Curr HIV/AIDS Rep (2014) 11:52–62
DOI 10.1007/s11904-013-0196-2

THE SCIENCE OF PREVENTION (SC KALICHMAN, SECTION EDITOR)

The Paradigm of Universal Access to HIV-Treatment and Human Rights Violation: How Do We Treat HIV-Positive People Who Use Drugs?

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Published online: 27 December 2013

Abstract HIV-positive people who use drugs (PWUDs) are particularly vulnerable for suboptimal access to highly active antiretroviral therapy (HAART). We conducted a systematic review to identify factors associated with suboptimal HAART access among this population. Studies evaluating HAART access among active PWUDs as a primary outcome, presenting multivariate analysis and conducted after January 1997 were included. Of 122 studies matching the search criteria, only 14 (11.4 %) met the inclusion criteria. All selected studies were prospective cohorts and included young adults, 13 were conducted in North America or western Europe and one in Ukraine. Selected studies measured HAART access using different strategies, however, all identified PWUDs as less likely to receive HAART, when compared to those who never used drugs or former PWUDs. Additional factors associated with suboptimal HAART access include: recent incarceration, lack of health insurance, unstable housing, depression, non-white ethnicity, female PWUDs, and health professionals stigma/prejudice. Factors associated with higher rates of HIV-treatment access included: alcohol and/or drug addiction treatment (especially methadone maintenance therapy), regular source of primary care, treatment and care from the same provider (most of the time) and larger physician experience in HIV-management. PWUDs face a synergy of social and structural factors that influence their suboptimal access to HAART, struggling with poor living conditions, inadequate access to specialized care and stigma/discrimination from health professionals. Renewed strategies and effective interventions should be developed and scaled-up, in order to assure equitable HAART access, decrease morbidity and mortality among PWUDs.

Keywords HIV-treatment · HIV-treatment access · People who use drugs (PWUDs) · PWUDs · HIV-positive people · Highly active antiretroviral therapy (HAART) · HAART · Science of prevention · Human rights · People living with HIV (PLWHA) · Treatment · HIV · HIV-positive drug users · Drug use

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Introduction

Improvement in quality of life of people living with HIV (PLWHA) under highly active antiretroviral therapy (HAART) has been comprehensively reviewed in recent years [1–3]. Findings from the HIV Prevention Trials Network 052 (HPTN 052) and subsequent studies also showed that early treatment of PLWHA not only improve the patients' health and their overall quality of life, but also dramatically cuts the rate of new infections [4, 5]. Studies of communities with high concentrations of people who use drugs (PWUDs) and men who have sex with men (MSM) have also shown that as HAART use increased within the community, the community's viral load declined, as did rates of new HIV diagnoses [6, 7]. However ARV prophylaxis for PWUDs remains tentative and new protocols and/or additional analyses of existing protocols (e.g. The Bangkok Tenofovir Study) are sorely needed [8].

Following the same patterns identified among PLWHA, HIV-positive drug users who have access to timely treatment and achieve adequate adherence levels reach similar levels of viral suppression as the ones identified among other populations [6, 9, 10]. Resistance to one or more than one major class of antiretrovirals constitutes a major concern, worldwide, but no significant differences have been made evident between PLWHA who inject and do not inject drugs [11]. Similar rates of HIV-1 RNA suppression and rebound after HAART initiation have also been identified among HIV-positive drug users and patients who do not inject drugs [12]. However, in spite of growing evidence supporting the efficacy of early HAART initiation, drug users are disproportionately less likely to receive HAART than other patients, and levels of HAART access for active drug users are likely to be even lower, worldwide [13, 14].

Donoghoe and colleagues [15] evaluated HAART access among people who inject drugs (PWID) from 52 countries in the WHO European region, identifying a great inequity in drug users' access to HAART. Among 19 countries that provided data from 2002 to 2004, the authors identified a stable number of new infections among PWID: 45 % in 2002 and 42 % in 2004. Notwithstanding, the inequities in HAART access were striking: in 2002 only 5 % of HAART recipients were PWID, 'increasing' to 6 % in 2004. Grigoryan et al. [16] evaluated US national HIV surveillance data from 1996-2004. The study identified 27,572 PWID (42.2 %) who were diagnosed in a late stage. The three years survival rate after HIV diagnosis was lower for both male and female injection drug users, when compared to both men who have sex with men (MSM) and heterosexuals (male/female). The same study documented PWID also had a high risk for progression from HIV to AIDS.

Drug addiction is a chronic and relapsing condition, and a large percent of those patients usually experience periods of abstinence and relapses across their lifespan. As discussed in the seminal paper by McLellan [17], the course of this complex, multidimensional chronic disease does not markedly differ from other major chronic conditions, but such conceptual advances had not been translated into concrete improvements in drug abuse management [18]. Drug users tend to cycle in and out of settings providing either inpatient or outpatient treatment for addiction, HIV/AIDS, mental health and other co-morbidities. While barriers to receive proper HIV care remain for all drug users, active drug users face an even greater synergy of problems to access those life-saving interventions [13, 14].

There is a widely held view that active drug users are poor candidates for HAART because it is believed that drug addiction undermines adherence, or because medical complications and frequent co-infections such as HIV/HCV could make those patients more difficult to treat and less responsive to HAART [19]. It is indeed challenging to provide treatment for HIV-positive active drug users, while patients co-infected with hepatitis C or tuberculosis present greater clinical needs. However, those are the ones most in need of comprehensive and timely treatment.

While the World Health Organization recommended that physicians do not discriminate patients on the basis of current or former drug use [20], physicians from Russia and Ukraine, for instance, have declined to treat active drug users HIV-positive and eligible to start HAART [21]. In response to the growing evidence that drug users disproportionately under-utilize HIV/AIDS, HCV, addiction prevention and treatment services, recent reviews have urged for equitable and universal access [14, 22]. Aiming to contribute to this ongoing debate and to evidence-based policies targeting this population, we conducted a systematic review of studies evaluating access to HAART among HIV-positive active drug users.

Methods

The systematic review was conducted using PRISMA guidelines [23].

Inclusion and Exclusion Criteria

Studies were included if they were conducted among HIV-positive active drug users or carried out stratified analyses on subsamples of current drug users. Only studies evaluating access to HAART among active DU as a primary outcome and conducted after January 1997 were included. Active drug users were defined as those who have used any illicit drug (except cannabis) over the last six months. Only studies conducting multivariate analysis were selected in order to control for confounding factors, something key in studies dealing with complex psychosocial phenomena, such as addiction and HIV/AIDS treatment access. Studies were excluded if they were based exclusively on qualitative data; were reviews themselves or assessed other populations without disaggregating active drugs users from the overall sample. Studies addressing exclusively alcohol users and/or cannabis smokers were not included.

Data Search

Search terms that reflect HAART access were identified. Searches combined these terms with Medical Subject Headings (MeSH) for HIV and active drug abuse. MEDLINE via PubMed and Web of Science were searched from 1996 to October 31, 2013. We also reviewed the citation lists of included studies to identify additional eligible references.

Study Selection

Using a predefined protocol (available from the corresponding author on request), two investigators (M.M., M.R.C.)

extracted the full text of peer-reviewed papers addressing access to HAART among HIV-positive active DU and assessed their eligibility independently. After all potentially relevant peer-reviewed papers were identified, the two investigators met to achieve consensus.

Data Extraction

Data extraction was conducted using a standardized form. Data abstractors collected information about the country where the study was conducted, characteristics of the sample (e.g. age, sex, ethnicity), sample size, study design and access to HAART, as well as treatment outcomes such as viral load and CD4 count, when available.

Results

From the initial searches, 122 peer-reviewed papers were identified. Of these, there was close to perfect agreement between reviewers on the eligibility of 42 papers: 49 did not evaluate HAART access among active drug users, whereas 27 were reviews and four qualitative studies. In a second screening, 21 studies were excluded because of their exclusive use of biological markers as outcomes (i.e. HIV-1 viral load and/or CD4 cell counts). Agreement between reviewers was perfect on the second screening. A third screening excluded seven studies: two presenting repeated data, two conducted before the availability of HAART and three without multivariate analysis. Agreement on the last screening was also perfect. We thus included 14 eligible reports for full data extraction (Fig. 1).

Characteristics of selected studies are summarized in Table 1. In spite of searching for papers published in different languages, all studies identified were published in English and the vast majority were conducted in developed countries (13 of 14). The majority was conducted in North America (six in the United States, five in Canada). One study was conducted in Spain, one in France and one in Ukraine. All selected studies were prospective cohorts and included young adults.

Main results and variables associated with HAART access are presented in Table 2. Each study measured HAART access (or lack of access) using a different strategy, therefore we were unable to present comparisons across studies.

A high percentage of HIV-positive active drug users had never received HIV treatment before the study [24] or received late HIV-diagnosis, therefore initiating HAART at more advanced stages of HIV-infection [25]. Westergaard and colleagues [24] evaluated 790 participants of the AIDS Linked to the Intravenous Experience (ALIVE) study from 1998 through 2011. Authors identified that 93.6 % of study participants were ever linked to care, while 76.7 % had ever received HAART. However, among those only 30.5 % were continuously retained with no 6-month lapses in HIV care and only 10.2 % had sustained viral suppression at every study visit after first receiving HAART. Patients who had lapses in care (gap greater than 6 months without an HIV care visit) were more likely to be active PWID (AOR=1.25; 95 %CI:1.06-1.49) and more likely to be incarcerated in the past 6 months (AOR=1.49; 95 %CI:1.09-2.03). When Westergaard and colleagues [24] evaluated healthcare access variables, the strongest predictor of avoiding lapses in HIV-care was having a regular source of primary care (AOR=0.29; 95 %CI:0.17-0.49), followed by having the same provider at >90 % of visits (AOR=0.40; 95 %CI:0.29-0.56) and having health insurance (AOR=0.68; 95 %CI:0.52-0.90).

Rodríguez-Arenas et al. [26] evaluated a multicentre hospital-based cohort of HIV-infected patients attending ten hospitals in Spain, including 2621 PWID - 56.4 % of their participants. PWID had a 33 % lower probability of HAART initiation, when compared to MSM. According to authors fear of less than optimal adherence of active drug users, health professionals' inexperience and misconceptions influence treatment delay are key predictors of late entry into ARV treatment - some physicians delay HAART treatment until the patient was able to 'control his/her addiction'.

A multisite study conducted with 970 HIV-positive participants in the US (71.8 % active drug users), identified that across all types and patterns of drug use, active drug users were more likely to have suboptimal ambulatory care, miss scheduled appointments, use the emergency department, have unmet support services needs, and, as a direct consequence, were less likely to receive HAART once eligible [27].

Inadequate HAART prescription and less than optimal HIV monitoring are also faced by HIV-positive active drug users. Wood and colleagues [28] evaluated a cohort of HIV-positive PWID from British Columbia, a setting providing all medical care free of charge — including HIV-treatment. The authors identified that less than 5 % of HIV-positive active PWID under follow-up had CD4 monitoring consistent with local therapeutic guidelines, while around 20 % received inappropriate antiretroviral prescription.

An innovative study was conducted by Carrieri and colleagues [29]. Researchers evaluated 123 drug users enrolled on the cohort study MANIF, comparing three groups: (1) former PWID, perceived as such (i.e. abstinent patients) by physicians; (2) active PWID not perceived as such by physicians; and (3) active PWID perceived as such (i.e. active drug users) by physicians. According to the study, physicians clearly distinguish PWUDs that they identify as such as "less adherent" patients. However, physicians' perceptions contrast with patients' higher self-reported adherence and lower satisfaction with medical staff — active PWID perceived as such by physicians were the less satisfied. The authors did not actually

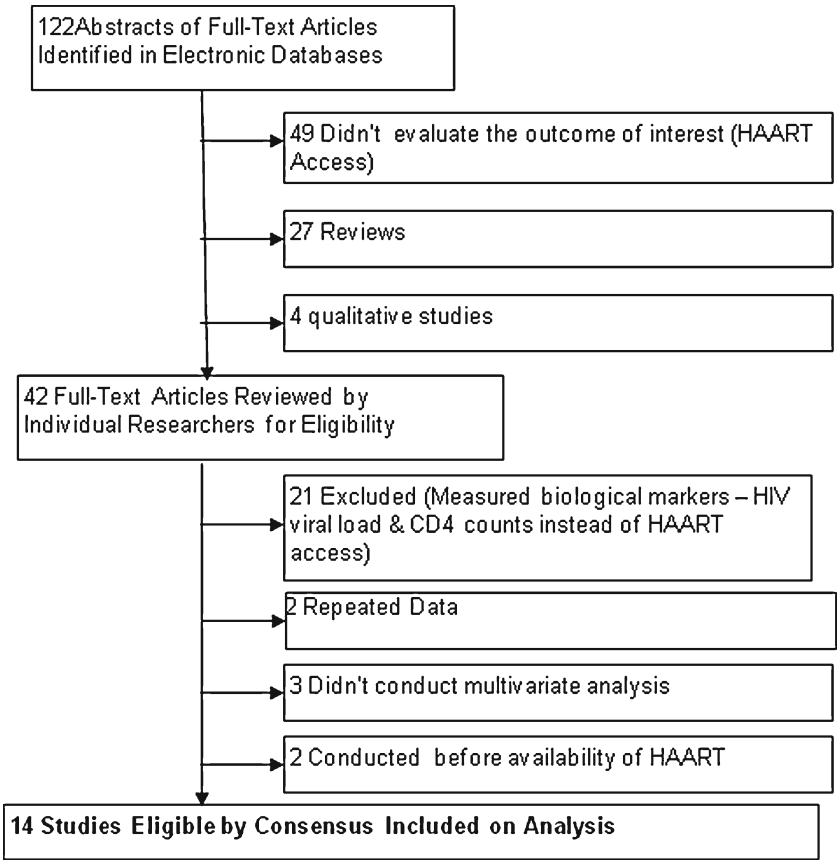

Fig. 1 Flow Diagram of Studies Included in Analysis of HAART Access

measure stigma and prejudice in the context of patient/provider relationship. However, those variables could be interpreted as *proxy* of a differential treatment offered to patients *perceived as* abstinent, when compared to those *perceived as* active drug users. Physicians have a major role on HAART access — Strathdee et al. [30] identified that physicians with the least experience were 5.5 times less likely to prescribe HAART for active drug users.

Lack of access to primary care services and frequent experiences of stigma/prejudice within health services, as well as unstable housing and lack of health insurance usually prompt active drug users to rely on emergency department as their first health service option [27, 31]. Although factors other than HIV infection also drive emergency department use (e.g. skin and soft tissue infections), the identification of emergency department as the first option for HIV-positive active drug users, usually in need of specialized care, is of great concern in terms of both unreliable provision of care over time and less than optimal use of health services and systems.

According to Fairbairn and colleagues [31], stable living environment facilitate patients ability to stay connected with a primary care service and seek care earlier on disease progression, therefore reducing the use of emergency departments and hospitalizations. The authors suggest that emergency departments should have a better link with specialized services offering infectious disease treatment, mental health and social support strategies.

Strathdee et al. [30] identified a three-fold increased odds for PWID not enrolled in alcohol and/or drug addiction treatment to not receive HAART among those eligible. Arasteh and Des Jarlais [32] also identified increased likelihood of receiving HAART among patients engaged in substance use treatment. An important venue for improving access to HAART is methadone maintenance therapy (MMT), which has been shown to improve access and also adherence to HIV-treatment. Uhlmann et al. [33] conducted a study with 231 antiretroviral-naive HIV-infected opioid-using, identifying that participants on MMT initiated HAART at a significantly elevated rate (RH=1.62; p=0.006). Tapp et al. [34] identified more than two-fold increased odds of those on MMT to receive and reach≥95 % adherence to HAART (AOR=2.35, 95 % CI: 1.88-2.94, p-value<0.001). MMT has also been associated with more regular monitoring of CD4+ cell counts, an important factor in timing ART initiation [28].

Celentano et al. [25] showed that men enrolled in MMT were 80 % more likely to start HAART, while this effect was not observed among women. More than two-fold increased odds of not receiving HAART among women were also identified by Strathdee et al. [30]. Researchers from the British Columbia Centre for Excellence in HIV/AIDS also

Table 1 Characteristics of selected studies, 1998-2013

Source	N	Country	Design (period)	Characteristics of study population			
				Population (%)	Age, y (range)	Female (%)	Ethnicity (%)
Westergaard et al. [24]	790	United States	Prospective cohort study (1998-2011)	Current PWID: 486 (61.5)	43.4 (38-50)	260 (33.0)	African American 737 (93.3) Never linked to HIV care: 46 (5.8) Linked but not fully retained in care: 468 (59.2) Fully retained: 223 (28.2)
Celentano et al. [25]	528	United States	Prospective cohort study (1996-1999)	Current PWID: 528 (100.0)	NA	NA	NA
Rodriguez-Arenas et al. [26]	4643	Spain	Hospital-based prospective cohort (1997-2003)	Current PWID: 2621 (56.4)	35 (31-39)	1252 (27.0)	NA
Sohler et al. [27]	970	United States	Prospective cohort study (2003-2005)	Current PWID: 697 (71.8)	42.1 (±8.8)	340 (35.0)	Black: 506 (52.3) Latino: 234 (24.2) White: 161 (16.6) Other: 67 (6.9)
Wood et al. [28]	460	Canada	Prospective cohort study (1996-2004)	Current PWID: 460 (100.0)	34.0 (28-40)	198 (43.0)	White: 245 (53.3) Aboriginal Ethnicity: 171 (37.2) Asian: 17 (3.7) Black; 10 (2.1) Others: 17 (3.6)
Carrieri et al. [29]	123	France	Prospective cohort study (1995-1996)	Current PWID: 55 (44.7)	Former PWID: 32 y(30-36) Active PWID undetected by physicians: 33 y(30-36) Active PWID detected by physicians: 34 y(30-37)	40 (32.5)	NA
Strathdee et al. [30]	177	Canada	Prospective cohort study (1996-1997)	Current PWID: 177 (100.0)	PWID not on HAART: 33y (27-40) PWID on HAART: 36y (31-41)	69 (39.0)	Aboriginal Ethnicity: 47 (26.5)
Fairbairn et al. [31]	428	Canada	Prospective cohort study (2005-2008)	Current PWID: 428 (100.0)	41.0 (36.0-47.0)	170 (39.7)	Aboriginal Ethnicity: 178 (41.6)
Arasteh & Des Jarlais [32]	643	United States	Prospective cohort study (1997-2002)	Current PWID: 643 (100.0)	Recruited by MMP: 41 (NA) Recruited by Detox Program: 40 (NA)	147 (22.8)	White: 104 (16.2) Black: 224 (34.8) Hispanic: 315 (49.0)
Uhlmann et al. [33]	231	Canada	Prospective cohort study (1996-2008)	Current PWID: 231 (100.0)	> 24 y: 213 (92.2)	95 (41.1)	Aboriginal Ethnicity: 78 (33.7)
Tapp et al. [34]	548	Canada	Prospective cohort study (1996-2008)	Current PWID: 548 (100.0)	≥ 24 y Male: 332 (97 %) Female: 179 (88 %)	204 (37.2)	Aboriginal Ethnicity: 185 (33.7)
Gardner et al. [35]	273	United States	Prospective cohort study (1995-1999)	Current PWID: 57 (20.8)	18-29y: 13 (4.8) 30-44y: 188 (68.9) ≥45 y: 72 (26.4)	273 (100.0)	NA
Rompalo et al. [36]	579	United States	Prospective cohort study (1996-1997)	Current PWID: 299 (51.6)	< 38y: 283 (48.9) ≥ 38y: 296 (51.1)	579 (100.0)	African Americans: 349 (60.3) White: 127 (21.9) Latino (95 (16.4) Native Americans: 8 (1.4)
Thorne et al. [37]	6,200	Ukraine	Prospective cohort study (2000-2010)	Current PWID: 1111 (17.9)	PWID 28.1 (24.6 - 31.8) Non-PWID 25.5 (22.4 - 29.5)	6,200 (100.0)	White: 6,200 (100.0)

Abbreviations: PWID: people who inject drugs; MMT: methadone maintenance therapy; NA: not available

Table 2 Threshold of measurement, percent who accessed HAART and variables associated with HAART access of selected studies, 1998-2013

Source	Measurement of HIV-treatment access	period of measurement	accessed HAART (%)	Variables associated with HAART access
Westergaard et al. [24]	Partially retained: reported at least one lapse in HIV-care Fully retained: attended HIV-care at every semi annual assessment	6-month interval	81.6 % of eligible participants received HAART Among PWID eligible to HAART: 6.3 % never linked to HIV-care 63.2 % partially retained into HIV-care 30.5 % fully retained into HIV-care	Factors associated with HIV-lapses in care: Sociobehavioral variables Active injection drug use AOR=1.25; 95 %CI:1.06-1.49 Recent incarceration AOR=1.49; 95 %CI:1.09-2.03 Healthcare access variables Had health Insurance AOR=0.68; 95 %CI:0.52-0.90 Had usual source of primary care AOR=0.29; 95 %CI:0.17-0.49 Same provider at >90 % of clinic visits AOR=0.40; 95 %CI:0.29-0.56
Celentano et al. [25]	Time from treatment eligibility to first self-reported HAART use	6-month interval	33.7 % of eligible PWID received HAART during follow up	Current injection drug use: RH:0.42; 95 %CI:0.28-0.63 MMT: 1.78; 95 %CI:1.14-2.76 Health Insurance: HR:2.05; 95 %CI:1.21-3.49 Regular source of care: HR:1.74; 95 %CI:1.01-3.00 Received ART before 1996: HR:2.29; 95 %CI:1.57-3.35
Rodriguez-Arenas et al. [26]	Participants receiving HAART prior to study entry Participants who started HAART during follow-up	Two years	HAART prevalence at study entry: PWID: 655 (24.9 %) MSM: 237 (35.4 %) HAART incidence per 100py: PWID: 39.4 MSM: 74.3	Probability of initiating HAART during follow-up, antiretroviral naive patients: PWID: HR: 0.67; 95 %CI: 0.57-0.79 Probability of initiating HAART during follow-up, antiretroviral naive patients with CD4 count <200 cells/μL at study entry: PWID: HR:0.64; 95 %CI:0.57-0.71
Sohler et al. [27]	Number of ambulatory primary care visits Number of missed appointments Emergency room use	6-month interval	Have a regular HIV care provider: 833 (92.1 %) Had fewer than two ambulatory visits: 326 (33.9 %) Missed at least one appointment: 402 (44.8 %) Used ED instead of HIV service: 342 (35.4 %) Had unmet support service need: 617 (63.6 %)	Current drug users: Missed at least one appointment: AOR=2.93;95 %CI: 2.04-4.22 Used ED instead of HIV-specialized care: AOR=2.24; 95 %CI:1.37-3.66 Received HAART: AOR=0.19; 95 %CI:0.06-0.55 Had unmet support service need: AOR=1.81; 95 %CI: 1.00-3.29
Wood et al. [28]	Proportion of participants on HAART	6-month interval	Access to HAART at baseline: 99 (22.0 %) Access do HAART during study period: 299 (66.4 %)	Factors associated with HAART access and continuous CD4 monitoring: Female: AOR=0.71; 95 %CI: 0.57-0.89, p=0.003

Table 2 (continued)

Source	Measurement of HIV-treatment access	period of measurement	accessed HAART (%)	Variables associated with HAART access
	Proportion of participants who had CD4 test during study period		Had CD4 test during study period: 334 (72.6 %)	Non-white: AOR=0.75; 95 %CI:0.60-0.94, p=0.014 MMT: AOR=1.66; 95 %CI:1.42-1.94, p,0.001 Daily heroin use: AOR=0.72; 95 %CI:0.61-0.85, p<0.001
Carrieri et al. [29]	Current HAART use according to physician perception of patients' drug use	6-month interval	43.9 % of eligible PWID received HAART during follow-up	Former PWID were more likely to receive HAART during follow-up than: Active PWID *undetected* by physicians AOR=0.36; 95 %CI:0.15-0.85 Active PWID *detected* by physicians AOR=0.26; 95 %CI:0.08-0.87
Strathdee et al. [30]	HAART use after eligibility	1 year interval	40.1 % of eligible PWID received HAART during follow-up	Factors associated with not receiving HAART among eligible PWID: Female less likely to receive HAART: AOR=2.53; 95 %CI:1.08-5.93 PWID not enrolled in drug/alcohol treatment less likely to receive HAART: AOR=3.49; 95 %CI:1.45-8.40 Participants treated by physicians with low HIV-experience (treating 4 or less HIV-patients): AOR=5.55; 95 %CI:2.49-12.37
Fairbairn et al. [31]	Visits do ED instead of HIV-specialized service	1 year interval	63.7 % of participants accessed ED instead of HIV-specialized service Among those, participants with unstable housing were more likely to access ED (69.2 % vs. 50.5 %)	Factors associated with visits to emergency care unit, instead of HIV-specialized care: Unstable housing RH =1.47; 95 %CI:1.11–1.96 (p=0.007) Inability to access needed health services RH=2.24; 95 %CI:1.22–4.12 (p=0.01)
Arasteh & Des Jarlais [32]	Participants receiving HAART prior to interview	6-month interval	Received HAART prior to interview: 94 (14.6 %) Access to HAART during follow-up, according to addiction treatment Detox Program: 43 (12.2 %) MMT: 51 (17.5 %)	At risk drinkers who use crack-cocaine: AOR=3.61; 95 %CI: 1.56-8.35, p<0.01 Daily injectors (vs. less than daily injectors): AOR=1.72; 95 %CI:1.05-2.81, p<0.05
Uhlmann et al.[33]	Time to first HAART use	6-month interval	24 months after recruitment: Initiated HAART :152 (65.8 %) Participants on MMT: 64.2 % Participants not on MMT: 44.8 %	Access to HAART, 24 months after recruitment Participants on MMT AOR=1.62; 95 %CI:1.15-2.28, p=0.006
Tapp et al. [34]	Proportion of participants on HAART in the 6-month period preceding semi-annual visits	6-month interval	Participants who were on HAART 6-months prior to baseline interview: Men: 133 (39 %) women: 62 (30 %)	Factors associated with access and≥95 % adherence to HAART: MMT: AOR=2.35; 95 %CI:1.88-2.94, p<0.001

Table 2 (continued)

Source	Measurement of HIV-treatment access	period of measurement	accessed HAART (%)	Variables associated with HAART access
	Participants who accessed and reached ≥95 % adherence to HAART			Female: AOR=0.70; 95 %CI:0.53-0.93, p=0.013
Gardner et al. [35]	Participants attending HIV-specialist care Participants receiving HAART	6-month interval	14.6 % of PWID with <500 CD4 cells received HAART Among those: 13.9 % under care of HIV specialist 16.7 % without care of HIV specialist	Probability of receive HIV-specialist care No health insurance: AOR=0.14; 95 %CI: 0.04-0.5 PWID: AOR=0.4; 95 %CI:0.1-0.95 Depression: AOR=2.8; 95 %CI:1.3-6.2
Rompalo et al. [36]	HAART use in the previous 6 months	6-month interval	55.2 % of eligible PWID received HAART in previous 6 months	PWID less likely to receive HAART: AOR=0.54; 95 %CI:0.38-0.79 (p<0.001) PWID less likely to receive NRTIs: AOR=0.55; 95 %CI:0.38-0.79 (p ≤0.05)
Thorne et al. [37]	Prevention of mother to child transmission of HIV (PMTCT) Mother to child transmission rates (MTCT)	6-months after delivery	Didn't received PMTCT: PWID: 12.2 % non-PWID: 4.7 % Received only sdNVP PWID: 26.6 % non-PWID: 9.4 % Received ZDV and sdNVP PWID: 24.8 % non-PWID: 44.7 % received ZDV: PWID: 20.1 % non-PWID: 23.2 % Received HAART PWID: 16.4 % non-PWID: 18.0 %	Didn't receive PMTCT: Current PWID: AOR=2.75, p<0.001 Former PWID: AOR=1.97, p<0.001 Mother-to-child transmission of HIV: Current PWID: AOR=2.43, p<0.001 Former PWID: AOR=1.75, p<0.001

Abbreviations: PMTCT: prevention of mother to child transmission of HIV, HAART: highly active antiretroviral therapy, sdNVP: single-dose nevirapine, ZDV: zidovudine, PWID: people who inject drugs, ED: Emergency Department, py: persons-year, HR: hazard-ratio, CI: confidence interval, AOR: adjusted odds ratio, MMT: methadone maintenance therapy, ART: antiretroviral therapy; NRTIs: Nucleoside analog reverse transcriptase inhibitors

identified lower access to HAART among women [28, 34]. The studies conducted by Gardner et al. [35] and Rompalo et al. [36] showed that women who are currently PWID have fewer indications to start HAART, regardless of using HIV specialist care or not.

A study conducted in Ukraine with 6200 HIV-positive pregnant women [37] identified important challenges faced by female PWID. According to Thorne and colleagues [37], late diagnosis is higher among female PWID: 20 % of new infections were diagnosed intrapartum versus 4 % among non-PWUDs (P<0.01). PWUDs also had higher rates of preterm delivery and low birth weight: 16 % vs. 7 %; 22 % vs. 10 % (P< 0.001]). PWUDs had nearly three-fold higher odds to receive no neonatal or intrapartum prophylaxis compared with non-PWUDs (OR 2.81, p<0.001). Mother to child transmission rates were 10.8 % in PWUDs versus 5.9 % in non-PWUDs; and fewer PWUDs with treatment indications received HAART compared with non-PWUDs (58 % versus 68 %, P=0.03).

Discussion

Conclusion

Most studies discussed how social and/or structural exposures interact with individual characteristics and behaviours to determine lower access to HAART among HIV-positive active drug users, compared to other populations. According to selected studies, key aspects that might jeopardize this population engagement into HAART are related to the characteristics and operations of health services: limited access to primary care and physicians' stigma/prejudice towards drug users. According to Wolfe [13, pg. 251]: *"often IDUs are required to meet the needs of health care systems, and rarely the reverse is true"*. Strathdee et al. [14] also state that it is urgent to integrate HIV and addiction treatment with prevention strategies such as voluntary counseling and testing and needle exchange programs. Greater and better communication between health care providers and their clientele is pivotal, as well as tailoring medical and psychological procedures and services' characteristics to the special needs of people who misuse drugs/are drug-dependent.

The provision of timely HIV diagnosis and HAART for HIV-positive active drug users is far from impossible, but it calls for a shift in the social framing of patients who are current or former drug users. One should not minimize the challenges of working with active drug users or the multiple needs of those patients, frequently co-infected with hepatitis C or tuberculosis, usually struggling with psychiatric comorbidities and severe social exclusion. It is necessary to provide proper counseling, treatment and care, while trying to distinguish between the needs of former and current drug users, in order to improve treatment efforts and conduct timely referrals. According to Wolfe [13], greater obstacles to provide adequate treatment and care to HIV-positive drug users are not in individual behaviours and socio-demographic characteristics, but rely mostly in unfriendly health services that usually blame and segregate those most in need of care. According to Strathdee et al. [14, pg. 323]: *"Most of all, we need to overcome addictophobia, which manifests as the desire to refer drug users somewhere else, anywhere else, or to deny them access to life-saving interventions 'for their own good.'"*

HIV-positive active drug users who have been incarcerated, homelessness or with unstable housing were also identified as those facing greater hurdles and difficulties to access HAART. Unstable living conditions are very frequent among active drug users, and might be associated with suboptimal HIV-treatment outcomes. Different contextual dimensions of homelessness, such as food insecurity and lack of space to store medication, as well as the need to prioritize immediate survival over HIV-treatment might also influence HAART initiation and adherence to treatment among this population. Milloy et al. [38] indicate that additional social support interventions (e.g. referral to services providing low-barrier housing alternatives and/or strategies addressing food insecurity) have been shown to increase HAART access, adherence, retention, as well as viral load suppression. A few studies have shown female drug users face additional barriers to engage in HIV-treatment and care, therefore gender-specific interventions should be implemented to address unique barriers such as domestic violence, adequate and timely prenatal care (including comprehensive prevention of mother to child HIV transmission), family planning, fertility desire, among others.

Access to drug addiction treatment was identified as an important facilitator to HAART access in several studies, and MMT contributes to more rapid HAART initiation HAART among opioid-dependent individuals. MMT is a key strategy to address the specific needs of this population, and could be a very effective 'entrance door' for different programs and services. MMT (as well as other low-threshold addiction treatment alternatives) allows regular contact of HIV-positive drug users with health professionals and may allow the health team to offer directly observed therapy for HIV and tuberculosis, among other medical and psychological interventions. Enrollment in MMT or other user-friendly addiction treatment modalities can also mitigate previous negative experiences of stigma and prejudice with health care providers.

This review has a few limitations. We aimed to reduce reviewer bias by conducting abstraction independently, in parallel. However, we did not conduct our review on the so-called 'gray literature' (e.g. non-peer reviewed manuscripts), and therefore publication bias could not be avoided. Qualitative studies were not included in our analysis, but those might bring additional understanding to the complex interplay of drug addiction, HIV, social and contextual factors, and HAART access. Different interpretations of how to measure

HAART access made between-study comparisons difficult. We identified only one study conducted in developing countries, making it difficult to generalize our findings to those settings. Finally, our review relied upon the information reported in peer-reviewed scientific publications, all published in English. Therefore, these findings are unlikely to represent the treatment experience of a high proportion of HIV-positive PWUDs living in other contexts, such as Russia and eastern Europe, where the HIV epidemic is driven mainly by drug-using populations and access to HAART is uneven [13, 14].

HAART has transformed the nature of HIV/AIDS from an imminent death sentence to a chronic, manageable condition. There is also a growing interest in the potential impact of "treatment as prevention" ─ a notion that expanded coverage with HAART would substantially reduce HIV transmission at the population level. However, late diagnosis and, even more serious, late entry into HAART for eligible patients may compromise and even nullify this putative benefit. Patients who start HAART at more advanced disease stages are more likely to experience HIV-related morbidity and untimely mortality. Optimal timing for HAART initiation is a key strategy for both the individual patient and affected communities. In the absence of a vaccine and cure for HIV, undiagnosed HIV cases and untreated patients represent the biggest challenge in the fight against HIV/AIDS to be fully addressed in the efforts to have an actual AIDS-free generation in the near future.

Degenhardt et al. [39] summarize findings from modeling scenarios about the effect of increased HIV-treatment coverage combined with HIV-prevention interventions targeting PWUDs. The authors showed that when simultaneous scale-up of needle and syringe programs, voluntary counseling and testing, MMT and HAART were implemented, targeting HIV-positive PWID with CD4 cell counts<350, HIV incidence could be reduced by up to 63 % within this population. Strathdee and colleagues [14, pg.324] reinforce those findings and state that *"providing combination HIV-prevention to IDUs under one umbrella, in a point-of-care, one-stop venue that addresses their myriad needs may seem like a Holy Grail, but it is ultimately what substance users need and is likely to be cost-effective."*

More strong political commitments to universal access to HIV-treatment for PWUDs are clearly needed, as well as approaches based on human rights protection which help fight against stigma and discrimination [40]. Future research and interventions targeting PWUDs should also consider broader social and environmental factors that influence lower treatment access, higher morbidity and mortality among HIV-positive PWUDs [41].

Compliance with Ethics Guidelines

Conflict of Interest Michelle Ralil da Costa declare that she has no conflict of interest.

Francisco Inácio Bastos has received travel/accommodations expenses covered or reimbursed as a reserach for Imperial College, UK (May-July 2013), sponsored by Brazilian agency for postgraduate studies (CAPES). Monica Malta received support from CAPES (grant 0060/2013) and CNPq (PAPES VI, grant 407780/2012-2).

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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