Addiction

REVIEW

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Adherence to antiretroviral therapy for human immunodeficiency virus/acquired immune deficiency syndrome among drug users: a systematic review

Monica Malta[1], Steffanie A. Strathdee[2], Monica M. F. Magnanini[3] & Francisco I. Bastos[4]

Social Science Department, Sergio Arouca School of Public Health (DCS/ENSP), Oswaldo Cruz Foundation, Rio de Janeiro, Brazil,[1] Division of International Health and Cross Cultural Medicine, Department of Family and Preventive Medicine at University of California, San Diego (UCSD) School of Medicine, San Diego, CA, USA,[2] Institute of Public Health Studies, Federal University of Rio de Janeiro (IESC/UFRJ), Rio de Janeiro, Brazil[3] and Health Information Department, Center for Scientific and Technological Information (DIS/CICT), Oswaldo Cruz Foundation, Rio de Janeiro, Brazil[4]

ABSTRACT

Aims Adherence to highly active antiretroviral therapy (HAART) is a key predictor of survival for human immunodeficiency virus (HIV)-infected people. Suboptimal adherence among marginalized populations such as HIV-positive drug users could be associated with clinical failure and the emergence of viral resistance. **Objective** To conduct a systematic review of studies assessing adherence to HAART among HIV-positive drug users (DU) and identify factors associated with non-adherence to HIV treatment. **Data sources** Seven electronic databases were searched for peer-reviewed papers published in English, French, Spanish or Portuguese, from 1996 to 2007. **Study selection and data abstraction** Studies were excluded if they presented only qualitative data, were reviews themselves or assessed other populations without disaggregating data on DU. Findings on adherence were extracted and summarized. **Data synthesis** Forty-one studies were considered, which studied a total of 15 194 patients, the majority of whom were HIV-positive DU ($n = 11\ 628$, 76.5%). Twenty-two studies assessed adherence using patient self-reports, eight used pharmacy records, three used electronic monitoring [i.e. Medication Event Monitoring Systems (MEMS) caps], six studies used a combination of patient self-report, clinical data and MEMS-caps, and two analyzed secondary data. Overall, active substance use was associated with poor adherence, as well as depression and low social support. Higher adherence was found in patents receiving care in structured settings (e.g. directly observed therapy) and/or drug addiction treatment (especially substitution therapy). **Conclusion** While lower than other populations—especially among users of stimulants, incarcerated DU and patients with psychiatric comorbidities—adherence to HAART among HIV-positive DU can be achieved. Better adherence was identified among those engaged in comprehensive services providing HIV and addiction treatment with psychosocial support.

Keywords Adherence, antiretroviral therapy, AIDS, drug use, HAART, HIV, methadone maintenance therapy, psychosocial support, systematic review.

Correspondence to: Monica Malta, Oswaldo Cruz Foundation, Rua Leopoldo Bulhoes, 1480—Room 905, Manguinhos, Rio de Janeiro, RJ 21041-210, Brazil. E-mail: momalta@cict.fiocruz.br

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INTRODUCTION

Highly active antiretroviral therapy (HAART) has improved the health and quality of life of people living with human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS) (PLWHA) since its introduction in 1996/7. Treatment efficacy relies, however, upon sustained adherence, which constitutes a challenge [1,2]. Most regimens are complex, with varying dosing schedules and dietary restrictions, and may cause serious adverse effects [3]. While some of the recent regimens have decreased pill burden and alleviated these problems, adherence is required for reliable viral suppression [4,5] and prevention of the emergence of resistant viruses [6], disease progression [7] and death [8].

Disparities in HIV-related mortality have been observed due to problems with access to HAART and/or poor retention in HIV-related treatment, particularly among disadvantaged or marginalized populations [9].

Historically, HIV-positive drug users (DU) have not only had suboptimal access to HAART [10,11], but tend to initiate HAART at more advanced stages of infection [12,13]. This raises concern, as injection drug use is a major vector for HIV/AIDS transmission in seven of 10 regions around the world [14]. Non-injecting DU are also at high risk for HIV infection due to high-risk sexual behaviors [15,16].

Some providers prescribing HAART to DU have been concerned that clinical improvement may lead to behavioral relapse, and that suboptimal adherence may favor the emergence of viral resistance and the transmission of drug-resistant HIV strains [17–19]. Beyond adherence, other factors such as pre-existing mutations and incorrectly prescribed drugs might influence both viral load reduction and/or the reconstitution of the immune system [20].

While some studies have found that adherence to HIV medication is lower among current drug users [11], or that adherence declines in periods of relapse [21], other studies have found that HIV-positive drug users who have access to drug abuse and mental health treatment, and particularly former drug users who are abstinent, can reach the same levels of adherence found among PLWHA who have never used illicit drugs [22]. However, the specific barriers that might jeopardize HIV-positive drug users' adherence to HAART remain to be elucidated further. Are concerns of poor adherence to HAART among DU justified? To the best of our knowledge, no review has summarized the growing body of research on this topic. We conducted a systematic review of available data on HAART adherence among HIV-positive DU, and identified barriers and promoters associated with non-adherence among these studies.

METHODS

Inclusion and exclusion criteria

Only studies assessing adherence to HAART among DU as a primary outcome were included. Drug users were defined as those who have used any illicit drug (except cannabis) over the last 12 months. Studies had to have reported a given threshold/cut-off defining optimal adherence (e.g. 90% or 95%) and include multivariate analyses assessing correlates of adherence. 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 adherence.

Studies were excluded if they were based exclusively on qualitative data (due to the fact that we aimed to carry out both a systematic review and a meta-analysis); were reviews themselves; were not published in English, Spanish or Portuguese; or assessed other populations without disaggregating DU from the overall sample. DU were defined herein as users of heroin, cocaine/crack or methamphetamine. Studies addressing exclusively alcohol users and/or cannabis smokers were not included.

Data search

Search terms that reflect adherence (e.g. adherence, compliance, pill counts) or specific equipment used to measure adherence (e.g. Medication Event Monitoring Systems [MEMS-caps] an electronic adherence monitoring system that uses a microchip in the prescription bottle-cap) were identified. Searches combined these terms with Medical Subject Headings (MeSH) for HIV and drug abuse. MEDLINE via PubMed, Cochrane CENTRAL, AIDSLINE, AMED, CINAHL, TOXNET, SciELO and Web of Science were searched from 1996 to 29 February 2008, except for AIDSLINE, which was searched from 1996 to 2000, when the inclusion of new citations was discontinued.

Study selection

Using a predefined protocol (available from the corresponding author on request), two investigators (M.M., F.I.B.) extracted the full text of peer-reviewed papers addressing adherence among HIV-positive 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 (age, sex, ethnicity), sample size, study design and measures of adherence, as well as other treatment outcomes such as viral load and CD4 count, when available. When more than one adherence measurement was used (e.g. MEMs cap and patient's self-report), data from all methods were collected and compared.

RESULTS

From the initial searches, 219 peer-reviewed papers were identified. Of these, there was perfect agreement between reviewers on the eligibility of 69 papers, with 150 papers not meeting the study inclusion criteria. In a second screening, 13 studies were excluded because of their exclusive use of biological markers as outcomes (i.e. HIV-1 viral load and/or CD4 cell counts), instead of measuring adherence itself. Agreement between reviewers

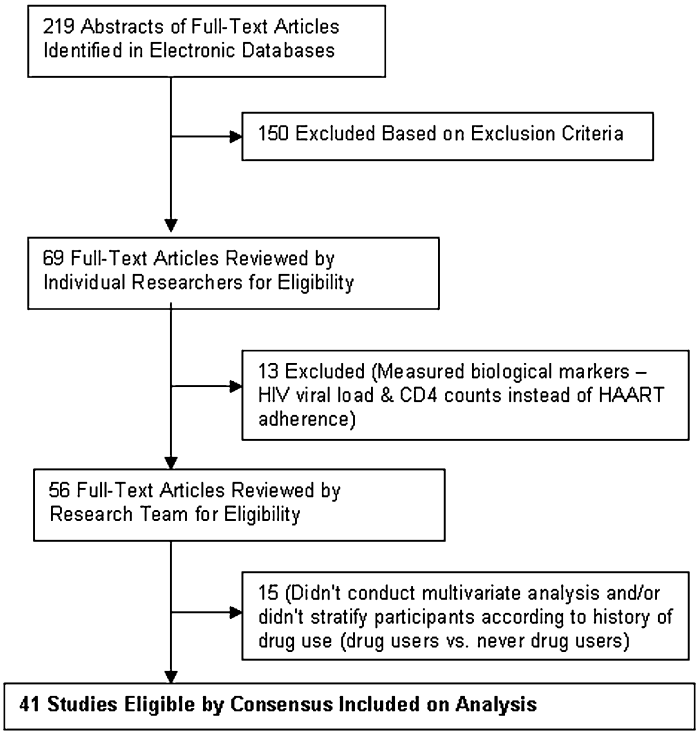

Figure 1 Flow diagram of studies included in analysis

was also perfect on the second screening. A third screening excluded 15 studies, primarily because authors did not stratify results according to drug use status. Agreement on the last screening was close to perfect. We thus included 41 eligible reports for full data extraction (Fig. 1).

Study characteristics

Forty-one studies were considered, which studied a total of 15 194 patients, the majority of whom were HIV-positive DU ($n = 11\,628$, 76.5%). Characteristics of the 41 selected studies are summarized in Table 1. In spite of searching for papers published in different languages, almost all studies identified were published in English (40 of 41). All were conducted in developed countries—the vast majority in North America (22 in the United States, eight in Canada), and 11 in Europe (six in France, three in Spain, one in Italy and one in Ireland).

Two studies used secondary data from the US Medicaid Program [22,23]. In New York, Turner and colleagues [23] had the largest sample among all selected studies ($n = 5103$). Crystal and colleagues [22] used data from the New Jersey Medicaid Program and evaluated 1048 patients. Both studies were evaluated separately to avoid bias due to Type 2 errors. All other selected studies assessed primary data: 24 were longitudinal, four were randomized controlled trials and 11 were cross-sectional. The vast majority of selected studies evaluated HIV-positive injection drug users (IDU) and a few addressed a subsample of non-injecting drug users (Table 1).

Optimal adherence cut-offs

Twenty-two studies assessed adherence using patient self-reports, eight used pharmacy records on prescription refill compliance and three used MEMS-caps. Six studies used a combination of patient self-report, clinical data and MEMS-caps, and two analyzed secondary data.

Main results and adherence cut-offs adopted by selected studies are presented in Table 2. Eleven (26.8%) studies defined optimal adherence as 100% uptake of the prescribed doses. Eight studies (19.5%) assessed optimal adherence as greater than 95%, three as greater than 90%, eight as greater than 80%, and one study as greater than 75%. One study used two different cut-offs (90% and 100%). Three studies using MEMS-caps evaluated adherence as a continuous variable, and six studies used a combination of adherence measurements (e.g. self-report and pharmacy records).

Adherence was measured across various time-periods, ranging from the previous day to the last 2.5 years. However, the majority of selected studies evaluated adherence using a time-frame which included the previous day up to the previous 15 days (19 studies; 46.3%); three studies evaluated adherence over a period of 1–2 months, and two studies used a 4–6-month time-frame. A few studies used an extended time-frame: 10 studies assessed adherence for a 1 year period, one study evaluated adherence over 2.5 years, three studies used a com-

Table 1 Characteristics of selected studies, 1999–2007.

				Characteristics of study population			
Source	*n*	*Country*	*Design (period)*	*Population (%)*	*Age, years (range)*	*Female (%)*	*Ethnicity (%)*
Arnsten *et al.* 2007	636	United States	RCT (2001–03)	IDU (100.0)	>40 years: 63.0%	223 (35.0)	Non-Hispanic white: 43 (7.0) Non-Hispanic black: 412 (66.0) Hispanic: 124 (20.0) Non-Hispanic other: 42 (7.0)
Hinkin *et al.* 2007	150	United States	Prospective cohort study (2001–05)	Current IDU: 102 (68.0)	41.3 (18–61)	26 (17.3)	African American 94 (62.6) White: 22 (14.6) Hispanic: 21 (14.0)
Palepu *et al.* 2006	278	Canada	Prospective cohort study (1996–2003)	IDU: 276 (99.3) All HIV/HCV co-infected	Adherents 36 (32–42) Non-adherents 35 (28–42)	Adherents 48 (37.2) Non-adherents 70 (46.9)	Adherents Aboriginal: 41 (31.1) Non-adherents Aboriginal: 41 (31.1)
Waldrop-Valverde *et al.* 2006	57	United States	Cross-sectional survey (NA)	IDU (100.0)	42.7 (±5.6)	13 (22.8)	African American 51 (89.4)
Liu *et al.* 2006	148	United States	Prospective cohort study (1999–2003)	Cocaine: 89 (61.0) Heroin: 39 (27.0) All DU with history of child sexual abuse	40.0 (±8)	148 (100.0)	African American 80 (54.0) Hispanic 59 (39.8)
Knowlton *et al.* 2006	466	United States	Cross-sectional study (2001–04)	IDU (100.0) 91% current illicit drug users	43 (25–59)	159 (34.1)	Non-Hispanic black: 321 (68.8)
Waldrop-Valverde *et al.* 2005	58	United States	Cross-sectional study (NA)	IDU (100.0)	Non-homeless: 42.7 (±5.9) Homeless: 43.4 (±4.4)	14 (24.1)	African American 52 (89.6)
Haug *et al.* 2005	78	United States	RCT (2001–2004)	78 patients under MMT	Men: 42.9 (±7.95) Women: 45.4 (±7.62)	36 (46.1)	Non-white men: 21 (50.0) Non-white women:25 (69.4)
Kerr *et al.* 2005	160	Canada	Prospective cohort study (2001–02)	IDUs	39 (±7.04)	69 (43.1)	NA
Martín *et al.* 2005	100	Spain	Cross sectional study (2003)	IDUs under MMT	37 (±5.32)	20 (20.0)	NA
Bouhnik *et al.* 2005	243	France	Prospective cohort study (NA)	IDUs	35 (NA)	68 (28.0)	NA
Martini *et al.* 2004	214	Italy	Cross-sectional study (1998)	Ex-DU: 154 (71.9)	Ex-DU: >34 (51.2%) DU: >34 (56.6%)	Ex-DU: 64 (41.5%) DU: 14 (23.3%)	NA
Sharpe *et al.* 2004	1196 (785 in analysis)	United States	Cross-sectional study (1997–2000)	Non-DU: 448 (37.4) Crack users: 306 (25.6) Other drugs: 442 (36.9)	Non-users: 38 (18–78) Crack users: 38.2 (20–59) Other drugs: 38.4 (18–70)	1196 (100)	African American 1196 (100)
Altice *et al.* 2004	72 (62 in analysis)	United States	RCT (NA)	IDU	42.1	23 (31.9)	African American 43 (60.0) Hispanic 13 (18.0) White 16 (22.0)
Purcell *et al.* 2004	1161 (560 in analysis)	United States	RCT (2001–03)	IDU (100.0)	42 (22–60)	426 (36.7)	African American 740 (63.7) Hispanic 201 (17.3)

Table 1 *Cont.*

Source	*n*	*Country*	*Design (period)*	*Characteristics of study population*			
				Population (%)	*Age, years (range)*	*Female (%)*	*Ethnicity (%)*
Palepu *et al.* 2004	349	United States	Prospective cohort study (1997–2001)	IDU (59%) Homeless (29%)	41.0	40 (20.6)	Non-white: 121 (62.4)
Palepu *et al.* 2004a	1746	Canada	Prospective cohort study (1997–2002)	Incarcerated: 101 Non-incarcerated: 1645 IDU/ex-IDU: 395 Never-IDU: 1351	Incarcerated: 34 (29–40) Non-incarcerated: 37 (32–44)	Incarcerated: 10 (9.9) Non-incarcerated: 296 (17.9)	NA
Crisp *et al.* 2004	137	United States	Cross-sectional study (1999–2000)	112 (81.7%) smoke crack daily, last 7 days	39.7 (21–53)	37 (27.0)	African American 137 (100)
Wood *et al.* 2004	1522	Canada	Prospective cohort study (1996–2002)	IDU: 371 Never-IDU: 1151	IDUs: 38 (32–43) Never-IDU: 37 (32–44)	IDUs: 86 (23.2) Never-IDU: 154 (13.4)	NA
Kerr *et al.* 2004	108	Canada	Prospective cohort study (2001–02)	IDU	39 (±7.1)	49 (45.4)	NA
Wood *et al.* 2003b	1422	Canada	Prospective cohort study (1996–2000)	IDU: 359 (25.3) Never-IDU 1063 (74.7)	Among IDU 37.6 (32.3–43.0)	Among IDU 85 (23.7)	NA
Clarke *et al.* 2003	150	Ireland	Cross-sectional study (2000)	IDU	<19: 1.3% 19–29: 36% >29: 62.7%	63 (42.0)	NA
Turner *et al.* 2003	5073	United States	Retrospective cohort study (NYS Medicaid patients, 1997)	3322 DU under addiction treatment	<30: 3.7% 30–39: 38.0% 40–49: 48.4% 50+: 9.9%	1122/5103 (21.9)	NA
Palepu *et al.* 2003	578	Canada	Prospective cohort study (1996–2000)	IDU: 78 (13) Ex-IDU: 96 (17) Never IDU: 404 (70)	38 (33–45)	NA	NA
Palepu *et al.* 2003a	234	Canada	Prospective cohort study (1996–2000)	IDU: 128 (54.7) Injected cocaine/heroin on a daily basis	36 (30–42)	89 (38.0)	NA
Escobar *et al.* 2003	283	Spain	Cross sectional Study (2000–01)	Alcohol and/or drug use: 203 (71.7) IDUs: 196 (69.3)	36 (25–72)	89 (31.4)	NA
Carrieri *et al.* 2003	96	France	Prospective cohort study (1995–1998)	IDUs	NA	30 (31.2)	NA
Wagner 2003	82	United States	Prospective cohort study (1999–2002)	IDUs	40 (±6)	NA	NA

Arnsten *et al.* 2002	85	United States	Prospective cohort study (1998–2000)	Active drug use during study: 32 (37.6)	42 (NA)	34 (40.0)	Hispanic 51 (60.0) African American 19 (22.3)
Bouhnik *et al.* 2002	210	France	Prospective cohort study (1997–99)	Ex-IDU 114 (54.3) IDU: 96 (45.7)	Ex-IDU: 33.3 IDU: 34.3	Ex-IDU 33 (28.9) IDU: 28 (29.1)	NA
Duran *et al.* 2001	57	France	Prospective cohort study (1995–99)	IDU (100.0)	NA	NA	NA
Lucas *et al.* 2001	764 (558 in analysis)	United States	Prospective cohort study (1998–99)	Ex-IDU: 376 (49.2) IDU: 199 (26.0) NIDU: 189 (24.7)	40 (35–45)	279 (37.0)	African American 613 (80.0)
Altice *et al.* 2001	205	United States (Prisions)	Cross-sectional survey (April–October, 1996)	Incarcerated population Ex-IDU (100.0)	36.2	98 (48.0)	Black: 84 (41.0) Hispanic: 81 (40.0) White: 40 (19.0)
Arnsten *et al.* 2001	67	United States	Prospective cohort study (1998–99)	Active drug use during study: 22 (32.8) MMT 64 (96.0)	43 (23–61)	26 (38.9)	African American 16 (24.0) Hispanic 40 (60.0) White 8 (12.0)
McNabb *et al.* 2001	40	United States	Prospective cohort study (February–August 1999)	IDU	42 (26–51)	10 (25.0)	African American 9 (22.5) Hispanic 30 (75.0)
Crystal *et al.* 2001	1739*	United States	Prospective cohort study (New Jersey Medicaid patients, 1996–98)	IDU: 1048 (60.3%)	18–29: 14.4% 30–39: 49.4% 40–49: 30.1% >50: 6.1%	669 (38.5)	African American 1005 (58.1) Hispanic 333 (19.3) White 391 (22.6)
Pradier *et al.* 2001	119	France	Prospective cohort study (1995–98)	IDU	Age by ARV-drug group†: SQV: 34.0 (±4.7) IDV: 33.0 (±4.7) Other: 33.1 (±3.4)	Male by ARV-drug group: SQV: 24 (57.1) IDV: 38 (71.7) Other: 16 (66.7)	NA
Avants *et al.* 2001	42	United States	Prospective cohort study (NA)	IDU	41.2 (±5.2)	NA	NA
Moatti *et al.* 2000	164	France	Prospective cohort study (1995–99)	Ex-IDU 113 (68.9)	Non-adherent: 33.2 (±4.1) Adherent 34.8 (±4.8)	52 (31.7)	NA
Roca *et al.* 1999	133	Spain	Prospective cohort study (1997–98)	IDU 95 (71.0) Non-IDU 38 (29.0)	Ex-IDU 31.7 (±4.7) Non-IDU 36.5 (±9.6)	Ex-IDU 27 (28.4) Non-IDU 15 (39.5)	NA
Gordillo *et al.* 1999	366	Spain	Cross-sectional study (1997–98)	Former IDUs: 97 (26.5) Current IDUs: 65 (17.8) Non-IDUs: 204 (55.7)	<32: 111 (30.3) 32–35: 79 (21.6) 35–40: 91 (24.9) >40: 85 (23.2)	87 (23.7)	Spanish: 342 (93.4) African: 6 (1.6) South African: 5 (1.4) Others: 13 (3.6)

DU = drug users (not necessarily injection drug users); MMT = methadone maintenance therapy; *ethnicity data available for only 1729 patients. †SQV: Saquinavir, IDV: Indinavir. RCT: randomized controlled trial; NA: not available; ARV: antiretroviral; IDU: intravenous drug user; HCV: hepatitis C virus; HIV: human immunodeficiency virus; NIDU: non-injection drug users.

Table 2 Threshold of measurement and adherence levels of selected studies, 1999–2007.

Source	*Assessor*	*Threshold of measurement*	*Period of measurement*	*n adherent (%)*
Arnsten *et al.* 2007	Patient (self-report)	≥ 90; No. of pills taken/no. pills prescribed	1–15 days (previous day)	477 (75.0) *Association w/adherence*, adjusted OR (95% CI)* ↑ High school graduation: 1.57 (1.03–2.41) ↑ 'ARV do not *eat*' methadone': 1.53 (1.00–2.36) ↑ No syringe/needle sharing: 2.30 (1.46–3.62) ↑ Positive attitudes toward ARV: 2.04 (1.16–2.00) ↑ Higher self-efficacy for taking ARV: 2.13 (1.55–2.92) ↑ Higher sense of responsibility: 1.42 (1.04–1.93) ↓ Higher depressive symptoms: 0.74 (0.58–0.94)
Hinkin *et al.* 2007	MEMS cap	≥ 90; No. of pills taken/no. pills prescribed	Previous 6 months	DU+: 63.6% (with positive urine analysis for drug use previous 2–3 days) DU–: 79.8% (with negative urine analysis)
Palepu *et al.* 2006	Pharmacy records (refill compliance)	≥ 95; No. days patient receives HAART refills/no. days of medical follow-up	Previous 1 year of follow-up	129/278 (46.4) *Association w/adherence, adjusted OR (95% CI)* ↑ IDU under MMT: 1.52 (1.16–2.00) ↓ weekly heroin use: 0.52 (0.42–0.79)
Waldrop-Valverde *et al.* 2006	Patient (self-report)	= 100; No. of pills taken/no pills prescribed	1–15 days (last 1 and 7 days)	Adherence past 7 days: 33 (57.8) Adherece preceeding day: 40 (70.1)
Liu *et al.* 2006	Patient (self-report)	= 100 and ≥ 90; No. doses taken/no. doses prescribed	1–15 days (last 1, 2, 3 and 14 days)	Adherence on 1, 2, 3 and 14 days: Adherence = 90% 88, 90, 92, 73% Adherence = 100% 88, 90, 92, 59%
Knowlton *et al.* 2006	Patient (self-report)	≥ 95; No. pills taken/no. pills prescribed	1–15 days (last day)	350 (75.1) 239/350 (68.3) adherents with detectable HIV-VL ($P < 0.05$)
Waldrop-Valverde *et al.* 2005	Patient (self-report)	= 100; No. pills taken/no. pills prescribed	1–15 days (last day)	35 (60.3) *Association w/ adherence* ↓ Higher depression ($P = 0.02$)
Haug *et al.* 2005	Patient (self-report) and MEMS cap	= 100; No pills taken/no. pills prescribed	*Self-report* Previous day and previous 4 days on time adherence *MEMS cap* 4 weeks on-time adherence	*Self-reported adherence:* ♂ Previous day: 76% ♀ Previous day: 78% Average: 76.7% ♂ Previous 2–4 days: 82% ♀ Previous 2–4 days: 78% Average: 80.4% *MEMs cap* ♂ Previous 4 weeks: 54% ♀ Previous 4 weeks: 58% Average: 56.4%

Kerr *et al.* 2005	Patient self-report and pharmacy records	= 100; HAART discontinuation: (i) picked up at least one HAART prescription and (ii) reported discontinuation of HAART for 1 month or over (confirmed by pharmacy dispensation records)	Discontinuation over a 1-year follow-up period	Discontinued HAART: 71 (44.4) *Association w/ discontinuation* Incarceration: OR: 4.84, $P = 0.022$ Negative outcome expectations: OR: 1.41, $P = 0.001$ Adherence efficacy expectations OR: 0.70, $P = 0.003$ Self-regulatory efficacy OR:/0.86, $P = 0.050$
Martín *et al.* 2005	Patient (self-report)	= 100 No. pills taken/no. pills prescribed	Previous day, week and month	61%, 58% and 43% (previous day, week and months, respectively)
Bouhnik *et al.* 2005	Patient (self-report)	≥ 80%; No. pills taken/no. pills prescribed	1–15 days (last 7 days)	*Non-adherents* Baseline: 31.0% Follow-up: 27.5% (5 years)
Martini *et al.* 2004	Patient (self-report)	No. errors made (e.g. missing doses, interruption, changing time) High adherence: ≤ 2 Medium: 3–4 Low: ≥ 5	Previous 2 months	DU: 19/60 (31.6) Non-DU: 65/154 (42.3) Adherent DU versus non-DU (31.6% versus 42.3%, $P < 0.05$)
Sharpe *et al.* 2004	Patient (self-report)	= 100 No. pills taken/no. pills prescribed	NA	Overall adherence: 534/784 (68.0) Non-DU: 245/312 (78.5%) DU: 289/472 (61.2%) Non-crack-users: 63.5% Crack-users: 57.2% *Association w/non-adherence, adjusted OR (95% CI)* ↓ Crack use: 0.37 (0.24–0.56) ↓ Other drugs: 0.47 (0.36–0.68)
Altice *et al.* 2004	MEMS-cap	>75%; No. pills taken/no. pills prescribed	1–15 days (last 3 days)	Baseline adherence: 25.0% Supervised doses: 76.2% Unsupervised doses: 50.0% *Association w/ adherence* ↑ Supervised versus unsupervised pills administration ($P < 0.0001$)
Purcell *et al.* 2004	Patient (self-report)	= 100 % of those who missed at east 1 dose	1–15 days (Last day)	420/560 (75.0)
Palepu *et al.* 2004	Patient (self-report)	≥ 95; No. of pills taken/no. pills prescribed	Previous 30 days	146/194 (75.3)
Palepu *et al.* 2004a	Pharmacy records (refill compliance)	= 100; No. days patient received HAART refills/no. days of follow-up	1st year of therapy	Adherents: 1044 (59.8) *Association w/ non-adherence, adjusted OR (95% CI)* ↑ incarceration: 2.40 (1.54–3.75) ↑ injection drug use: 1.49 (1.17–1.90)
Crisp *et al.* 2004	Patient (self-report)	=100; No. pills taken/no. pills prescribed	NA	Full compliance: 73/137 (53.3) 43/137 (31.3) compliant more than half the time
Wood *et al.* 2004	Pharmacy records (refill compliance)	≥ 95; No. days patient received HAART refills/no. days of follow-up	1st year of therapy	IDUs: 167 (45.0) Never-IDUs: 722 (62.7)

Table 2 *Cont.*

Source	*Assessor*	*Threshold of measurement*	*Period of measurement*	*n adherent (%)*
Kerr *et al.* 2004	Pharmacy records (refill compliance)	≥ 95; No. days with filled prescription/no. days under therapy	During 1 year of follow-up	37 (34.3)
Wood *et al.* 2003b	Patient (self-report)	≥ 95; Non-adherents: Received HAART for less than 95% of the follow-up period	1st year of therapy	160/359 (44.6)
Clarke *et al.* 2003	Pharmacy records (refill compliance)	≥ 80; Pharmacy records demonstrate at least 80% rate of HAART refills	NA	55/85 (64.7)
Turner *et al.* 2003	Pharmacy records (refill compliance)	≥ 95; No. days with filled prescription/no. days under therapy	During 1997 (1 year)	Overall: 1141/5073 (22.5%) ♀ 329/1827 (18.0%) ♂ 812/3246 (25.0%)
Palepu *et al.* 2003	Pharmacy records (refill compliance)	= 100; No. days patient received HAART refills/no. days of follow-up	1st year of therapy	IDU: 76.9% Ex-IDU: 81.5% Non IDU: 91.6%
Palepu *et al.* 2003a	Pharmacy records (refill compliance)	= 100; No. days patient received HAART refills/no. days of follow-up	1st year of therapy	Overall: 167/234 (71.4%) 100/133 (75.2) IDUs who achieved HIV viral suppression and were adherents 67/101 (66.3) IDUs who did not achieve HIV viral suppression and were adherents
Escobar *et al.* 2003	Pharmacy records (refill compliance)	≥ 95% No. of pills taken/no. pills prescribed	Previous 4–6 months	Overall sample: 147/283 (51.9) Alcohol/drug users: 94/203 (46.3) IDUs: 90/196 (45.9)
Carrieri *et al.* 2003	Patient (self-report)	≥ 80; No. of pills taken/no. pills prescribed	1–15 days (last 7 days)	74 (77.1%) Factors associated w/non-adherence: lack of stable relationship; active drug use, depression; anxiety.
Wagner 2003	MEMS cap and Patient (self-report)	Continuous variable No. MEMS cap openings/no. prescribed doses	1–15 days (last 14 days)	*MEMs adherence* Average adherence: 74.4% ≥ 90% adherence: 39.0% ≥ 95% adherence: 25.6% Self-reported adherence: 86%
Arnsten *et al.* 2002	MEMS cap	Continuous variable No. MEMS cap openings/no. prescribed doses	Previous month	50.6%
Bouhnik *et al.* 2002	Patient (self-report)	≥ 80%; No. pills taken/no. pills prescribed	1–15 days (last 7 days)	Ex-IDU: 74.6% IDU: 63.5%
Duran *et al.* 2001	Patient (self-report)	≥ 80; No. of pills taken/no. pills prescribed	1–15 days (last 7 days)	39/57 (68.4)
Lucas *et al.* 2001	Patient (self-report)	Non-adherence: >2 missed doses	1–15 days (last 2 weeks)	Non-adherents: 34% active IDU versus 17% Ex-IDU versus 24% non-IDU ($P < 0.001$, both comparisons)

Altice *et al.* 2001	Patient (self-report)	≥ 80; No. of pills taken/no. pills prescribed	1–15 days (last 7 days)	137/164 (83.5) 62.4% ever self-discontinued HAART (118/189)
Arnsten *et al.* 2001	MEMS cap and patient (self-report)	Continuous variable No. MEMS cap openings/no. prescribed doses	1–15 days (last day and 7 days)	*Self-reported adherence* 1-day adherence: 79.1% (±22.5) 1-week adherence: 78.1% (±22.1) *MEMS cap adherence* 1-day adherence: 57.3% (±31.9) 1-week adherence: 53.7% (±33.9)
McNabb *et al.* 2001	MEMS cap, pill counts, and patient (self-report)	*MEMS* No. MEMS cap openings/no. prescribed doses *Pill counts and self report* No. pills taken/no. pills prescribed	*MEMS and pill counts* Previous 6 months *Self-report* Previous1 and 2 days Previous 2 weeks	*Self-reported adherence* ~100% *Pill count adherence* 79.8% (±26.0) *MEMS cap adherence* 53.5% (±28.7)
Crystal *et al.* 2001	Pharmacy records (refill compliance)	Proportion (0–1.0); No. days on PI/NNRTI drugs/no. days from first prescription to the end of study	~2.5 years of follow-up (March 1996–December 1998)	IDUs: 0.66 Non-IDUs: 0.68 (non-statistically significant)
Pradier *et al.* 2001	Patient (self-report)	= 100%; No. pills taken/no. pills prescribed	1–15 days (last 7 days)	85 (71.4)
Avants *et al.* 2001	Patient (self-report)	≥ 80; No. pills taken/no. pills prescribed	1–15 days (last 7 days)	Non-adherents: 15 (35.7) Non-adherence associated w/: low education, high viral load, low fluid intelligence, depression, low cognitive function (*Ps* < 0.01)
Moatti *et al.* 2000	Patient (self-report)	≥ 80; No. pills taken/no. pills prescribed	1–15 days (last 7 days)	107 (65.2)
Roca *et al.* 1999	Patient (self-report) and medical charts	*Adequate adherence* (i) patients kept the appointments; (ii) >80% of prescribed doses; (iii) HIV-RNA level at least 1.5 $\log_{10}$ below pre-treatment level *Inadequate adherence* (i) or (ii) were not met *Indeterminate adherence* (i) and (ii) were met, but condition (iii) was not	Previous 1 year of follow-up	43/133 (32.3) IDUs: 26/95 (27.4) Non-IDUs: 17/38 (44.7)
Gordillo *et al.* 1999	Patient (self-report)	≥90%; No. pills taken/no. pills prescribed	1–15 days (last 7 days)	IDUs: 134/204 (65.7) Non-IDUs: 77/162 (47.5) Non-IDUs versus IDUs adherence: AOR: 2.05, 95%CI: 1.28–3.29

*↑ Positive association; ↓ negative association; MEMS cap = medication event monitoring system; MMT = methadone maintenance treatment; VL = plasma viral load; NA: not available. OR: odds ratio; AOR: adjusted odds ratio; CI: confidence interval; IDU: injection drug user; HIV: human immunodeficiency virus; HAART: highly active antiretroviral therapy; DU: drug users.

bination of days, weeks and months of recall. Time-frames were not defined clearly in three studies.

Major study findings

Adherence assessment: longitudinal studies versus randomized controlled trials

Longitudinal studies using MEMS-caps were roughly comparable. Arnsten *et al.* [24] found an overall monthly adherence of 51.0% among IDU, while another study conducted by the same group [25] reported an adherence of 57.3% for the day before evaluation and 53.4% for the previous week. Wagner and colleagues [26] reported an average electronically monitored adherence of 74% over a 2-week period among 81 IDU, with 39% of participants having at least 90% adherence. Two studies used MEMS-caps to evaluate adherence over a period of 6 months. McNabb and collaborators [27] reported an adherence level of 53.5%, while a recent study [28] found a higher adherence for both active drug users (63.6%) and former drug users (79.8%), using the same time-frame.

Two studies used MEMS-caps to evaluate adherence in the context of randomized controlled trials (RCT). Altice *et al.* [29] found a significantly higher adherence level among those receiving directly administered HAART compared to those self-administering their HAART (76.2% versus 49.9%; $P < 0.0001$). Haug *et al.* [30] found an overall adherence of 54.0% among men and 58.0% among women, after a 4-week observation period. A recent study conducted by the Intervention Research Addressing the Primary and Secondary Prevention Needs of HIV-seropositive IDUs (INSPIRE) study team [31] used self-reported adherence in the context of a randomized controlled trial (RCT), with an overall adherence of 75.0%.

Purcell and colleagues [32] found one of the highest total (100%) adherence levels: 75.0%. Comprehensive management, as well as the strict eligibility criteria and the willingness to join an intensive intervention study such as this RCT, might have contributed for these auspicious findings.

Adherence assessment: MEMS cap, pharmacy refill and self-report

A few longitudinal studies compared adherence measured by MEMS-caps and self-report. Overall, self-report tended to overestimate adherence compared to MEMS-caps [25–27,30]. For instance, Arnsten and collaborators [25] reported a mean self-reported 1-day adherence of 79%, but 57% when measured by MEMS-caps.

Two longitudinal studies conducted in Canada, by Palepu and colleagues [33,34], found very similar results using data from pharmacy refill compliance, although evaluating different drug-using populations. The first study was implemented in a province-wide Drug Treatment Program in British Columbia, while the second was developed in the context of a cohort study of IDU. These studies found that 76.9% versus 75.2% of the participants were 100% adherent to their scheduled pharmacy refills after 12 months. A third study conducted in Ireland found that 64.7% of 85 IDU attending a reference center in Dublin, Ireland, refilled their antiretroviral medications at least 80% of the time [35]. Lower compliance to pharmacy refills was found in a study conducted with HIV/hepatitis C virus (HCV) co-infected DU from Canada: 46.4% [36].

Self-reported adherence tended to be higher than the other adherence measurements used. One of the highest self-reported adherence levels was found in a cross-sectional assessment of an incarcerated population: 83.5% [2]. Knowlton and colleagues [37] found that 75.0% of participants took at least 95% of prescribed pills on the day before assessment. Palepu *et al.* [38] found a similar adherence over the previous 30 days (75.2%). One study found that 60.3% of patients were 100% adherent to antiretroviral therapies (ARTs) prescribed the previous day [39]. Another study by the same group found an adherence of 70.1% on previous day and 57.8% on previous 7 days [40]. In a study conducted among black women, a slightly higher adherence was found by Sharpe and colleagues [41] (68.0%). Although the overall adherence was higher, the authors found lower proportions of adherence between non-DU, users of other drugs and crack cocaine users, with 78.5%, 63.5% and 57.2%, respectively.

Liu and collaborators [42] conducted another study exclusively with women, where all participants had a history of child sexual abuse and drug addiction. Interestingly, this study found the highest self-reported adherence. The proportion of participants with adherence = 90% were 88%, 90%, 92% and 73% for 1, 2, 3 and 14 days, respectively. The proportion of participants who were 100% adherent to HAART were 88%, 90%, 92% and 59% for 1, 2, 3 and 14 days, respectively [42]. According to the authors, self-reported medication adherence tended to overestimate patients' true adherence levels by as much as 10–20%.

Roca *et al.* [43] defined as adherent those patients who kept all medical appointments, took at least 80% of prescribed doses and had an HIV-RNA level at least 1.5 $\log_{10}$ below pre-treatment level. With a median follow-up of 12 months, 32% of the patients showed optimal adherence in all clinical appointments (27% IDU and 32% non-IDU). The use of a synthetic indicator (combining self-reported adherence, compliance with medical appointments and viral load suppression) may have influenced the findings.

Facilitators of HAART adherence among HIV-positive DU

Studies showed that major facilitators of HAART adherence among HIV-positive DU are access to drug abuse treatment, mainly substitution therapy for opiate dependence, psychological characteristics and access to mental health treatment among those in need.

Palepu *et al.* [36] found that methadone maintenance therapy (MMT) was associated positively with optimal adherence [adjusted odds ratio (AOR) 1.52, 95% CI 1.16–2.00]. Findings from the French Cohort Study of HIV-infected IDUs (MANIF 2000 study group), in France, also underscored the importance of substitution therapy in reducing drug injection behaviors and improving adherence to HAART. Moatti *et al.* [44] showed that IDU receiving buprenorphine maintenance therapy reached higher levels of adherence (78.1%) than IDU who had stopped injecting drugs for more than 6 months, but were out of maintenance therapy (65.5%). Other studies conducted by the same group suggest that, once under substitution therapy, patients follow a structured daily routine, a possible reason for higher adherence among this population [44–49].

Liu and collaborators [42] identified that participants with adherence levels over 90% reported significantly higher self-esteem (20.4 versus 18.2; $P < 0.05$) and adherence self-efficacy (24.1 versus 19.9; $P < 0.001$) than those with adherence less than 90%; similar findings were identified using a 100% adherence cut-off.

In the New York Medicaid sample [23], women with depression who were receiving both psychiatric care and antidepressants had higher adherence than those receiving psychiatric care alone (AOR: 1.92; 95% CI: 1.00–3.68). Among those without a diagnosis of depression, drug treatment was found to be associated with better adherence among men ($P < 0.001$), but not among women.

According to a study conducted by Arnsten and colleagues [31], good adherence was associated with being a high-school graduate, not believing that antiretrovirals have a counteractive effect on methadone, not sharing or lending drug injection equipment with HIV-negative or unknown status partners and the following psychosocial characteristics: positive attitudes toward HIV medicines, greater self-efficacy for taking medicines as prescribed, sense of responsibility for protecting others from HIV and fewer depressive symptoms.

Barriers to HAART adherence among HIV-positive DU

Significant barriers to HAART adherence reported among HIV-positive DUs were related to psychological problems and active drug use. Kerr and colleagues [50] evaluated the underlying reasons for HAART discontinuation among IDU in Vancouver, Canada, where 44% discontinued HAART during a 1-year follow-up period. The major factor associated with HAART discontinuation was recent incarceration (OR = 4.84, $P = 0.022$). A second study carried out in Vancouver [51] also documented incarceration as a major barrier for optimal adherence.

Psychological problems were found to be associated with poor adherence by different studies. According to Kerr *et al.* [52], negative outcome expectations were associated inversely with adherence (OR = 0.8; 95% CI: 0.7–0.9). Similar findings were identified by a study conducted in Spain with IDU receiving MMT [53]. Another study conducted in Spain [54] found that non-adherent patients were more likely to present higher rates of anxiety. Gordillo and collaborators [55] also found higher adherence levels among participants who were not depressed and had good social support (OR: 1.86; 95% CI: 0.98–3.53). Findings from the MANIF 2000 study group highlight the role of depression and others psychiatric problems as barriers to optimal adherence [44,46–49].

Active drug use has been found consistently to be associated with non-adherence. Crisp and colleagues [56] conducted a study with African American active crack cocaine users. The study identified that 53.3% self-reported full compliance with their physicians' recommendations; while one-third (31.3%) reported they were compliant more than half of the time. Another study conducted with active IDU found similar rates of self-reported non-adherence in the previous 2 weeks: 44% [57]. The study conducted by Martini and colleagues [58] also found fewer high-compliant patients among active DU when compared to non-drug users: 31.6% versus 42.3% ($P < 0.05$).

According to the study conducted by Crystal and collaborators [22], conducted with beneficiaries from the New Jersey Medicaid Program, IDU experienced longer delays in initiating HAART than did non-IDU. However, once the treatment was initiated, IDU were as adherent to treatment as non-IDU.

DISCUSSION

We identified 41 studies assessing adherence to HAART among HIV-positive drug users. Although these studies used heterogeneous cut-offs, different measures and various study designs, most found that HIV-positive drug users had moderate levels of adherence to HAART. Most papers suggest that the adherence to HAART among HIV-positive drug users can be similar to those found among other PLWHA, once proper timing to initiate treatment is followed, comorbidities are properly managed and treated, psychosocial support is provided, and drug treatment, particularly substitution therapy, is instituted.

The selected studies bring understanding to the complex inter-relationship of drug addiction, HIV-infection and adherence to HAART. The high prevalence of comorbid medical conditions and social disadvantages identified by the studies suggest the need for drug treatment, case-management, medical services and psychosocial support to optimize adherence. Several studies documented that once HIV-positive drug users have access to the necessary support, they are able to adhere to ARV regimens and hence experience treatment benefits.

Overall, most studies which found higher adherence were carried out among DU receiving HAART in structured settings, particularly those engaged in integrated services offering both addiction treatment and psychosocial support [32] and/or directly observed therapy (DOT) [29,59]. For instance, one of the highest self-reported adherence levels was found in a cross-sectional assessment of an incarcerated population: 83.5% [2]. According to the authors, possible reasons for the high acceptance of and adherence to HAART among these patients might include the drug-free environment, the availability of HIV specialists and the lack of concern that 'street drugs' will interfere with the therapeutic benefits of ART[2]. Patients receiving methadone maintenance therapy (or alternatively, buprenorphine maintenance therapy) also presented higher levels of adherence than out-of-treatment opiate users. The literature suggests that these patients reduced their drug using habits significantly and attained a more stable living style that promoted better adherence to HAART [35,43]. These findings suggest that the extent to which one's daily life is routinized constitutes a key factor to improve adherence [60].

Illicit stimulant use represents a key challenge for optimal adherence [24,28,41]. The study by Hinkin and collaborators [28] found that stimulant users were seven times more likely to have less than optimal adherence than non-stimulant users and had a more precipitous decline in adherence over a 6-month period than did non-users. Unfortunately, one of the most worrisome aspects of the link between substance abuse and HIV is the absence of effective prevention and treatment interventions for cocaine and other stimulant users—in particular an effective pharmacotherapy for stimulant abuse [61–63].

Several studies highlighted the role of social/structural factors on HAART adherence. According to some studies, the importance of the patient–provider relationship and communication supports the need for low-threshold/user-friendly health care delivery systems, targeted to the specific needs of HIV-positive DU [37,56,64]. According to Knowlton and colleagues [37], besides the role of a positive patient–provider relationship, the access to social support and ancillary services is also pivotal in effective HAART access and adherence among HIV-positive active DU. Social instability (e.g. unemployment, history of incarceration, homelessness) was associated with poor HAART adherence [34,39,49]. These findings underscore a major role of social support in effective and long-term HAART adherence in this population.

The use of HAART by HIV-positive DU remains a complex medical, social and legal issue. Relative to other at-risk populations, active DU initiate HAART at a more advanced stage of infection compared to other populations [12,13]. Frequently, the prescription of HAART by physicians tends to be influenced not only by decreasing CD4 cell counts and increasing HIV-RNA levels, but also by the anticipated adherence levels, which can compromise enrollment of DU into treatment [65].

This review has several 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, as our aim was to conduct both a systematic and a meta-analysis. However, qualitative studies might bring additional understanding to the complex interplay of drug addiction, comorbidities, HAART adherence and different psychosocial and contextual factors, and should be evaluated by future studies. This review was not able to evaluate possible relationships between different regimen characteristics and adherence (e.g. putative higher adherence among patients under best-tolerated regimens and/or regimens with less pill burden), because this information was rarely available among the identified studies. Finally, it is possible that our conclusions might be overestimating patients adherence levels, due mainly to the fact that half of selected studies relied only on self-reported adherence—a measure known to overestimate patients' true adherence levels.

Different interpretations of what constitutes optimal adherence made between-study comparisons difficult. We were unable to identify studies 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, the vast majority of them published in English. Therefore, these findings are unlikely to represent the treatment experience of a high proportion of HIV-positive individuals 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 [14].

Evidence-based studies on barriers and facilitators to adherence among HIV-positive DU have been very scarce in developing countries. This is of great concern, given

that the largest HIV epidemics among DU have taken place in recent years in developing/transitional countries. In the coming decades, PLWHA from developing countries will constitute a growing proportion of the world's HAART recipients as treatment access expands.

While there is significant reluctance among medical care providers to deliver HAART to DU, the evidence supporting this decision is limited [18,66]. The reviewed studies highlight that in a context of a non-coercive, comprehensive HIV management and care patients marginalized traditionally by the health care system can access, accept and are able to adhere to complex therapeutic regimens. Because HIV-positive DU are frequently involved in high-risk social networks, by providing effective treatment and significantly reducing their HIV load and hence their infectivity it is possible to reduce sexual and parenteral transmission of HIV to the broader community. Overcoming stigma and discrimination towards HIV-positive DU, and improving the quality and efficacy of available treatment/care are essential for optimal treatment for this population.

Declarations of interest

None.

References

1. Mannheimer S. B., Matts J., Telzak E., Chesney M., Child C., Wu A. W. *et al.* Quality of life in HIV-infected individuals receiving antiretroviral therapy is related to adherence. *AIDS Care* 2005; **17**: 10–22.
2. Altice F. L., Mostashari F., Friedland G. H. Trust and the acceptance of and adherence to antiretroviral therapy. *J Acquir Immune Defic Syndr* 2001; **28**: 47–58.
3. Ferguson T. F., Stewart K. E., Funkhouser E., Tolson J., Westfall A. O., Saag M. S. Patient-percieved barriers to antiretroviral adherence: associations with race. *AIDS Care* 2002; **14**: 607–17.
4. Paterson D. L., Swindells S., Mohr J., Brester M., Vergis E. N., Squier C. *et al.* Adherence to protease inhibitor therapy and outcomes in patientswith HIV infection. *Ann Intern Med* 2000; **133**: 21–30.
5. Bangsberg D. R., Hecht F. M., Charlebois E. D., Zolopa A. R., Holodniy M., Sheiner L. *et al.* Adherence to protease inhibitors, HIV-1 viral load, and development of drug resistance in an indigent population. *AIDS* 2000; **14**: 357–66.
6. Bangsberg D. R., Charlebois E. D., Grant R. M., Holodniy M., Deeks S. G., Perry S. *et al.* High levels of adherence do not prevent accumulation of HIV drug resistance mutations. *AIDS* 2003; **17**: 1925–32.
7. Bangsberg D. R., Perry S., Charlebois E. D., Clark R. A., Roberston M., Zolopa A. R. *et al.* Nonadherence to highly active antiretroviral therapy predicts progression to *AIDS*. *AIDS* 2001; **15**: 1181–3.
8. Wood E., Hogg R. S., Yip B., Harrigan P. R., O'Shaughnessy M. V., Montaner J. S. Is there a baseline CD4 cell count that precludes a survival response to modern antiretroviral therapy? *AIDS* 2003; **17**: 711–20.
9. Wood E., Montaner J. S., Bangsberg D. R., Tyndall M. W., Strathdee S. A., O'Shaughnessy M. V. *et al.* Expanding access to HIV antiretroviral therapy to marginalised populations in the developed world. *AIDS* 2003; **17**: 2419–27.
10. Bassetti S., Battegay M., Furrer H., Rickenbach M., Flepp M., Kaiser L. *et al.* Why is highly active antiretroviral therapy (HAART) not prescribed or discontinued? Swiss HIV cohort study. *J Acquir Immune Defic Syndr* 1999; **21**: 114–19.
11. Celentano D. D., Vlahov D., Cohn S., Shadle V. M., Obasanjo O., Moore R. D. Self-reported antiretroviral therapy in injection DU. *JAMA* 1998; **280**: 544–6.
12. Celentano D. D., Galai N., Sethi A. K., Shah N. G., Strathdee S. A., Vlahov D. *et al.* Time to initiating highly active antiretroviral therapy among HIV-infected injection DU. *AIDS* 2001; **15**: 1707–15.
13. Wang C., Vlahov D., Galai N., Bareta J., Strathdee S. A., Nelson K. E. *et al.* Mortality in HIV-seropositive versus seronegative persons in the era of highly active antiretroviral therapy: implications for when to initiate therapy. *J Infect Dis* 2004; **190**: 1046–54.
14. World Health Organization/Joint United Nations Programme on HIV/AIDS (WHO/UNAIDS). *2007 Report on the Global AIDS Epidemic*. Geneva: WHO and UNAIDS; 2007.
15. Inciardi J. A., Surratt H. L. Drug use, street crime, and sex-trading among cocaine-dependent women: implications for public health and criminal justice policy. *J Psychoact Drugs* 2001; **33**: 379–89.
16. Latkin C. A., Knowlton A. R., Sherman S. Routes of drug administration, differential affiliation, and lifestyle stability among cocaine and opiate users: implications to HIV prevention. *J Subst Abuse* 2001; **13**: 89–102.
17. Wensing A. M., van de Vijver D. A., Angarano G., Asjo B., Balotta C., Boeri E. *et al.* Prevalence of drug-resistant HIV-1 variants in untreated individuals in Europe: implications for clinical management. *J Infect Dis* 2005; **192**: 958–66.
18. Vlahov D., Celentano D. D. Access to highly active antiretroviral therapy for injection DU: adherence, resistance, and death. *Cad Saude Publica* 2006; **22**: 705–18.
19. Wainberg M. A., Friedland G. Public health implications of antiretroviral therapy and HIV drug resistance. *JAMA* 1998; **279**: 1977–83.
20. Escoto-Delgadillo M., Vazquez-Valls E., Ramirez-Rodriguez M., Corona-Nakamura A., Amaya-Tapia G., Quintero-Perez N. *et al.* Drug-resistance mutations in antiretroviral-naive patients with established HIV-1 infection in Mexico. *HIV Med* 2005; **6**: 403–9.
21. Lucas G. M., Gebo K. A., Chaisson R. E., Moore R. D. Longitudinal assessment of the effects of drug and alcohol abuse on HIV-1 treatment outcomes in an urban clinic. *AIDS* 2002; **16**: 767–74.
22. Crystal S., Sambamoorthi U., Moynihan P. J., McSpiritt E. Initiation and continuation of newer antiretroviral treatments among Medicaid recipients with AIDS. *J Gen Intern Med* 2001; **16**: 850–9.
23. Turner B. J., Laine C., Cosler L., Hauck W. W. Relationship of gender, depression, and health care delivery with antiretroviral adherence in HIV-infected DU. *J Gen Intern Med* 2003; **18**: 248–57.
24. Arnsten J. H., Demas P. A., Grant R. W., Gourevitch M. N., Farzadegan H., Howard A. A. *et al.* Impact of active drug use on antiretroviral therapy adherence and viral suppression in HIV-infected DU. *J Gen Intern Med* 2002; **17**: 377–81.
25. Arnsten J. H., Demas P. A., Farzadegan H., Grant R. W., Gourevitch M. N., Chang C. J. *et al.* Antiretroviral therapy

adherence and viral suppression in HIV-infected DU: comparison of self-report and electronic monitoring. *Clin Infect Dis* 2001; **33**: 1417–23.
26. Wagner G. Placebo practice trials: the best predictor of adherence readiness for HAART among DU? *HIV Clin Trials* 2003; **4**: 269–81.
27. McNabb J., Ross J. W., Abriola K., Turley C., Nightingale C. H., Nicolau D. P. Adherence to highly active antiretroviral therapy predicts virologic outcome at an inner-city human immunodeficiency virus clinic. *Clin Infect Dis* 2001; **33**: 700–5.
28. Hinkin C. H., Barclay T. R., Castellon S. A., Levine A. J., Durvasula R. S., Marion S. D. *et al*. Drug use and medication adherence among HIV-1 infected individuals. *AIDS Behav* 2007; **11**: 185–94.
29. Altice F. L., Mezger J. A., Hodges J., Bruce R. D., Marinovich A., Walton M. *et al*. Developing a directly administered antiretroviral therapy intervention for HIV-infected DU: implications for program replication. *Clin Infect Dis* 2004; **38**: S376–87.
30. Haug N. A., Sorensen J. L., Lollo N. D., Gruber V. A., Delucchi K. L., Hall S. M. Gender differences among HIV-positive methadone maintenance patients enrolled in a medication adherence trial. *AIDS Care* 2005; **17**: 1022–9.
31. Arnsten J. H., Li X., Mizuno Y., Knowlton A. R., Gourevitch M. N., Handley K. *et al*. Factors associated with antiretroviral therapy adherence and medication errors among HIV-infected injection drug users. *J Acquir Immune Defic Syndr* 2007; **46**: S64–71.
32. Purcell D. W., Metsch L. R., Latka M., Santibanez S., Gomez C. A., Eldred L. *et al*. Interventions for seropositive injectors-research and evaluation: an integrated behavioral intervention with HIV-positive injection DU to address medical care, adherence, and risk reduction. *J Acquir Immune Defic Syndr* 2004; **37**: S110–18.
33. Palepu A., Tyndall M., Yip B., O'Shaughnessy M. V., Hogg R. S., Montaner J. S. Impaired virologic response to highly active antiretroviral therapy associated with ongoing injection drug use. *J Acquir Immune Defic Syndr* 2003; **32**: 522–6.
34. Palepu A., Tyndall M. W., Li K., Yip B., O'Shaughnessy M. V., Schechter M. T. *et al.* Alcohol use and incarceration adversely affect HIV-1 RNA suppression among injection DU starting antiretroviral therapy. *J Urban Health* 2003; **80**: 667–75.
35. Clarke S., Delamere S., McCullough L., Hopkins S., Bergin C., Mulcahy F. Assessing limiting factors to the acceptance of antiretroviral therapy in a large cohort of injecting DU. *HIV Med* 2003; **4**: 33–7.
36. Palepu A., Tyndall M. W., Joy R., Kerr T., Wood E., Press N. *et al*. Antiretroviral adherence and HIV treatment outcomes among HIV/HCV co-infected injection DU: the role of methadone maintenance therapy. *Drug Alcohol Depend* 2006; **84**: 188–94.
37. Knowlton A., Arnsten J., Eldred L., Wilkinson J., Gourevitch M., Shade S. *et al*. Individual, interpersonal, and structural correlates of effective HAART use among urban active injection DU. *J Acquir Immune Defic Syndr* 2006; **41**: 486–92.
38. Palepu A., Horton N. J., Tibbetts N., Meli S., Samet J. H. Uptake and adherence to highly active antiretroviral therapy among HIV-infected people with alcohol and other substance use problems: the impact of substance abuse treatment. *Addiction* 2004; **99**: 361–8.
39. Waldrop-Valverde D., Valverde E. Homelessness and psychological distress as contributors to antiretroviral nonadherence in HIV-positive injecting DU. *AIDS Patient Care STDS* 2005; **19**: 326–34.
40. Waldrop-Valverde D., Ownby R. L., Wilkie F. L., Mack A., Kumar M., Metsch L. Neurocognitive aspects of medication adherence in HIV-positive injecting DU. *AIDS Behav* 2006; **10**: 287–97.
41. Sharpe T. T., Lee L. M., Nakashima A. K., Elam-Evans L. D., Fleming P. L. Crack cocaine use and adherence to antiretroviral treatment among HIV-infected black women. *J Commun Health* 2004; **29**: 117–27.
42. Liu H., Longshore D., Williams J. K., Rivkin I., Loeb T., Warda U. S. *et al*. Substance abuse and medication adherence among HIV-positive women with histories of child sexual abuse. *AIDS Behav* 2006; **10**: 279–86.
43. Roca B., Gomez C. J., Arnedo A. Stavudine, lamivudine and indinavir in drug abusing and non-drug abusing HIV-infected patients: adherence, side effects and efficacy. *J Infect* 1999; **39**: 141–5.
44. Moatti J. P., Carrieri M. P., Spire B., Gastaut J. A., Cassuto J. P., Moreau J. Adherence to HAART in French HIV-infected injecting DU: the contribution of buprenorphine drug maintenance treatment. The Manif 2000 study group. *AIDS* 2000; **14**: 151–5.
45. Bouhnik A. D., Preau M., Vincent E., Carrieri M. P., Gallais H., Lepeu G. *et al*. Depression and clinical progression in HIV-infected DU treated with highly active antiretroviral therapy. *Antivir Ther* 2005; **10**: 53–61.
46. Carrieri M. P., Chesney M. A., Spire B., Loundou A., Sobel A., Lepeu G. *et al*. Failure to maintain adherence to HAART in a cohort of French HIV-positive injecting DU. *Int J Behav Med* 2003; **10**: 1–14.
47. Pradier C., Carrieri P., Bentz L., Spire B., Dellamonica P., Moreau J. *et al*. Impact of short-term adherence on virological and immunological success of HAART: a case study among French HIV-infected IDU. *Int J STD AIDS* 2001; **12**: 324–8.
48. Duran S., Solas C., Spire B., Carrieri M. P., Fuzibet J. G., Costagliola D. *et al*. Do HIV-infected injecting DU over-report adherence to highly active antiretroviral therapy? A comparison between patients' self-reports and serum protease inhibitor concentrations in the French Manif 2000 cohort study. *AIDS* 2001; **15**: 1075–7.
49. Bouhnik A. D., Chesney M., Carrieri P., Gallais H., Moreau J., Moatti J. P. *et al*. Nonadherence among HIV-infected injecting DU: the impact of social instability. *J Acquir Immune Defic Syndr* 2002; **31**: S149–53.
50. Kerr T., Marshall A., Walsh J., Palepu A., Tyndall M., Montaner J. *et al*. Determinants of HAART discontinuation among injection drug users. *AIDS Care* 2005; **17**: 539–49.
51. Palepu A., Tyndall M. W., Chan K., Wood E., Montaner J. S., Hogg R. S. Initiating highly active antiretroviral therapy and continuity of HIV care: the impact of incarceration and prison release on adherence and HIV treatment outcomes. *Antivir Ther* 2004; **9**: 713–19.
52. Kerr T., Palepu A., Barness G., Walsh J., Hogg R., Montaner J. *et al*. Psychosocial determinants of adherence to highly active antiretroviral therapy among injection drug users in Vancouver. *Antivir Ther* 2004; **9**: 407–14.
53. Martin L. L., Hermandez S. O., Carrobles J. A. [Psychosocial variables in the antiretroviral treatment adherence in methadone maintenance patients]. *Psicothema* 2005; **17**: 575–81 [in Spanish].

54. Escobar I., Campo M., Martin J., Fernandez-Shaw C., Pulido F., Rubio R. Factors affecting patient adherence to highly active antiretroviral therapy. *Ann Pharmacother* 2003; **37**: 775–81.
55. Gordillo V., del Amo J., Soriano V., Gonzalez-Lahoz J. Sociodemographic and psychological variables influencing adherence to antiretroviral therapy. *AIDS* 1999; **13**: 1763–9.
56. Crisp B. R., Williams M., Timpson S., Ross M. W. Medication compliance and satisfaction with treatment for HIV disease in a sample of African-American crack cocaine smokers. *AIDS Behav* 2004; **8**: 199–206.
57. Lucas G. M., Cheever L. W., Chaisson R. E., Moore R. D. Detrimental effects of continued illicit drug use on the treatment of HIV-1 infection. *J Acquir Immune Defic Syndr* 2001; **27**: 251–9.
58. Martini M., Recchia E., Nasta P., Castanotto D., Chiaffarino F., Parazzini F. *et al*. Illicit drug use: can it predict adherence to antiretroviral therapy? *Eur J Epidemiol* 2004; **19**: 585–7.
59. Smith-Rohrberg D., Mezger J., Walton M., Bruce R. D., Altice F. L. Impact of Enhanced services on virologic outcomes in a directly administered antiretroviral therapy trial for HIV-infected DU. *J Acquir Immune Defic Syndr* 2006; **43**: S48–53.
60. Wagner G. J., Ryan G. W. Relationship between routinization of daily behaviors and medication adherence in HIV-positive DU. *AIDS Patient Care STDS* 2004; **18**: 385–93.
61. McCance-Katz E. F., Kosten T. A., Kosten T. R. Going from the bedside back to the bench with ecopipam: a new strategy for cocaine pharmacotherapy development. *Psychopharmacology (Berl)* 2001; **155**: 327–9.
62. Vocci F. J., Acri J., Elkashef A. Medication development for addictive disorders: the state of the science. *Am J Psychiatry* 2005; **162**: 1432–40.
63. Vocci F. J., Elkashef A. Pharmacotherapy and other treatments for cocaine abuse and dependence. *Curr Opin Psychiatry* 2005; **18**: 265–70.
64. Parsons J. T., Rosof E., Punzalan J. C., Di Maria L. Integration of motivational interviewing and cognitive behavioral therapy to improve HIV medication adherence and reduce substance use among HIV-positive men and women: results of a pilot project. *AIDS Patient Care STDS* 2005; **19**: 31–9.
65. van der Werf M. J., Schinkel J., van Santen G., Vergouwe I., Wix R. A., van Ameijden E. J. Highly active antiretroviral therapy among DU in Amsterdam: self-perceived reasons for not receiving therapy. *AIDS* 1999; **13**: 1280–1.
66. Aceijas C., Oppenheimer E., Stimson G. V., Ashcroft R. E., Matic S., Hickman M. Antiretroviral treatment for injecting DU in developing and transitional countries 1 year before the end of the 'Treating 3 million by 2005. Making it happen. The WHO strategy' ('3 by 5'). *Addiction* 2006; **101**: 1246–53.