. However, the mechanism of HAART-taking behaviour in HIV-positive drug users remains to be elucidated. This would be fruitful area for further work to ensure appropriate system, services, and support for this group of the HIV population.

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Figure 1: Flowchart of the study selection process

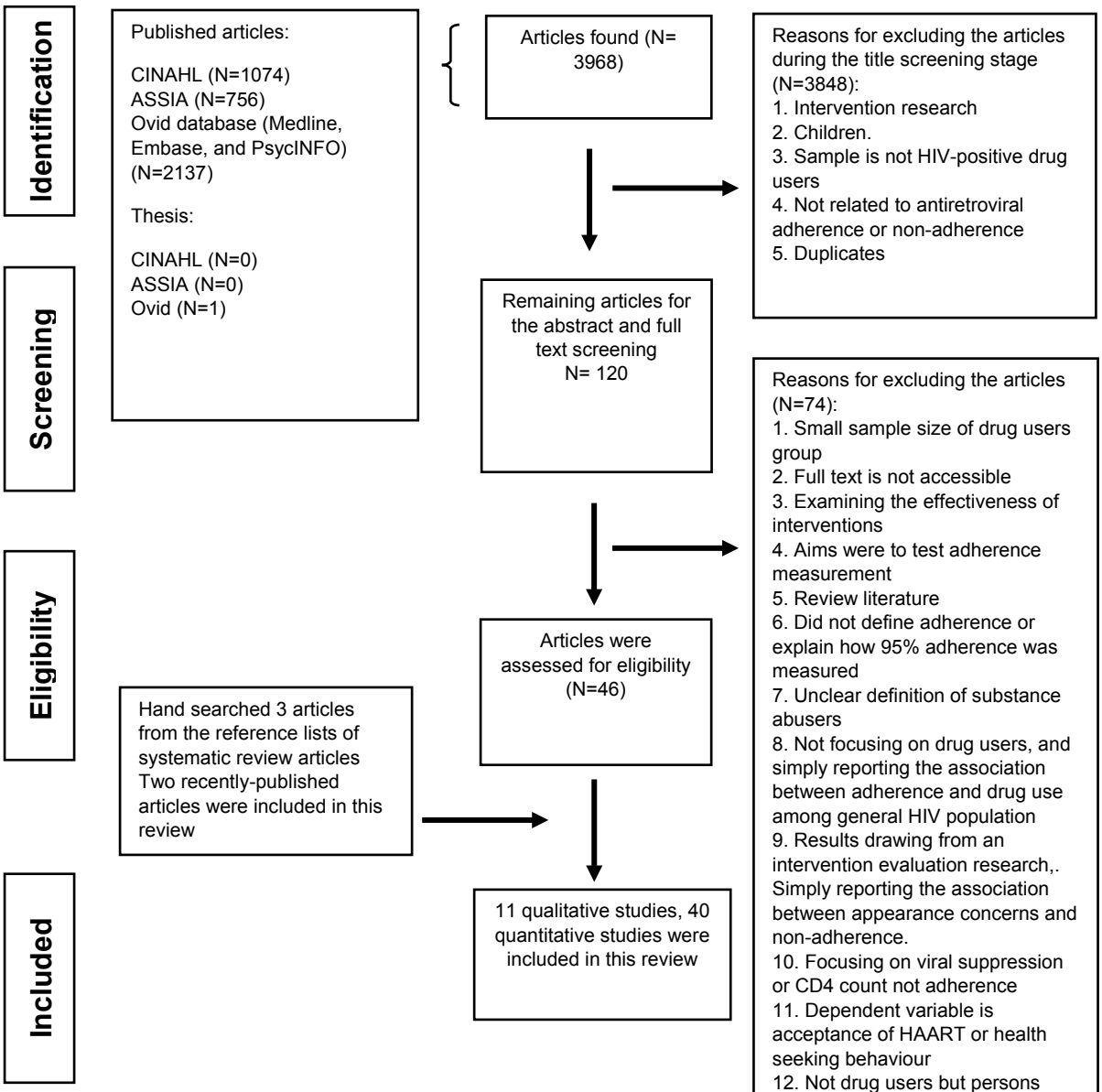

Table 1: Summary of the included quantitative studies (N=40)

	Method	Authors /Project period	Sample size	Sample	Sampling	Measure of adherence	Results
Canada	An ongoing prospective observational cohort study conducted in Vancouver since 1996	Azar et al. (2015)/(1996-2013) Title: Drug use patterns associated with risk of non-adherence to antiretroviral therapy among HIV-positive illicit drug users in a Canadian setting: A longitudinal analysis	N=692	HIV-positive illicit drug users	Convenient sampling Snowball sampling	Pharmacy dispensation record The ratio of number of days the patients received HAART refills/Total number of days of medical follow-up	Heroin and cocaine use was associated with lower likelihoods of optimal adherence (≥95% adherence rate); MMT was associated with greater likelihood of adherence. 51% of the participants were categorised by ≥95% adherence.
		Hadland et al. (2012) /(1996-2008) Title: Young Age Predicts Poor Antiretroviral Adherence and Viral Load Suppression Among Injection Drug Users	N=545	HIV-positive IDUs	Convenient sampling	Pharmacy dispensation record	Follow-up period: 8.5months to 91.6 months. Adherence rate was significantly lower among young IDUs. Adherence is a mediator of the relationship between age and viral load suppression 66 (33.8%) discontinued ART during follow-up period.

							There were 26.6% periods in which individuals were more than 95% adherent in 4460 observations
		Hayashi et al. (2016) / (2005-2013) Title: Factors associated with optimal pharmacy refill adherence for antiretroviral medications and plasma HIV RNA nondetectability among HIV-positive crack cocaine users: a prospective cohort study	N=438	HIV-positive crack cocaine users	Convenient sampling	Pharmacy dispensation record	54.8% of the participants exhibited optimal pharmacy refill adherence (≥ 95%) in the previous 6 months. 89% attained ≥95% adherence at some point during the study period. Older age and higher CD4 count were associated with optimal adherence. Daily Cocaine and Heroin use and homelessness was negatively associated with optimal adherence
		Lappalainen et al. (2015) / (2005-2013) Title: Dose-response relationship between methadone dose and adherence to antiretroviral	N=297	HIV-positive individuals who use opioid	Convenient sampling Snowball sampling	Pharmacy dispensation record	Median follow-up period: 42.1 months MMT dose > 100mg per day was associated with optimal adherence (≥95% adherence rate)

		therapy among HIV-positive people who use illicit opioids					
		Joseph et al. (2015) /(1996-2012) Title: Factors linked to transitions in adherence to antiretroviral therapy among HIV-infected illicit drug users in a Canadian setting	N=703	HIV-positive illicit drug users	Convenient sampling	Pharmacy dispensation record	27% of the participants (n=190) had optimal adherence. Transition out of optimal adherence (≥ 95%) was associated with younger age, periods of homelessness, active injecting drug use, and incarceration. Individuals who transitioned into optimal adherent were older. Periods of sex work and injecting drug use were barriers to becoming optimally adherent. MMT was associated with optimal adherence and had a protective effect against being non-adherent.

		Mann et al. (2012) /(1996-2009) Title: Improved adherence to modern antiretroviral therapy among HIV-infected injecting drug users	N=682	HIV-positive IDUs	Convenient sampling	Pharmacy dispensation record	The proportion of achieving at least 95% adherence increased over time from 19.3% in 1996 to 65.9% in 2009. Initiation year was associated with ≥ 95% adherence.
		Nolan et al. (2011) /(1996-2008) Title: Adherence and plasma HIV RNA response to antiretroviral therapy among HIV-seropositive injection drug users in a Canadian setting	N=267	HIV-positive IDUs	Convenient sampling	Pharmacy dispensation record	17-95months of follow-up. 30% of the 267 participants had ≥ 95% of adherence during the first year of ART. ≥95% adherence, participation in MMT, and older age, year of ART initiation was positively associated with viral suppression.
		Palepu et al. (2006) / (1996-2003) Title: Antiretroviral adherence and HIV treatment outcomes among HIV/HCV co-infected injection drug users: The role of methadone maintenance therapy	N=278	HIV/HCV co-infected IDUs	Convenient sampling	Pharmacy dispensation record	129 out of 278 had ≥ 95% adherence 36.76 months of follow-up Enrollment in MMT is associated with reduced heroin use and improved adherence

		Palepu et al. (2011) / (1996-2008) Title: Homelessness and Adherence to Antiretroviral Therapy among a Cohort of HIV-Infected Injection Drug Users	N=545	HIV-positive IDUs	Convenient sampling	Pharmacy dispensation record	26.6% had ≥ 95% adherence Follow-up duration: 23.8 months (8-91 months) Homelessness and frequent heroin use were negatively associated with optimal adherence (≥ 95%), whereas MMT was positively associated.
		Lee et al. (2016) /(2005-2013) Title: Psychosocial Factors in Adherence to Antiretroviral Therapy Among HIV-Positive People Who Use Drugs	N=667	HIV-positive IDUs	Convenient sampling	Pharmacy dispensation record	85.9% of 650 participants achieved 95% or greater ART adherence at some point during the study period. In multivariable analyses, factors positively associated with 95% or greater ART adherence included adherence self-efficacy, age, current enrollment in MMT, and CD4 cell count, while drug use patterns and negative outcome

							expectancy were negatively associated with optimal adherence to ART.
		Ti et al. (2014)/ (1996-2012) Suboptimal plasma HIV-1 RNA suppression and adherence among sex workers who use illicit drugs in a Canadian setting: an observational cohort study	N=587	HIV-positive sex workers who use illicit drugs	Convenient sampling	Pharmacy dispensation record	18-60 months follow-up Average adherence rate was 50% Adherence mediated the relationship between sex work and suppression of viral load
	Prospective cohort study in Vancouver	Wood et al. (2004) Title: Elevated rates of antiretroviral treatment discontinuation among HIV-infected injection drug users: implications for drug policy and public health	N=1422	HIV-positive individuals (non-IDUs and IDUs)	Convenient sampling	Discontinuation was defined as the first day of a ≥3-month period without receiving any antiretrovirals	359 were IDUs (25.3%). History of injection drug use was associated with more rapid discontinuation of therapy At 12 months of after ART initiation, 30.3% of non-IDU versus 42.5% of IDU had discontinued HAART ($P <$ 0.001).
	Dissertation	Kerr (2003) Title: Psychosocial determinants of maintenance of, and adherence to, antiretroviral	N=160	HIV-positive IDUs	Convenient sampling	Self-report Maintenance refers to the sustained use of ART, and is the opposite of	In total, 71 (44%) participants discontinued HAART, and 89 (56%) remained on HAART.

	Published article	therapy among injection drug users living with HIV/AIDS Kerr et al. (2005) Title: Determinants of HAART discontinuation among injection drug users				discontinuation, which refers to the cessation of ART. Discontinuation: They had not picked up any components of their HAART regimen for one month.	Variables that were negatively associated with ART maintenance included negative outcome expectations and incarceration. Variables that were associated positively with ART maintenance included efficacy expectations and self-regulatory efficacy. Efficacy expectations, self-regulatory efficacy, recent incarceration are negatively associated with HAART discontinuation
USA	Longitudinal study in New York	French et al. (2011) Title: Changes in Stress, Substance Use and Medication Beliefs are Associated with Changes in Adherence to HIV Antiretroviral Therapy	N=2089/4340 were included (48.1%)	HIV-positive substance users (use of cocaine, crack, heroin in the past 3 days)	Convenient sampling	Self-report: The number of pills prescribed per day and the number of doses they missed in the 3 days	71.7% of 2089 had ≤ 95% adherence Clients who changed from no substance use at one interview to substance use at the subsequent interview were approximately 2-3 times as likely to

							be consistently non-adherent. Clients who transitioned from being not sure to very sure about the effectiveness of ART were significantly more likely to transition from non-adherent to adherent. Clients who changed from low stress to high stress were three times more likely to change from adherent to non-adherent.
	Cross-sectional study in 9 states of the USA	Chitsaz et al. (2013) Title: Contribution of substance use disorders on HIV treatment outcomes and antiretroviral medication adherence among HIV-infected persons entering jail	N=1270	HIV-positive substance users	Convenient sampling	Self-report: The number of pills prescribed per day and the number of doses they missed in the 7 days	Among all subjects, 72% had used drugs in the 30 days. Drug use severity was negatively correlated with 1) having an HIV care provider, 2) being prescribed ART, 3) high levels of adherence (>95%) Being employed and paid for work was associated with a two-fold

							increased likelihood of optimal adherence. The commonly used drugs were marijuana, cocaine, and heroin.
	Cross-sectional study in multiple sites of USA	Sharpe et al. (2004) Title: Crack cocaine use and adherence to antiretroviral treatment among HIV-infected black women	N=785	HIV-positive black women	Convenient sampling	The outcome variable, ART adherence, was measured with a single question, "How often are you able to take the HIV/AIDS drugs exactly the way your doctor told you to take them?" The four-category Likert scale (always, usually, sometimes, rarely) was dichotomized into always and not always.	Crack users and users of other drugs were less likely than non-users to take their ART medicines exactly as prescribed
	Cross-sectional study in South Florida	Surratt et al. (2015) Title: Medication adherence challenges among HIV positive substance abusers: the role of food and housing insecurity	N=503	HIV-positive substance abusers (Heroin and Cocaine users)	Convenient sampling	Total ARV doses prescribed and total doses missed in the past 7 days	Nearly 60% of those reported ART diversion 47.2% achieved >95% adherence. Food/ housing insecurity was associated with lower HIV

							medication adherence.
	Cross-sectional study in USA	Shrestha and Copenhaver (2018) Title: Viral suppression among HIV infected methadone-maintained patients:The role of ongoing injection drug use and adherence to antiretroviral therapy (ART)	N=133	HIV-infected methadone-maintained patients	Convenient sampling	Self-report measure: percent of doses taken during the previous 30 days Optimal adherence means 95% adherence.	One in five was not able to achieve viral suppression Opioid-dependent individuals who are stabilised on methadone remain at high risk for poor virologic suppression and increased HIV transmission
	Prospective observational study in Florida	Waldrop-Valverde et al. (2013) Title: Medication-Taking Self-Efficacy and Medication Adherence Among HIV-Infected Cocaine Users	N=99	HIV-infected Cocaine users	Convenient sampling	Using an electronic monitoring device (MEMs) and self-report Adherence was defined using percent of doses taken during the previous 7 days.	4-week interval for follow-up, over 6 month period Compared to the first month, there was a significant drop in adherence at Months 2, 3, 4, and 6 for percentage dose adherent. There was a reduction from 76.7 at Month 1 to 66.5 at Month 6 for percentage dose adherent (MEMs). From 66.4 at M1 to 57.3 at M6 for percentage days

							adherent (Self-report)
	Cross-sectional study	Harzke et al. (2004) Title: Psychosocial factors associated with adherence to antiretroviral medications in a sample of HIV-positive African American drug users	N=137	HIV-positive African American drug users	Convenient sampling	Self-rating their level of adherence (ranging from always missing doses to never missing doses)	Perceived efficacy of ART, and perceived barriers, simply forgetting to take medications were independently associated with adherence.
	Cross-sectional study	Hicks et al. (2007) Title: The impact of illicit drug use and substance abuse treatment on adherence to HAART	N=659	HIV-positive former, current, and never substance abusers	Convenient sampling	Self-report: The doses missed in the past 2 weeks. Adherence was defined as taking greater than or equal to 95% of prescribed doses of all antiretroviral drugs in the HAART regimen	67% had ≥ 95% adherence rate. Current users (60%) were significantly less likely to be adherent than former (68%) or never users (77%) Former users in substance abuse treatment were as adherent to HAART as never users Former users who had not received recent substance abuse treatment were significantly less adherent than never users Current substance users were significantly less adherent than

							never users, regardless of substance abuse treatment.
	Cross-sectional study	Carrico et al. (2010) Title: Affective Correlates of Stimulant Use and Adherence to Anti-retroviral Therapy Among HIV-positive Methamphetamine Users Carrico et al. (2007) Title: Affect Regulation, Stimulant Use, and Viral Load Among HIV-Positive Persons on Antiretroviral Therapy	N=122 N=858	HIV-positive methamphetamine users HIV-positive individuals (non-stimulant and stimulant users)	Convenient sampling	Self-report measure: percent of doses taken during the previous 7 days Optimal adherence means 100% adherence.	The majority of participants were MSM (94%). Among the MSM, 84% identified as predominantly or exclusively gay. Positive affect was independently associated with a decreased likelihood of reporting any injection drug use and an increased likelihood of reporting perfect ART adherence. Increase in affect regulation decreased the likelihood of regular stimulant use and non-adherence to ART
	A multisite cohort study	Mellins et al. (2009) Title: Adherence to antiretroviral medications and medical care in HIV-infected adults diagnosed with mental and	N=1138	HIV-positive with mental and substance abuse disorders (49% IDUs)	Convenient sampling	Self-report: The number of missed doses in the past three days	Complete adherence in the past 3 days: 55% of the participants 45% of those on ARVs reported skipping medications in the past three days

		substance abuse disorders					The factors associated with non-adherence were current drug and alcohol abuse, increased psychological distress, less attendance at medical appointments, non-adherence to psychiatric medications and lower self-reported spirituality. Increased psychological distress was significantly associated with non-adherence, independent of substance abuse.
	Cross-sectional study	Magidson et al. (2015) Title: Can behavioural theory inform the understanding of depression and medication non-adherence among HIV-positive substance users? To test three components of behavioural depression	N=83	Low-income HIV-positive substance abusers	Convenient sampling	Self-report: The number of doses missed versus doses prescribed over the past 4 days for all daily medications	Mean adherence rates ranged from 94.46 to 97.72 % in the past 4 days Crack use is significantly associated with missing doses There was only an indirect effect of environmental punishment; depressive symptoms were associated with

		theory—goal-directed activation, positive reinforcement, and environmental punishment					greater non-adherence through greater environmental punishment. Goal-directed activation and positive reinforcement were unrelated to adherence.
	Cross-sectional study	Moore et al. (2012) Title: Methamphetamine use and neuropsychiatric factors are associated with antiretroviral nonadherence	N=125	67 HIV-positive lifetime meth users 50 HIV-positive non-meth users 8 HIV-positive current meth users	Convenient sampling	Self-report: Taken doses/prescribed doses in the past 4 days Non-adherence: Any skipped doses	Major depressive disorder uniquely predicted ART non-adherence after controlling for the other variables. Ancillary analyses indicated that current METH users (use within 30 days) were significantly less adherent than lifetime METH users and non-Meth users. Of those, neurocognitive impairment was associated with non-adherence.

	Cross-sectional study	Tucker et al. (2004) Title: Psychosocial Mediators of Antiretroviral Nonadherence in HIV-Positive Adults With Substance Use and Mental Health Problems	N=1889	HIV-positive individuals (23% of those were IDUs)	Convenient sampling	Self-report Adherence: Not missing any doses	46% of the participants were adherent Those in the drug use only group were not significantly more likely to be nonadherent than those with no mental health or substance use problems. Substance use group was more likely than those with no problems to have poor access. Drug use group was more likely to report poorer fit of the medication regimen with their lifestyle.
	Secondary data analysis from another study	Kelly et al. (2012) Title: Social Networks of Substance Users With HIV Infection: Application of the Norbeck Social Support Scale	N=76	HIV-positive individuals who use methadone	-	Self-report measure	The presence of network drug users and HIV-infected network members was associated with less antiretroviral medication adherence Note: The dependent variable, antiretroviral adherence, was

							assessed through self-report over the past 7 days at three-time points, baseline, Week 12, and Week 24. Adherence was dichotomized as either 100% (no missed doses or pills any time in the past week) or <100%.
	Prospective cohort study	Lucas et al. (2001) Title: Detrimental effects of continued illicit drug use on the treatment of HIV-1 infection	N=764	HIV-positive individuals	Convenient sampling	Self-report Nonadherence means participants report of more than two missed doses over the 2 weeks	Active drug users were more likely to be non-adherent Forty-four percent of active drug users failed to utilise HAART compared with 22% of former drug users and 18% of non-drug users
	Longitudinal study	Hinkin et al. (2007) Title: Drug use and medication adherence among HIV-1 infected individuals	N=105	Stimulant users Non-stimulant users	Convenient sampling	MEMS caps Dividing actual dose events by prescribed doses during 1 month period Adherence: taking ≥ 90% doses	The drug-negative group's adherence rate was 79% as compared to 63% for the drug-positive group. Over time, adherence rates for the entire sample dropped from 74.4% for the first 2 months, to 68.5% for months

							3–4, down to 62.6% for months 5 and 6 of the study Stimulant positive group's adherence rate was significantly lower than both the other-drug positive group (P = .001) as well as the non-drug group. Between group comparisons revealed a trend toward the cocaine + methamphetamine group evidencing poorer adherence than did the cocaine only group. The mean adherence rate for the cocaine only group was 68.1% vs. 54.5% for the cocaine + methamphetamine group. Drug use was associated with 4.1 times greater risk of being a poor adherer. Although the non-abuse group's mean adherence

							rates dropped 10% points, from 77.4% to 68.4%, the drug abuse group experienced a more precipitous decline with their mean adherence rate dropping over 18% points (from 70.1% to 51.3%).
	Cross-sectional study	Arnsten et al. (2007) Title: Factors Associated With Antiretroviral Therapy Adherence and Medication Errors Among HIV-Infected Injection Drug Users	N=636	HIV-infected drug users	Convenient sampling	Self-report Good adherence: taking ≥ 90% doses	75% (n=477) self-reported good adherence Depressive symptom and self-efficacy were associated with poor adherence.
	Prospective study	Arnsten et al. (2002) Title: Impact of active drug use on antiretroviral therapy adherence and viral suppression in HIV infected drug users	N=85	HIV-positive current and former drug users	Convenient sampling	MEMS caps (electronic pill caps) –Dividing the number of cap opening by the number of doses prescribed	Mean overall adherence was 53% Active cocaine use, female, not receiving social security benefits, not being married, positive for depression, the tendency to use alcohol or drugs to cope with stress were all associated with poor adherence. The strong

							predictor of poor adherence was active drug use. Adherence among active cocaine users was 20%, compared to 66% in subjects who did not use cocaine.
	Prospective study	Kalichman et al. (2015) Title: Intentional Medication Nonadherence Because of Interactive Toxicity Beliefs Among HIV-Positive Active Drug Users	N=530	HIV-positive drug users	Convenient sampling	Telephone-based unannounced pill counts over a 6-week period	189 (35%) participants indicated that they intentionally miss their ART when they are using drugs. These participants perceived hazards of mixing HIV medications with alcohol and other drugs. Participants who reported intentional nonadherence at the initial assessment were significantly more likely to have poorer adherence over the subsequent 6 weeks
	Retrospective cohort study	Turner et al. (2003)	N=1827 (female) N= 3246 (male)	HIV-positive IDUs	Convenient sampling	Pharmacy-based measurement of	The mean adherence was 83.2%

		Title: Relationship of gender, depression, and health care delivery with antiretroviral adherence in HIV-infected drug users				adherence (filled prescription) Adherence means >95%	22% of the study population were adherent at a 95% level. Adherence was higher among those who received regular drug treatment and psychiatric care Women were less adherent than men In women, adherence was significantly poor for those with cocaine or heroin use.

France	MANIF2000 Cohort study	Carrieri et al. (2003) Title: Failure to Maintain Adherence to HAART in a Cohort of French HIV-Positive Injecting Drug Users	N=96	HIV-positive IDUs	Convenient sampling	Adherence failure is defined as a self-reported, non-adherence behaviour at any visit before the 18th month of treatment. Adherence measure: the daily number of prescribed pills they have effectively taken during the week prior to the visit. Non-adherence means taking less than <80% of prescribed doses	22 (22.9%) experienced adherence failure, whereas 74 (77.1%) remained adherent at all follow-up visits. Lack of a stable relationship, active drug injection, and depression were independently associated with adherence failure.
		Moatti et al. (2000) Title: Adherence to HAART in French HIV-infected injecting drug users: the contribution of buprenorphine drug maintenance treatment	N=164	HIV-positive IDUs	Convenient sampling	Self-report Non-adherence means taking less than <80% of prescribed doses in the past 7 days	34.8% took less than 80% of the prescribed HAART doses during the previous week Non-adherence was associated with younger age, alcohol consumption, frequency of negative life-events during the prior 6 months and active drug use

		Bouhnik et al. (2002) Title: Nonadherence among HIV-infected injecting drug users: The impact of social instability	N=210	HIV-positive former or current IDUs	Convenient sampling	Self-report Non-adherence means taking less than <80% of prescribed doses	Among ex-IDUs, the only factor associated with nonadherence was social instability Among opioid-dependent patients, injection behaviour was the only determinant of nonadherence behaviour
		Roux et al. (2008) Title: The impact of methadone or buprenorphine treatment and ongoing injection on highly active Antiretroviral therapy (HAART) adherence: evidence from the MANIF2000 cohort study	N=276	HIV-positive IDUs	Convenient sampling	The visual analogue scale was used to reclassify as non-adherent those whose score was <100%. Patient's adherence to HAART in the 4 days and in the 4 weeks prior to the interview.	Patients ceasing injection during OST and abstinent patients exhibited comparable adherence. Patients reporting injection, on OST or not, had a twofold and threefold risk, respectively, of non-adherence compared with abstinent patients

The Netherlands	Prospective cohort study	Lambers et al. (2011) Title: Harm reduction intensity—Its role in HAART adherence amongst drug users in Amsterdam	N=102	HIV-positive drug users	Convenient sampling	Self-report measure: the number of days that medication was not taken in the last 6 months.	The rate of non-adherence (95%) ranged from a minimum rate of 6.2% (in 2002) to a maximum rate of 18.9% (in 2005) of the visits per year. Of the 76 participants who were adherent on their first included visit and who had a follow-up visit, 26 became non-adherent at least once in the study period. Non-injecting DUs with low dependence on harm reduction were less adherent than DU with complete harm reduction. Unsupervised housing (no access to structural support at home) and having a steady partner were significantly associated with respectively more and less non-adherence.

Vietnam	Prospective study	Jordan et al. (2014) Title: Correlates of non-adherence to antiretroviral therapy in a cohort of HIV-positive drug users receiving antiretroviral therapy in Hanoi, Vietnam	N=100	HIV-positive individuals with a history of drug use	Convenient sampling	Subjective rating (perfect, very good, good, fair, or poor adherence)	48% of participants reported drug use within the previous 6 months, with 22% reporting current drug use. Overall levels of self-reported ART adherence in this cohort were high (83% reporting perfect/very good adherence at the time of study enrollment) Active drug use and duration of ART increase the odds of suboptimal ART adherence

India	Cross-sectional study	Sharma et al. (2007) Title: Access, adherence, quality and impact of ARV provision to current and ex-injecting drug users in Manipur (India): An initial assessment	N=226	Current and ex-injecting drug users	Purposive sampling and convenient sampling	Treatment discontinuation	One-third of the sample reports ever having discontinued ART (74/226). Experience of side effects, whether ART is provided free, whether patients received counselling, and alcohol use was associated with ART discontinuation.

Table 2: Summary of the included qualitative studies (N=11)

Country	Authors	Title of the article	Sample size	Sampling	Data collection method	Data analysis method	Major themes
USA	Batchelder et al. (2013	"Damaging what wasn't damaged already": Psychological tension and antiretroviral adherence among HIV-infected methadone-maintained drug users	15 HIV-positive drug users who use methadone maintenance	Convenient sampling	Semi-structured interviews	Thematic analysis	**Negative themes are related to continued drug use** 1. Denial and resistance 2. Shame 3. Perceived isolation **Positive themes are related to decreased drug use** 1. Acceptance of HIV and motivation to adhere 2. Empowerment 3. Perceived connectedness
	Pach et al. (2003)	A qualitative investigation of antiretroviral therapy	34 HIV-positive IDUs	Convenient sampling Snowball sampling	Ethnographic interviews	-	**Group 1 (N=8): Never on ART** 1. Involving in active drug use

Country	Authors	Title of the article	Sample size	Sampling	Data collection method	Data analysis method	Major themes
		among injection drug users					2.Lacking information from health professionals about HAART 3. Having ambivalent or negative attitudes about the safety of the medication and the intentions of health care providers **Group2 (N=7): Stopped AZT and never sought other treatment.** 1. Active drug use 2. Lack of contact with HIV services 3. Negative experience with side effects from AZT 4. Exposure to negative attitudes about AZT deterred members of this group from continuing their use of ART or later considering the use of ART **Group 3 (N=9): Stopped undergoing HAART** 1. Perceptions of HAART that altered in significance as their circumstances and experiences with the medication changed (e.g. level of drug use, lack of available drug treatment, severity of side effects, prior experience with clinicians) **Group 4 (N=10): Undergoing HAART** Working, living with relatives, receiving disability payments,

Country	Authors	Title of the article	Sample size	Sampling	Data collection method	Data analysis method	Major themes
							improved health, trusted medical doctors, taking HAART in their own ways
	Ware et al. (2005)	Adherence, stereotyping and unequal HIV treatment for active users of illegal drugs	52 HIV-positive active drug users	Convenient sampling	Qualitative interviews	Analytic approach – Glaser and Strauss, Strauss and Corbin	1. Daily lives of participants 2. How drug use impedes adherence *Acquiring drugs * Consuming drugs *Recovering from drug use 3. Not carrying medication 4.Competing priorities 5. Redefining regimens 6. Efforts to adhere to HAART *Taking medications while using *Prioritising adherence * Sticking with a set of rules: the significance of routines for adherence
Canada	Small et al. (2009)	The impact of incarceration upon adherence to HIV treatment among HIV positive injection drug users: A qualitative study	12 HIV-positive IDUs	Sampling at correctional settings	In-depth individual interviews	Thematic analysis	1. Entry into the correctional system and interruption of treatment 2. Difficulties accessing HIV medications within the correctional system 3. Challenges related to institutional health care services and HIV care 4. The importance of advocacy and communication 5. HIV discrimination amongst prisoners 6. Problems upon release to the community

Country	Authors	Title of the article	Sample size	Sampling	Data collection method	Data analysis method	Major themes
	McNeil et al. (2017)	Antiretroviral therapy interruption among HIV positive people who use drugs in a setting with a community-wide HIV treatment-as-prevention initiative	39 HIV-positive drug users who had not filled an ART prescription for a period of at least 30 days	Purposeful sampling	Semi-structured interviews	Coding framework: individual and socio-structural influences	**Individual** 1.Individual and contextual influences on treatment fatigue 2. Negotiating prior adverse ART experiences 3. Social isolation and treatment motivation **Socio-structural** 1. Structural vulnerability and discontinuities in the continuity of HIV care
Russian	Rhodes and Sarang (2012)	Drug treatment and the conditionality of HIV treatment access: a qualitative study in a Russian city	42 HIV-positive IDUs 11 health practitioners	Chain referral sampling	In-depth qualitative interviews	Thematic analysis	1. HIV treatment conditionality and delay 2. The problem of drugs in HIV treatment access 3. The problem of inadequate drug treatment
	Kiriazova et al. (2016)	"It is easier for me to shoot up": stigma, abandonment, and why HIV-positive drug users in Russia fail to link to HIV care	HIV-positive drug users	Convenient sampling	Individual interviews	Thematic analysis	1.Stigma and poor patient-provider relationships 2. Fragmentation of health care
Ukraine	Mimiaga et al. (2010)	"We fear the police, and the police fear us": structural and individual barriers and facilitators to HIV medication adherence among injection drug users in Kiev, Ukraine	16 HIV-positive IDUs	Convenient sampling	Two semi-structured focus groups	Content analysis	B**arriers** 1. Harassment and discrimination by police 2. Opioid dependence 3. Complexity of drug regimen 4. Side effects 5. forgetting 6. Co-occurring mental health problems 7. HIV stigma **Facilitators**

Country	Authors	Title of the article	Sample size	Sampling	Data collection method	Data analysis method	Major themes
							1. Cues for pill taking 2. Support and reminders from family, significant other, and friends 3. Opioid substitution therapy 4. Wanting improved health 5. Knowledge about HAART 6. Storage of medications 7. IDUs and sexual risk behaviours
India	Chakrapani et al. (2014)	Barriers to antiretroviral treatment access for injecting drug users living with HIV in Chennai, South India	19 HIV-positive IDUs 4 key informants	Recruited by peer outreach workers	Semi-structured interviews	Framework analysis	**Family and social barriers** 1.Lack family support and fear of societal discrimination 2.Unmet basic needs - food and shelter **Health care system barriers** 1.Actual or perceived unfriendly hospital environment and procedures 2. Provider-perceived nonadherence 3. Actual or perceived inadequate counselling services and lack of confidentiality 4. Lack of effective linkages between ART centres, needle/syringe programs, and drug dependence treatment centres **Individual-level barriers** 1. Active drug use 2. Lack of self-efficacy and low motivation **Inadequate knowledge about ART**

Country	Authors	Title of the article	Sample size	Sampling	Data collection method	Data analysis method	Major themes
Spain	De la Hera et al. (2011)	The opinions of injecting drug user HIV patients and health professionals on access to antiretroviral treatment and health services in Valencia, Spain	23 HIV-positive IDUs 9 health professionals	Convenient sampling	Semi-structured interviews	The codification process followed Strauss and Corbin's (1990) analytic procedure	**Health professionals** 1.Lack of coordination among hospital services 2. Difficulties in accessing non-specialised services 3. Their perceptions of a patient's likelihood of treatment adherence **IDUs** 1. A good doctor-patient relationship 2. Family responsibility (Female participants) 3. Complexity and side effects of the treatment 4. lack of social support 5. active use of recreational drugs 6. Accessibility of services 7. Beliefs about HAART