REVIEW ARTICLE

Drugs 2006; 66 (6): 769-789
0012-6667/06/0006-0769/$44.95/0



# Substance Abuse and Psychiatric Disorders in HIV-Positive Patients

## Epidemiology and Impact on Antiretroviral Therapy

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## Abstract

There is a high prevalence of substance abuse and psychiatric disorders among HIV-infected individuals. Importantly, drug and alcohol-use disorders are frequently co-morbid with depression, anxiety and severe mental illness. Not only do these disorders increase the risk of contracting HIV, they have also been associated with decreased highly active antiretroviral therapy (HAART) utilisation, adherence and virological suppression. The literature evaluating the relationship between substance abuse and HIV outcomes has primarily focused on injection drug users, although there has been increasing interest in alcohol, cocaine and marijuana. Similarly, the mental health literature has focused largely on depression, with a lesser focus on severe mental illness or anxiety. To date, there is little literature evaluating the association between co-occurring HIV, substance abuse and mental illness on HAART uptake, adherence and virological suppression. Adherence interventions in these populations have demonstrated mixed efficacy.

Both directly observed therapy and pharmacist-assisted interventions appear promising, as do integrated behavioural interventions. However, the current intervention literature has several limitations: few of these studies are randomised, controlled trials; the sample sizes have generally been small; and co-occurring substance abuse and mental illness has not specifically been targeted in these studies. Future studies examining individual substances of abuse, psychiatric disorders and co-occurring substance abuse and psychiatric disorders on HIV outcomes will inform targeted adherence interventions.

With the introduction of highly active antiretroviral therapy (HAART), AIDS-related morbidity and mortality has significantly decreased.[1-3] Poor adherence to HAART is associated with lower rates of virological suppression, disease progression, opportunistic infections and death.

Both substance abuse and mental illness have been associated with decreased medication adherence in the general population.[4-7] Among schizophrenic patients, non-adherence to antipsychotics has been reported to be as high as 49.5%.[8] Alcohol and illicit drug use have been associated with poorer adherence to antihypertensives.[9] A disproportionate number of HIV-infected individuals have substance use disorders and/or mental illness, both of which have been linked to non-adherence to HAART. Importantly, these disorders frequently co-occur, which may further worsen disease outcomes. Both substance use and mental disorders have the potential to be treated pharmacologically and behaviourally; consequently, interventions directed at these individuals may improve HIV-related outcomes.

We reviewed the English language literature on (i) the prevalence of alcohol and illicit drug use, mental health disorders and co-occurring mental health and substance use disorders in HIV-infected individuals; (ii) their effect on antiretroviral efficacy/effectiveness and adherence; and (iii) interventions to improve antiretroviral effectiveness and adherence in these populations. This literature review is based on MEDLINE and EMBASE searches using a combination of the keywords 'HIV', 'adherence', 'substance abuse', 'illicit drug use', 'alcohol', 'alcohol use disorders', 'cocaine', 'heroin', 'depression', 'anxiety', 'PTSD', 'bipolar', 'severe mental illness', 'schizophrenia', 'interventions' and 'prevalence'. We also reviewed the reference lists of abstracted articles to ensure the completeness of our search and the Cochrane Database of Systemic Reviews.

## 1. Substance Abuse and HIV: Prevalence and Effect on Antiretroviral Therapy

### 1.1 Injection-Drug Use (IDU), Illicit Drugs, Prevalence and HAART Utilisation

Drug use is prevalent worldwide and is associated with HIV transmission through high-risk sexual and injection behaviours including needle sharing, unsafe sexual practices, inconsistent condom use, and trading sex for money or drugs. Ten percent of HIV infections worldwide are attributed to injection-drug use (IDU) with >25 countries reporting ≥20% prevalence of HIV attributable to IDU.[10] In the HSCUS (HIV Cost and Service Utilisation Study), a US-based national probability sample, as many as 40% of HIV-infected individuals (n = 2864) admitted to illicit drug use in the previous 12 months.[11]

Not only is drug use prevalent among HIV infected individuals, HIV-infected injection-drug users are less likely to access HAART.[12-17] Gebo and colleagues,[16] examining data from ten HIV primary care sites in the US, found that individuals with IDU as their risk factor had decreased odds of receiving HAART (adjusted odds ratio [AOR]: 0.86 95% CI: 0.76, 0.99) compared with non-IDU. Bassetti et al.,[12] studying the Swiss Cohort, reported that a history of both IDU and ongoing IDU were associat-

ed with decreased HAART prescription. Similarly, in the French MANIF (Marseille, Avignon, Nice, Ile de France) cohort, active injection-drug users were three times less likely to receive HAART.[15] In addition, injection-drug users have also not derived the same benefit from HAART as non-users.[18,19] Moore and colleagues[18] examined the incidence of AIDS-defining illnesses (ADIs) from the time of their first HAART regimen. Comparing 827 injection-drug users with 1314 non-users, the incidence of ADIs decreased from 31.9 to 16.2 cases per 100 person-years of follow-up, compared with a decline from 37.0 to 9.7 cases per 100 person-years, respectively.

### 1.2 IDU and Adherence

Several cohort and cross-sectional studies have evaluated the association between drug use and HIV medication adherence, and virological and immunological outcomes (table I).[20-29] Lucas and colleagues[25] found that active drug users were more likely to report HAART non-adherence and had lower reductions in HIV-RNA than either former drug users or those who had never used drugs. Importantly, they found no difference in outcomes between former users and those who had never used drugs. In addition, they later reported that changing from non-use to active substance abuse was associated with decreased adherence and poorer virological outcomes.[24]

Other large cohort studies have demonstrated similar associations. Wood and colleagues,[20,21] evaluating 1422 antiretroviral-naive individuals initiating HAART between 1996 and 2000, reported a cumulative 12-month suppression rate of 70.8% for non-injection-drug users and 51.4% for those with a history of IDU. Injection-drug users were also more likely to experience rebound (54.7% vs 23.8%). Studying the same population, the authors found that injection-drug users also had a slower CD4+ T cell response rate than non-users. In both studies, the differences between injection-drug users and non-users diminished after adjustment for adherence, implying that the former could respond well to HAART if their adherence issues were addressed. Mocroft and associates,[17] studying 6645 HIV-infected individuals throughout Europe, found that those with IDU exposure were significantly less likely to receive HAART, but of those receiving HAART, virological and immunological outcomes were similar among injection-drug users and men who have sex with men (MSM). While Mocroft et al.[17] did not find any difference in virological and immunological outcomes by exposure group, it is important to note that HAART use differed significantly by exposure group and, thus, there may have been a selection bias. Furthermore, the IDU exposure group did not distinguish between current and past drug use, which also may have affected their results.

In addition to studies examining the effect of IDU on HIV outcomes, other studies have examined the effect of individual drugs, including cocaine, amphetamines and marijuana, on antiretroviral adherence. Studies by Arnsten et al.[29] and Tucker et al.[39] support an association between active cocaine use and antiretroviral non-adherence (table I). The studies on marijuana in this context have had mixed results, with Tucker and colleagues[39] demonstrating an association between marijuana use and poorer adherence, and de Jong et al.[40] demonstrating improved adherence among HIV-infected individuals using marijuana for nausea.

The literature on substance use and antiretroviral use and adherence generally supports an association between ongoing illicit drug use (with the exception of marijuana) and poorer antiretroviral adherence. In turn, adherence affects virological and immunological response to therapy. However, former drug use does not appear to be related to poorer outcomes.[25,41] The literature on specific drugs of abuse and their impact on HAART adherence and virological outcomes, however, is far from comprehensive. Future studies examining the relationship between specific drugs of abuse, will further clarify the impact of drug use on HIV outcomes.

**Table I.** Prospective and cross-sectional studies examining the association between alcohol/illicit drugs and antiretroviral adherence, viral suppression, and antiretroviral discontinuation

| Study (country, year) | Population | Alcohol exposure | Drug exposure | Outcome variable | Findings |
|---|---|---|---|---|---|
| **Prospective studies** | | | | | |
| Arnsten et al.[29] (US, 2002) | n = 85<br>Male: 60%<br>Active cocaine use: 28%<br>Active heroin use: 25%<br>More than 5 drinks per week: 12% | More than 5 drinks per week, daily use or use several days per week | Active heroin or cocaine use during study period | Median adherence (MEMS caps)<br>Viral suppression (HIV-RNA <500) | Active cocaine use associated with decreased median adherence (27% vs 68%) and viral suppression (13% vs 46%; p = 0.005). Alcohol associated with lower adherence (37% vs 62%) and viral suppression (21% vs 41%; p = NS) |
| Berg et al.[27] (US, 2004) | n = 113<br>Male: 57%<br>Active cocaine use: 27%<br>Active heroin use: 24%<br>Problem drinking: 30% | More than 5 drinks per week, daily use or use several days per week | Active heroin or cocaine use during study period | Median adherence (MEMS caps) | Among women, problem drinking was associated with decreased mean adherence (25% vs 57%) compared with those without problem drinking (p = 0.003). Cocaine use was associated with decreased adherence in both men and women |
| Braithwaite et al.[30] (US, 2005) | 2702 HIV+ and HIV−<br>Male: 94%<br>Illicit drug use: 21%<br>Abstainer: 57%<br>Non-binge drinker: 34%<br>Binge drinker: 9% | Measured in past 30 days<br>Abstainer (no alcohol)<br>Non-binge (alcohol but four or less drinks per occasion)<br>Binge (5 or more drinks per occasion) | Illicit drugs in past 12 months | Adherence<br>Timeline follow-back | 11% of binge drinkers missed medications on drinking days compared with 3.5% of non-binge drinkers on drinking days and 2.4% of non-drinkers on any day (p < 0.001) |
| Carrieri et al.[31] (France, 2003) | n = 96<br>Male: 64%<br>IDU risk factor: 100%<br>All initially adherent to ART | Number of units per month | IDU or cocaine use | Adherence (self-report, non-adherence defined as <80% in past week) | Active IDU associated with failure to maintain adherence, (AOR 3.3; 95% CI 1.0, 10.3) |
| Golin et al.[32] (US, 2002) | n = 117<br>Male: 80%<br>Active drug use: 5%<br>Alcohol use: 37% | Any alcohol use in past 30 days | Any drug use in past 30 days | Adherence (self-report, MEMS, pill count) | Patients with active drug use took 59% ART doses compared with 72% in non-users. Alcohol users took 66% ART doses compared with 74% in non-users |
| Haubrich et al.[33] (US, 1999) | n = 135<br>Male: 92%<br>Drug or alcohol use: 32% | Any alcohol use | Any drug use | Adherence (self-report: missed doses in previous 4 weeks) | At month 6, any drug or alcohol use was associated with decreased 95% adherence (47% vs 80%) compared with those with no use. Drugs/alcohol also associated with poorer immunological and virological outcomes |

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**Table I.** Contd

| Study (country, year) | Population | Alcohol exposure | Drug exposure | Outcome variable | Findings |
|---|---|---|---|---|---|
| Howard et al.[28] (US, 2002) | n = 161<br>Female: 100%<br>Crack cocaine use: 13%<br>IDU: 9%<br>Alcohol use: 17% | More than 1 drink per day | Crack cocaine and IDU during study period | Adherence (MEMS caps) | Alcohol use (43% vs 56%) and active drug use (34% vs 57%) were associated with decreased adherence. These associations remained significant on multivariate analysis (active drug p = 0.002; alcohol p = 0.04) |
| Samet et al.[34] (US, 2004) | n = 267 with history of alcohol problems<br>Male: 81%<br>At-risk drinking: 16%<br>Moderate drinking: 24%<br>Heroin use: 10%<br>Cocaine use: 25% | At-risk drinking:<br>Women >7 drinks per week or >3 per occasion;<br>Men >14 drinks per week or >4 per occasion.<br>Moderate:<br>>0 drinks and < at-risk drinking | Cocaine or heroin in past 30 days | Adherence (self-report, non-adherence defined as one missed dose in 72 hours) | Compared with at-risk drinkers, non-drinkers were more likely to be adherent (AOR 3.6; 95% CI 2.1, 6.2). Non-drinkers more likely to be adherent than moderate drinkers (AOR 3.0; 95% CI 2.0, 4.5) |
| Lucas et al.[25] (US, 2001) | n = 764<br>Male: 63%<br>Never used drugs: 25%<br>Former drug user: 49%<br>Current drug user: 26% | Alcohol consumption minimum 5 days per week | Active (heroin/cocaine in past 6 months)<br>Former (past use, not in previous 6months)<br>Never | Adherence (self-report, non-adherence defined as >2 missed doses in 2 weeks)<br>Viral response (log decrease in HIV-RNA) | Active drug users more likely to report non-adherence than former or never users (34% vs 17% vs 24%). Active drug users had decreased virological and immunological response compared with former or never users. No differences in outcomes between former and never drug users |
| Lucas et al.[24] (US, 2002) | Male: 72%<br>Active drug use: 29%<br>Heavy alcohol use: 5% | Heavy drinking:<br>≥4 drinks per week | Heroin or cocaine use in the previous 6months | Adherence (self-report, non-adherence defined as >2 missed doses in 2 weeks)<br>Viral suppression (1 log decrease in HIV-RNA or HIV-RNA <400) | Switching from non-use of any substance to abuse was associated with decreased adherence (AOR 0.4; 95% CI 0.3, 0.6) and viral suppression, (AOR 0.5; 95% CI 0.3, 0.8) |
| Mocroft et al.[17] (Europe, 1999) | n = 6645<br>MSM: 50%<br>IDU risk factor: 26.4% | NA | IDU risk factor | HAART Receipt<br>HIV-RNA <500<br>CD4+ cell count increase | IDU significantly less likely to receive HAART. Of those on HAART there was no difference in virological or immunological outcomes by exposure group (MSM vs IDU vs HET) |
| Palepu et al.[35] (US, 2004) | n = 349<br>Male: 79%<br>Alcohol, heroin or cocaine use: 24%<br>Alcohol use only: 18%<br>Heroin/cocaine use only: 5% | Alcohol use in the past 30 days | Cocaine or heroin in past 30 days | Adherence (self-report, non-adherence defined as <95% adherence over 30 days)<br>Viral suppression (HIV-RNA <500) | Use of drugs or alcohol not associated with decreased HAART receipt, but was associated with decreased adherence (AOR 0.17; 95% CI 0.11, 0.28) and viral suppression, (AOR 0.53; 95% CI 0.35, 0.82) |

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**Table I.** Contd

| Study (country, year) | Population | Alcohol exposure | Drug exposure | Outcome variable | Findings |
|---|---|---|---|---|---|
| Wood et al.[20] (Canada, 2003) | n = 1422<br>Initiating HAART between 1996 and 2000: 100%<br>Male: 84%<br>IDU history: 25.2% | NA | History of IDU | Viral suppression (HIV-RNA <500)<br>Viral rebound (two HIV-RNA >500 after initial suppression) | On univariate analysis, history of IDU associated with lower rates of HIV-RNA suppression (HR 0.6; 95% CI 0.5, 0.7), and higher rates of rebound (HR 1.5; 95% CI 1.2, 1.9). On MVA, differences between IDU and non-IDU attenuated after adjustment for adherence |
| **Cross-sectional studies** | | | | | |
| Cook et al.[36] (US, 2001) | n = 219<br>Male: 72%<br>Cocaine use: 13%<br>Heroin use: 5%<br>Binge alcohol use: 17%<br>Hazardous alcohol use: 15%<br>Heavy alcohol use: 10% | Binge: >5 drinks per occasion in women, >6 drinks per occasion in men<br>Hazardous: AUDIT >7<br>Heavy: >12 drinks per week in women; >16 drinks per week in men | Heroin, cocaine, marijuana, methadone or amyl nitrite in past 30 days | Adherence (missed dose in previous 24 hours or off schedule in the past week) | Hazardous (AOR 2.64; 95% CI 1.07, 6.53) and heavy drinking (AOR 4.7; 95% CI 1.5, 14.8) associated with taking medications off schedule |
| Miguez et al.[37] (US, 2003) | n = 220<br>Male: 59%<br>Crack cocaine use: 63%<br>Heavy alcohol use: 63% | Heavy alcohol use: daily or 3–4 times per week. | Cocaine, crack, marijuana | Viral suppression (HIV-RNA <200) | 44% of non-drinkers achieved viral suppression compared with 24% of light alcohol users and 14% of heavy alcohol users ($p < 0.007$) |
| Stein et al.[38] (US, 2000) | n = 42<br>On methadone maintenance:100%<br>Male: 64%<br>Active IDU: 38%<br>Alcohol abuse: 14% | Alcohol abuse diagnosed by SCID | IDU in previous 6 months | Adherence (assessed by four questions querying drug holidays, missing doses, taking medications off schedule) | On bivariate analysis, IDU significantly associated with drug holidays, missing doses in the last month and taking pills off schedule. Alcohol abuse significantly associated with missing medication in the previous day |
| Tucker et al.[39] (US, 2003) | n = 1910<br>Male: 78%<br>Illicit drug use in past month: 28%<br>Heavy/frequent heavy alcohol use: 14% | Use in past 4 weeks<br>Moderate alcohol use: <5 drinks per occasion<br>Heavy alcohol use: ≥5 drinks per occasion on 1–4 occasions (in the past 4 weeks)<br>Frequent heavy alcohol use: ≥5 drinks per occasion on ≥5 occasions (in the past 4 weeks) | Use in past 4 weeks of heroin, cocaine, marijuana, amphetamines, sedatives or inhalants | Adherence (self report; non-adherence defined as any missed dose in the past 1 week) | Compared with non-drinkers, moderate (AOR 1.6; 95% CI 1.3, 2.0), heavy (AOR 1.7; 95% CI 1.3, 2.3), and frequent heavy (AOR 2.7; 95% CI 1.7, 4.5) alcohol use were associated with non-adherence. Any drug use (AOR 1.6; 95% CI 1.2, 2.2) compared with none, cocaine (OR = 2.2; 95% CI 1.2, 3.8), marijuana (OR = 1.7; 95% CI 1.2, 2.3), amphetamine (OR = 2.3; 95% CI 1.2, 4.2) and sedative (OR = 1.6; 95% CI 1.0, 2.4) use were associated with non-adherence |

**AHR** = adjusted hazard ratio; **AOR** = adjusted odds ratio; **AUDIT** = Alcohol Use Disorders Identification Test; **HAART** = highly active antiretroviral therapy; **HET** = heterosexual; **HR** = hazard ratio; **IDU** = intravenous drug use; **MSM** = men who have sex with men; **MVA** = multivariate analysis; **NA** = not applicable; **NS** = not stated; **OR** = odds ratio; **SCID** = Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, fourth edition.

## 2. Alcohol and HIV: Prevalence and Effect on Antiretroviral Therapy

### 2.1 Prevalence of Alcohol Use

The effect of alcohol use on antiretroviral efficacy and adherence is gaining increased attention. Alcohol use is both prevalent and widespread throughout the world. The WHO estimates that 2 billion people consume alcohol, 76.3 million of whom have diagnosable alcohol-use disorders.[42] In the US, a nationally representative sample reported the 1-month prevalence of current alcohol use among HIV-infected individuals to be 53%, with 8% classified as heavy drinkers.[43] In the same sample, Turner and colleagues[44] found that 15% drank five or more drinks on one occasion in the previous month. Alcohol use is also prevalent in resource-poor countries.[45-47] Shaffer and colleagues,[45] surveying both HIV-infected and non-infected individuals attending urban and rural clinics in Western Kenya, reported a 55% prevalence of hazardous alcohol use, defined as an AUDIT (Alcohol Use Disorders Identification Test) score of >8. Mbulaiteye and associates[46] investigated the association between alcohol consumption and HIV seropositivity among 2374 adults in rural Uganda and reported that 57% of those surveyed had ever consumed alcohol. Individuals who ever drank alcohol had twice the prevalence of HIV than those who never consumed alcohol (10% vs 5%).

### 2.2 Alcohol and Adherence

Not only is alcohol use prevalent among HIV-infected individuals but also several prospective studies in the US have linked alcohol use to decreased antiretroviral adherence (table I).[27-30,32-36,48] Studies report a range of adherence (>95%) of 25–57% among those with varying levels of alcohol use (current, moderate, at-risk and heavy), compared with 56–76% in non-drinkers. Fewer studies have examined the relationship between alcohol use and virological suppression, but there appears to be a relationship between alcohol consumption and poorer virological suppression.[37,48] While the literature supports an association between alcohol use and adherence, the definition of alcohol use has not been consistent among these studies, making them difficult to compare. In addition, a large proportion of the literature on alcohol and adherence is from the US, where there is a high prevalence of concurrent drug use. Currently, ongoing studies in sub-Saharan Africa may provide some insight into the effects of alcohol on HIV-related outcomes in non-drug-using populations.

## 3. Adherence Interventions for HIV-Infected Individuals with Concurrent Alcohol and Substance Abuse

To date, there have been several reviews of antiretroviral adherence interventions among HIV-infected individuals.[49-53] In 2000, Haddad and colleagues[51] systematically reviewed the literature on patient support and education interventions for HAART adherence. Only controlled trials with a concurrent control group were included. Reviewing the literature between 1996 and 1999, they found only one eligible study, published in Spanish, consisting of a single pharmacist-led educational intervention followed by phone support.[54] Almost 50% of study subjects had IDU. After 24 weeks, 76% of the intervention group had at least 90% adherence compared with 53% of the control group ($p = 0.002$).

More recently, Cote and Godin[49] systematically reviewed the adherence literature between 1996 and 2003 and found 16 published studies designed to evaluate strategies to improve adherence, half of which were designed for individuals with current or recent substance abuse. Three of these studies were randomised, controlled trials (RCTs) and five were either pilot studies or feasibility studies. Of the five pilot studies, two reported on the same population. The interventions in these studies included cognitive behavioural interventions consisting of monthly educational sessions with weekly medication dispensing,[55] a storefront drop-in centre for homeless individuals,[56] directly observed therapy with an outreach worker,[57] and on-site dispensing and medication management at a methadone clinic.[58]

While these studies were generally promising, the sample sizes were small, ranging from 12 to 68, and four of the pilot studies did not contain a control group.

Cote and Godin[49] reported on three RCTs with sample sizes ranging from 25 to 195. One of the studies examined zidovudine (AZT) adherence among 27 individuals on methadone maintenance randomised to supervised therapy or usual care, but did not evaluate HAART.[59] Rigsby and colleagues[60] randomised 55 individuals to three arms in an adherence intervention. The control group received four weekly sessions with inquiries into adherence, the second arm received cue-dose training and feedback using Medication Event Monitoring System (MEMS) caps, and the third group received the same training and cash reinforcement for correct bottle opening. Adherence improved in the third arm during the first 4 weeks of the study but returned to baseline 8 weeks after discontinuing the intervention. Similarly, Rawling and colleagues[61] evaluated an educational programme in 195 HIV-infected individuals (20% were injection-drug users). Randomising individuals to the educational programme plus counselling, educational programme alone and routine counselling, the investigators found no difference in adherence among the groups.

Recently, Samet and colleagues[62] performed a randomised trial evaluating a multi-component adherence intervention in HIV-infected individuals with a history of alcohol problems. The intervention consisted of four encounters over 3 months with a nurse trained in motivational interviewing. The encounters were designed to (i) address alcohol problems; (ii) provide a watch with a timer to facilitate pill taking; (iii) enhance perception of treatment efficacy; and (iv) deliver individually tailored assistance to facilitate medication use. A total of 151 individuals were enrolled in the trial, with 93% assessed at follow-up. At the end of follow-up, the authors found no difference in 3- or 30-day adherence, HIV-RNA suppression or alcohol use between the intervention and control groups. The authors concluded that this multi-component intervention was ineffective in this population, and that directly observed therapy or simplified dosage regimens may improve adherence.

Modified directly observed therapy (MDOT) as a means of improving adherence has gained increased attention (table II).[63-69] Based on the tuberculosis model of directly observed therapy (DOT), HIV-infected individuals receive antiretroviral therapy in an observed setting. Interventions have taken place in methadone maintenance centres where clients receive a minimum of one daily HAART dose and methadone concurrently. Other MDOT interventions have involved an outreach worker who delivers the medication, while others have taken place in prisons. Table II summarises selected studies where the MDOT specifically targeted individuals with substance abuse.

While the available data on MDOT do appear promising, particularly among this difficult-to-reach population, much of the current literature describes preliminary data and only one of these studies is an RCT. Further randomised trials with appropriate follow-up may elucidate the efficacy and durability of MDOT.

Research on adherence interventions in those with substance abuse in general is preliminary, and consists of pilot studies and small controlled trials that range from pharmacist-led educational interventions to MDOT. Importantly, many of these interventions do not take into account co-occurring psychiatric disorders that may complicate adherence issues. There are ongoing randomised trials targeted towards substance abusers.[70-72] The INSPIRE (Interventions for Sero-Positive Research and Education) study group is currently evaluating an integrated behavioural intervention for injection-drug users designed to improve antiretroviral adherence and decrease high-risk behaviours. Future randomised prospective trials of behavioural interventions, MDOT and educational interventions will further elucidate techniques to improve adherence in this population. Finally, trials evaluating interventions for concurrent mental illness and substance abuse may also provide useful information.

**Table II.** Studies describing directly observed therapy (DOT) in HIV-infected individuals with substance abuse

| Study (country, year) | Study design | Setting | Intervention | Population | Outcome variable | Duration of follow-up (mo) | No. of withdrawals | Findings |
|---|---|---|---|---|---|---|---|---|
| Altice et al.[63] (US, 2004) | RCT (interim study describing first 72 IDU recruited and initial outcomes in DOT group) | Mobile van | DOT in mobile van, pagers as DOT reminder | n = 72<br>Male: 68%<br>Alcohol use: 36%<br>ART naive: 15% | Adherence in DOT group (MEMS caps) | 10 | 4 | Of those randomised to DOT, 76% adherence with supervised doses, 49.9% adherence with unsupervised (evening and weekend) doses |
| Babudieri et al.[64] (Italy, 2000) | Controlled trial<br>DOT (n = 37)<br>Control (n = 47) | 18 Italian prisons: 9 sites DOT, 9 sites control | DOT delivered by nurse in prison setting | n = 84<br>Male: 95%<br>ART naive: 15% | Viral suppression (HIV-RNA <400) | 22 | 2 | 64% on the DOT group achieved viral suppression compared with 34% in the control group |
| Conway et al.[65] (Canada, 2004) | Prospective | Methadone maintenance clinic | One dose of HAART observed with receipt of methadone | n = 54<br>Male: 54%<br>Receiving once-daily HAART: 54%<br>22% ART naive | Viral suppression (HIV-RNA <400) | 25 | NR | Of those receiving once daily HAART, 59% achieved viral suppression and of those on twice daily HAART, 72% achieved viral suppression (p-value non-significant) |
| Lucas et al.[67] (US, 2004) | Prospective with matched controls<br>DOT (n = 38)<br>Control (n = 50)<br>Alternative intervention (n = 40) | Methadone maintenance clinic | One dose of HAART observed with receipt of methadone | n = 128<br>Male: 26%<br>ART naïve: 63% | Viral suppression (HIV-RNA <400) | 6 | 14 | Intention to treat analysis: 79% of those receiving DOT achieved viral suppression compared with 54% in the standard care group and 48% in the alternate intervention group |
| Mitty et al.[68] (US, 2005) | Prospective | Hospital-based clinic | Outreach worker delivers medicines 5–7 days/week | n = 68<br>IDU: 96%<br>Male: 61%<br>ART naïve: 7% | Log decrease in viral load | 6 | 37 | Among those in MDOT at 6 months, there was a 2.7 log decrease in viral load |
| McCance-Katz et al.[69] (US, 2002) | Pilot study | Methadone maintenance clinic | Twice daily HAART with one dose observed with methadone and evening/weekend dose riboflavin tagged | n = 5 | Viral suppression (HIV-RNA <400) | 8wk | NR | 4 of 5 achieved viral suppression at 8 weeks. |

**ART** = antiretroviral therapy; **DOT** = directly observed therapy; **HAART** = highly active antiretroviral therapy; **IDU** = intravenous drug use; **MDOT** = modified directly observed therapy; **NR** = not reported; **RCT** = randomised, controlled trial.

## 4. Depression and HIV: Prevalence and Effect on Antiretroviral Therapy

Depression is common among individuals with HIV. Estimates of the prevalence of depression among small, American regional samples of HIV-infected individuals have ranged from 0% to 47.8%.[73-82] The wide variance of these estimates may be due to small sample sizes, regional variation and inconsistent use of diagnostic criteria for depression.[83] On the basis of these estimates, a systematic review and meta-analysis comparing HIV sero-positive individuals with HIV sero-negative individuals for rates of depressive disorders revealed that HIV-infected individuals were nearly twice as likely to be diagnosed with major depression as HIV sero-negative patients.[84] Overcoming some of the methodological limitations of previous studies, the HCSUS (HIV Cost and Services Utilization Survey) found 36% (95% CI 33.6, 38.3) of individuals screened positive for major depression and 26.5% (95% CI 23.5, 29.5) screened positive for dysthymia. As the study did not use a formal diagnostic interview, a clinically confirmed diagnosis of depression was not made.[11] Re-estimation of the prevalence of major depression from the HCSUS using a sub-sample of the HCSUS cohort who completed the full Composite International Diagnostic Interview (CIDI) reported the prevalence of depression to be 22.0% (95% CI 19.5, 24.5) and dysthymia to be 5.0% (95% CI 3.5, 6.5).[85]

Women with HIV may be at particular risk for depression. Many,[86-89] but not all,[11] studies have found that HIV-infected women report significantly more depressive symptoms than men. Reasons for this may include lower social status and female sex being a risk factor for depression.[90-92]

### 4.1 Depression and HIV Disease Progression

Although many studies have sought to determine whether depression is associated with immune function (e.g. CD4+ cell count) or severity of HIV illness (e.g. AIDS), the outcomes of these studies are equivocal. Results of short-term studies have not demonstrated an association between depression and HIV disease progression.[93-95] This lack of association may be due the long latency period between being infected with HIV and AIDS progression.[96] Longer term studies (e.g. ≥5 years of follow-up) have had mixed results. Some, but not all,[97,98] long-term studies have found an association between depression at baseline and severity of HIV illness and CD4+ cell count decline. A limitation of these studies is the use of baseline depression as a predictor of HIV-related outcomes. One study that controlled for depression as a time-dependent variable found depression to be associated with both CD4+ cell count decline and with AIDS progression.[99]

Among individuals who have co-occurring HIV and depression, barriers to receiving medical care may be compounded by symptoms associated with depression, symptoms associated with HIV and other issues, such as social stigma and transportation problems. From a provider's perspective, identifying mental health problems among individuals with chronic medical problems can be daunting. According to the model of competing demands, physicians prioritise 'competing clinical demands' for their attention during time-limited encounters.[100] Since depression may mimic or exacerbate the somatic symptoms associated with other chronic medical conditions (such as HIV),[101] identifying and treating depressive symptoms may require multiple visits to address the symptoms of both physical and mental illness. In keeping with other research that has shown depression itself to be associated with non-compliance with medical treatment,[102] cross-sectional studies have shown that individuals with HIV and depressive disorders are also more likely to encounter greater delays in accessing protease inhibitors[103] and have worse adherence to antiretroviral medication[104] than those with HIV alone. Several cohort and cross-sectional studies have evaluated the impact of depression on HIV disease outcomes (table III).[23,39,104-110] These studies demonstrate an association between virological failure and non-adherence in individuals with depression. Spire and colleagues,[107] longitudinally evaluating a French cohort of 445 individuals found that worsening depression scores at 4 months with HAART was associated with decreased adherence.

**Table III.** Prospective and cross-sectional studies examining the association between depression and antiretroviral adherence, viral suppression and antiretroviral discontinuation

| Study (country, year) | Population | Depression measure | Outcome variable | Findings |
|---|---|---|---|---|
| **Prospective studies** | | | | |
| Paterson et al.[110] (US, 2000) | n = 81<br>Active drug use: 7%<br>Alcohol use: 13% | BDI and GHQ | 95% adherence, MEMS caps | Lower psychiatric morbidity as measured by GHQ associated with >95% adherence (AOR 1.7; 95% CI 1.0, 3.0) |
| Spire et al.[107] (France, 2002) | n = 445<br>Male: 78%<br>Alcohol use: 26%<br>Active drug use: 3.6% | CES-D | Adherence, self-report (non-adherence defined as any missed dose in past 4 days) | Evolution of depression over study period associated with increased odds of non-adherence (AOR 1.39; 95% CI 1.04, 1.85) |
| Li et al.[106] (US, 2005) | n = 873<br>Male: 100%<br>Depression: 28% | CES-D >15 | HAART interruption, HAART discontinuation | Depression was significantly associated with HAART interruption (AOR 1.97; 95% CI 1.38, 2.80) and HAART discontinuation (AOR 1.42; 95% CI 1.17, 1.72) compared with those who remained on HAART |
| Anastos et al.[23] (US, 2005) | n = 961<br>Women: 100%<br>IDU risk factor: 32%<br>Depression: 50% | CES-D >15 | Virological response (HIV-RNA <80)<br>Viral rebound (HIV-RNA >1000)<br>Immunological response (CD4+ cell count increase of 100 cells)<br>Immunological failure (CD4+ cell count decline below pre-HAART nadir) | Depression was significantly associated with poorer virological response (AHR 0.81), and increased immunological failure (AHR 1.98). Depression was not significantly associated with viral rebound or initial immunological response |
| Parienti et al.[108] (France, 2004) | n = 71<br>Male: 79%<br>IDU risk factor: 17% | Hospital Anxiety Depression scale | Virological failure (2 HIV-RNA >400) | Depression was associated with virological failure in persons on NNRTIs (AHR 2.5; 95% CI:1.0, 6.4) |
| **Cross-sectional studies** | | | | |
| Ammasarri et al.[109] (Italy, 2004) | n = 135<br>Male: 65%<br>Active alcohol use: 10%<br>Active drug use: 9%<br>Depression: 24% | Montgomery Asburg >19 | Adherence, self report (non-adherence defined as any missed dose in past week) | Worse depression scores were associated with an increased odds of non-adherence, (AOR 1.05; 95% CI 1.0, 1.10) |
| Barfod et al.[105] (Denmark, 2005) | n = 887<br>Male: 79%<br>IDU risk factor: 4%<br>Depression: 47% | Single question querying depression | Adherence, self-report (non-adherence defined as any missed dose in past 4 days)<br>Viral failure (2 HIV-RNA >400 or termination of care) | Depression was associated with an increased odds of viral failure (AOR 2.09; 95% CI 1.19, 3.68). There was a crude association between depression and non-adherence (OR 2.1; 95% CI 1.2, 3.7) |
| Gordillo et al.[104] (Spain, 1999) | n = 366<br>Male: 76%<br>IDU risk factor: 44%<br>Depression: 40% | BDI >14 | Adherence (pill count + self-report) | Individuals with social support and no depression were nearly 2 times more adherent than those with depression and without social support (AOR 1.86; 95% CI 0.98, 3.53) |

*Continued next page*

**Table III.** Contd

| Study (country, year) | Population | Depression measure | Outcome variable | Findings |
|---|---|---|---|---|
| Tucker et al.[39] (US, 2003) | n = 1910<br>Male: 78%<br>IDU in past month: 28%<br>Heavy alcohol use: 14%<br>Depression: 16% | CIDI | Adherence, self-report (non-adherence defined as any missed dose in the past 1 week) | Depression was associated with non-adherence to antiretroviral therapy, (AOR 1.7; 95% CI 1.3, 2.3) |

**AHR** = adjusted hazard ratio; **AOR** = adjusted odds ratio; **BDI** = Beck Depression Inventory; **CES-D** = Center for Epidemiologic Studies Depression scale; **CIDI** = Composite International Diagnostic Interview; **GHQ** = general health questionnaire; **HAART** = highly active antiretroviral therapy; **IDU** = intravenous drug use; **MVA** = multivariate analysis; **NNRTI** = non-nucleoside reverse transcriptase inhibitor; **OR** = odds ratio.

Li and associates,[106] prospectively studying 873 men in the US, demonstrated that depression was associated with both HAART interruption and discontinuation. In this study, HAART discontinuation was associated with virological failure.

Although previous studies have had conflicting results regarding whether or not depression is associated with increased mortality among those with HIV,[111] two recent studies have found that, among women, depression is associated with increased mortality. Results from the HERS (HIV Epidemiology Research Study),[112] a cohort of 871 HIV-infected women, found that among women with CD4+ cell counts <200 cells/mm$^3$, those with chronic depressive symptoms (as measured by the Center for Epidemiologic Studies Scale [CES-D]) had 4.3 (95% CI 1.6, 11.6) times the adjusted odds of death compared with compared with those without depression. Women with chronic depressive symptoms were also found to have greater declines in their CD4+ cell counts compared with those without depression. Similarly, results from the WIHS (Women's Interagency HIV Study),[113] a cohort of 2059 HIV-infected women, found that women with chronic depressive symptoms, as measured by the CES-D, had 1.7 (95% CI 1.1, 2.7) times the adjusted odds of death compared with women without depression. Strengths of these two studies include adjusting for potential confounders (e.g. CD4+ cell count, HAART) and length of follow-up. An acknowledged limitation of the HERS study is the lack of adjustment for medication adherence, whereas the WIHS cohort includes this adjustment. However, in the WIHS cohort, even after adjustment for adherence, depression was associated with an increased odds ratio for death. This suggests that the increased mortality among depressed HIV-infected women may be partially explained by adherence, but other mediators, including access to HAART, are likely to influence mortality among this population. A limitation of both studies is the use of a self-reported depression scale rather than using a formal diagnostic tool.

### 4.2 Interventions to Improve Access to Care and Adherence in Depression

Several studies have found that mental health treatment may increase the probability that individuals with depression receive and utilise HAART.[44,114,115]

One retrospective study in an urban clinic with integrated mental healthcare found that, compared with HAART-naive individuals with AIDS and without a mental disorder, HAART-naive individuals with AIDS and a mental disorder who were receiving mental health treatment were 50% more likely to receive HAART, had over twice the likelihood of remaining on HAART for at least 6 months and were 40% more likely to survive through the study period.[115] Results from the WIHS found that, after controlling for severity of depression, those who used mental health services had 1.21 (95% CI 1.10, 1.32) times the adjusted odds of utilising HAART compared with those who did not use mental health services.[116] However, a weakness of these studies was their inability to provide specific

information regarding what types of mental health interventions may lead to better outcomes.

Several studies provide suggestive evidence that antidepressant therapy improves antiretroviral adherence in depressed HIV-infected individuals.[117-119]

Yun and colleagues[119] recently published a retrospective analysis evaluating the effect of antidepressant treatment on antiretroviral adherence. Using clinical charts, administrative data and pharmacy records, abstractors retrieved depression information using International Classification of Diseases (9th edition) [ICD-9] codes, psychiatric diagnoses, primary care records and antidepressant prescription on 1713 HIV-infected patients with a minimum of 6 months of care between 1997 and 2001; there were 450 individuals receiving antiretroviral therapy and who had a diagnosis of depression. Adherence information was obtained through pharmacy refill records for those on HAART. Adherence of ≥95% was considered adherent. The authors found that depressed individuals receiving antidepressant therapy were more likely to be adherent than depressed individuals not receiving antidepressants (65% vs 35%; p = 0.01). Furthermore, there was a temporal association with higher HAART adherence in the 6-month period post-antidepressant initiation. Similarly, Turner and associates,[118] using New York State Medicaid data, evaluated the relationship of sex, depression, medical care and mental healthcare to adherence in HIV-infected drug users. In depressed individuals, both mental healthcare alone (AOR 1.52; 95% CI 1.03, 2.26) and psychiatric care plus antidepressants (AOR 1.49; 95% CI 1.04, 2.15) were associated with an increased adjusted odds of adherence.

While both of these studies demonstrate an association between antidepressant treatment and improved adherence, neither are prospective trials evaluating the efficacy of antidepressant treatment on antiretroviral adherence. Nor are they able to comment on a change in depressive symptoms with antidepressant therapy. RCTs with standard adherence and psychiatric measures are necessary to determine the efficacy of these treatments on antiretroviral adherence and virological and immunological outcomes.

An analysis of Medicaid claims data from New Jersey found that depressed HIV-infected individuals treated with antidepressants were almost twice as likely to be receiving antiretroviral therapy as depressed HIV-positive individuals who were not prescribed antidepressants.[117] Finally, a recent systematic review and meta-analysis evaluating the efficacy of antidepressant medication among HIV-infected individuals with depression found that antidepressant medication is efficacious in treating depression. The pooled effect size from the random effects model was 0.57 (95% CI 0.28, 0.85). The under-representation of women and minorities limits the generalisability of these findings and suggests that future studies be directed to address this disparity.[120]

## 5. Severe Mental Illness: Prevalence and Effect on Antiretroviral Therapy

### 5.1 Prevalence of HIV among Individuals with Serious Mental Illness

The definition of serious mental illness (SMI) is based on diagnosis, duration of illness and level of disability. The definition includes the diagnoses of schizophrenia, schizoaffective disorder and other non-substance-abuse-related psychoses, and bipolar affective disorder or another Axis I diagnosis (non-substance abuse) with extensive history of prior hospitalisation.[121] Several studies throughout the 1990s found high rates of HIV infection among samples of individuals with SMI, ranging from 5.0% to 23%.[122-124] A more recent convenience sample of 921 individuals with SMI (from four East coast states of the US) receiving inpatient or outpatient mental health treatment found the seroprevalence of HIV to be 3.1% [125,126] or nearly 8 times the seroprevalence of the general population. Methodological limitations of these studies include the use of convenience samples taken from Northeastern States; lack of adjustment for race, ethnicity, substance use or marital status; and lack of a comparison sample. A study that used Medicaid claims data

from Philadelphia reported that individuals with schizophrenia had 1.5 times the prevalence of HIV, while those with chronic depression or bipolar affective disorder had 3.8 times the prevalence of HIV compared with those without a mental disorder.[127,128] Although the study was able to adjust for age, race and ethnicity, it did not adjust for substance use or marital status. This is important, as descriptive studies have reported that individuals with SMI may be at risk for HIV as a result of IDU and engaging in high-risk sexual behaviours.[129,130]

### 5.2 Receipt of and Adherence to Antiretroviral Medication among Individuals with Serious Mental Illness and HIV

Previous research suggests that individuals with SMI are not only at high risk for chronic medical disorders,[131-134] but are less likely to receive potentially life-saving interventions for these chronic conditions.[135,136] Few studies have evaluated the degree to which HIV-infected individuals with SMI receive and adhere to antiretroviral medications. Barriers to care may include patient-related barriers and/or physician-related barriers.

Patient-related barriers to medical care include cognitive, social support and social skills deficits, as well as symptoms of disorganisation, avoidance or paranoia.[137] One study using New Jersey Medicaid claims data from 1996 to 1998 found that patients with SMI were more likely to have initiated new antiretroviral therapy (defined as receiving a protease inhibitor or a non-nucleoside reuptake inhibitor) than those without serious mental illness.[138] This study also found that those with schizophrenia were as likely to have persistent prescriptions for the medication as those without mental illness. There are several limitations to this study. First, the analysis did not include CD4+ cell count and, thus, the results are at risk of being confounded by severity of disease. Secondly, the analysis was based on receipt of a single medication rather than HAART itself. Finally, persistence of prescription refill does not indicate whether a person actually adhered to treatment. Only one study has directly evaluated adherence among those with SMI. In this study, 47 HIV-infected individuals with schizophrenia were followed for 2 weeks using electronic monitoring caps to evaluate whether these individuals were able to adhere adequately to the schedule of antiretroviral medication.[139] This study found that the mean adherence (proportion of prescribed doses taken) to antiretroviral medication was 66% (SD ± 34). The researchers noted that attendance at recent mental health clinical appointments was highly correlated with antiretroviral medication adherence and accounted for 49% of the variance in adherence. This study suggests that, with appropriate follow-up, individuals with schizophrenia are able to adhere to HAART, at least in the short term. From a health services' perspective, several studies have also found that individuals with psychiatric disorders, including those with SMI, have longer lengths of inpatient medical hospitalisation related to HIV.[140-142] Reasons for the increased length of hospital time may include extra time needed to treat psychiatric issues and arranging for complex care needs at discharge.

Physician-related barriers to receiving HIV-related medical care may include stigmatisation related to severe mental illness[143] or competing demands for clinical time.[100] One study reported that HIV clinicians were as likely to recommend HAART when presented with case vignettes of patients with new-onset AIDS when schizophrenia was present as when it was absent.[144] Compared with those HIV clinicians who received a case vignette without schizophrenia, those who received vignettes with schizophrenia were more likely to avoid prescribing efavirenz, a medication with known neuropsychiatric adverse effects, (17.7% vs 45.5%; $p < 0.01$); more likely to agree to be helped by a specialist (34.5% vs 12.9%; $p < 0.01$); and more likely to recommend directly observed therapy (20% vs 10%; $p = 0.01$). These findings suggest that HIV clinicians are willing to recommend HIV treatment for those with schizophrenia and AIDS, but are more likely to do so if they are receiving help from a mental health specialist and the patient is receiving more structured types of medical interventions.

## 6. Anxiety: Prevalence and Effect on Antiretroviral Therapy

In the US, anxiety disorders are prevalent. In the National Comorbidity Survey Replication (NCS-R), Kessler and colleagues[145] estimate the 12-month prevalence of any anxiety disorder to be 18.1%. The prevalence of any anxiety disorder or anxiety symptoms in HIV-infected individuals ranges widely among studies (from 10% to 72%),[85,146-148] as the instruments used to assess anxiety have ranged from symptom scales to diagnostic interviews. The HCSUS, using a diagnostic interview, reported a 16% prevalence of generalised anxiety disorder and 10.5% prevalence of panic.[11] Similar to depression, anxiety appears to impact on antiretroviral adherence.[149-151] Tucker et al.,[39] using HCSUS data, studied antiretroviral nonadherence as a function of specific psychiatric disorders and found that individuals with anxiety (OR 2.4; 95% CI 1.2, 5.0) and panic (OR 2.0; 95% CI 1.4, 3.0) were more likely to be nonadherent than those without a psychiatric disorder. Post-traumatic stress disorder (PTSD) has also been associated with decreased adherence to HAART.[152] Despite the relatively high prevalence of anxiety among HIV-infected individuals and its association with non-adherence, the research on anxiety in HIV-infected individuals is sparse, and there are few data on its association with immunological and virological outcomes.

## 7. Co-occurring Substance Use and Mental Disorders

Substance use and mental disorders are both prevalent among HIV-infected individuals, and are associated with adherence and virological outcomes. Importantly, mental and substance-use disorders frequently co-occur. Data from the ECA (Epidemiologic Catchment Area) study show that among individuals with a lifetime history of a drug-use disorder, over half were also affected by a mental disorder. Moreover, the odds of a mental health disorder was 4.5 times greater than for those without a history of another drug disorder.[153] Merikangas and colleagues,[154] using data from the International Consortium of Psychiatric Epidemiology (which included surveys from Canada, the Netherlands, Germany, Mexico and the US), found that mood and anxiety disorders were associated with drug abuse and dependence (range OR 1.9–5.3 and 1.8–5.2, respectively). When stratified by sex, the magnitude of comorbidity was greater for women, especially at lower levels of substance use.

Similarly, individuals with mental disorders are more likely to have substance-use disorders. For example, in the NCS-R, 24% of individuals with lifetime major depressive disorder also met diagnostic criteria for lifetime substance-use disorder and 8.5% met criteria for substance-use disorder in the previous year.[155]

Comorbid psychiatric disorders have the potential to exacerbate the negative health and social consequences of drug and alcohol abuse/dependence. Psychiatric disorders also interfere with successful treatment of the substance-use disorders, increasing risk of relapse and treatment withdrawal.[156] As described previously, both substance abuse and mental illness have been associated with decreased access to HAART and poor antiretroviral adherence. Therefore, it would not be surprising that HIV-infected individuals with co-occurring psychiatric and substance-use disorders may experience even greater difficulties in accessing and engaging in care than individuals with either substance-use or psychiatric disorders.

Among HIV-infected individuals, the prevalence of co-occurring substance use and mental health disorders has ranged from 10% to 28%.[157,158] There has been increasing interest in these 'triply' diagnosed individuals[159,160] but, to date, there have been few published studies specifically focusing on this population. Much of the literature has studied injection-drug users specifically and has examined depression as an independent variable affecting outcome.[29,31] Waldrop-Valverde and Valverde,[161] examining 58 injection-drug users receiving HAART, found that depression was associated with decreased odds of adherence (OR 0.92; 95% CI 0.86, 0.98). Avants and colleagues[162] studied adherence among injection-drug users receiving methadone and, similarly, found that depression was associated with

non-adherence. Bouhnik and associates[163] recently determined that depression predicted clinical progression among HIV-infected injection-drug users independently of adherence. Although literature examining the impact of co-occurring HIV, substance-use and mental health disorders on antiretroviral effectiveness is scant, there are ongoing trials studying the effect that triple diagnosis has on HIV disease progression and on adherence interventions.[164]

## 8. Conclusions

Both substance abuse and mental illness are prevalent among HIV-infected individuals, and are associated with decreased HAART uptake, adherence and virological suppression. However, the majority of the literature on substance abuse, mental health and HIV outcomes has focused on IDU and depression, with a smaller proportion focusing on polysubstance abuse, individual drugs of abuse, SMI, anxiety and co-occurring substance abuse and mental illness.

With the introduction of HAART, AIDS-related morbidity and mortality has significantly decreased, but not all infected individuals have derived equal benefit from therapy. Despite associations between IDU, alcohol use, depression and antiretroviral adherence, few interventions have been successful in improving HIV outcomes. Adherence interventions remain preliminary, with small sample sizes, few RCTs and little focus on co-occurring substance abuse and mental illness.

Further examination of the independent and joint effects of substance abuse and mental illness on HIV outcomes may better inform future adherence interventions among HIV-infected individuals with substance-use and mental health disorders, ultimately improving their outcomes.

## Acknowledgements

This research is supported by the National Institute of Alcohol Abuse and Alcoholism K23 AA015313 (Chander) and by the National Institute of Drug Abuse (NIDA) K23 DA 019820 (Himelhoch) and NIDA K24 DA00432. The authors have no conflicts of interest directly relevant to the contents of this article.

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