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Substance Use: Impact on Adherence and HIV Medical Treatment

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Abstract Substance use is highly prevalent among people living with HIV/AIDS, is often comorbid with other mental health problems, related to poor HIV medical outcomes, and, is associated with poor medication and treatment adherence. The current review reports on the recent state of the literature in terms of substance use and its relation to HIV medication and treatment adherence, and offers recommendations for advancing treatment and secondary HIV prevention efforts. Identifying substance users within HIV primary care and developing, evaluating, and refining integrative substance use-mental health-adherence interventions may be clinically important targets for effective disease management and may contribute to secondary HIV prevention efforts.

Keywords HIV · AIDS · Substance use · Adherence · Treatment utilization

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Introduction

The use of antiretroviral therapies (ART) to manage HIV/AIDS has resulted in greater control of viral replication, delays in clinical progression, and decreased AIDS-related deaths [1–4]. In addition, a high level of ART adherence (>95%) is optimal to achieve suppression of viral replication and improve immunity [5, 6]. Moreover, emerging data from 1763 HIV-serodiscordant couples enrolled in the HIV Prevention Trials Network [7••] suggest that among HIV-infected partners, immediate enrollment in ART compared to delayed ART initiation (based on CD4 T-cell count <250 or development of an AIDS-related illness) resulted in a significant 96% reduction in HIV seroconversion risk for uninfected partners. This is the first randomized clinical trial to demonstrate that treating an HIV-infected person early with ART can reduce the risk of sexual transmission for individuals without HIV. These results underscore the clinical and public health significance of effective treatment as prevention through engagement/retention in care and ART adherence regarding the use of ART among people with HIV/AIDS.

Substance use is highly prevalent among people living with HIV/AIDS, with 40–74% reporting comorbid substance use or related disorders [8–12]. This raises important public health concerns as substance use among people with HIV/AIDS has been consistently related to the presence of other psychiatric problems (eg, anxiety/depression) [8, 13], lower CD4 T-cell counts and poorer HIV viral suppression [14–16], and HIV medication *nonadherence* [17••, 18, 19••, 20].

Problematic substance use is typically categorized across two diagnostic categories, namely, substance abuse and dependence. Substance intoxication and withdrawal are less frequently studied with respect to health behaviors. Sub-

stance abuse describes a pattern of use resulting in interference and impairment in areas of daily living, whereas substance dependence describes various patterns of use characterized by lack of control and problematic regulation of use over time. According to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* [21], substance dependence is defined as a maladaptive pattern of substance use that leads to clinically significant impairment or distress, categorized by the presence of three or more of the following within the same 12-month period: tolerance of the substance; presence of withdrawal-related symptoms; using the substance in larger amounts or over longer periods of time than initially intended; persistent desire or unsuccessful attempts to reduce or control the use of the substance; spending a great deal of time in obtaining, using, or recovering from the effects of the substance; reducing or giving up social, occupational, or recreational activities because of substance use; and continued use of the substance despite persistent physical or psychological problems caused by or exacerbated by use of the substance. Substance abuse, often a less severe classification of substance use problems, is characterized by a maladaptive pattern of substance use that leads to clinically significant impairment or distress categorized by the presence of one or more of the following within a 12-month period: recurrent substance use resulting in failure to carry out major obligations at work, school, or home; recurrent substance use in situations in which it is physically hazardous; recurrent substance use–related legal problems; and persistent substance use despite ongoing or recurrent social/interpersonal problems caused or exacerbated by the effects of the substance [21]. Both disorders are related to clinically significant impairment and maladaptive management of HIV.

Substance use and related disorders stand out as prominent barriers to HIV medication adherence among people managing HIV. Indeed, recent reviews of the literature regarding factors related to adherence suggest that substance use and abuse are consistent predictors of HIV medication nonadherence [22, 23••]. Understanding and addressing these pathways continue to be paramount for successful HIV disease management and prevention.

The current review is designed to represent the emerging research in the area of substance use and HIV medication and treatment (defined as clinical care appointment attendance and management) adherence so as to offer directions for future research and suggestions for clinical practice. To that end, this review reports on the current state of the empirical research from 2009 to 2011 with respect to the comorbidity of substance use and HIV and its relation to medication and HIV treatment adherence, and is presented in four sections: 1) review of emerging research examining the relationships between substance use (broadly conceived) and comorbid mental health, and HIV medication and treatment adherence, including access to, utilization of, and retention in HIV medical care; 2) review of specific substances (ie, alcohol, heroin, cocaine, marijuana, methamphetamine, and tobacco) and their relation to HIV medication and treatment adherence; 3) review of recent related treatments targeting substance use and medication adherence among people with HIV/AIDS; and 4) concluding observations regarding HIV treatment and prevention implications and areas for future research.

Substance Use, Comorbid Mental Health, and ART and Treatment Adherence, and Access/Utilization/Retention in Care

Substance Use

A recent review ($n=88$ studies) of facilitators and barriers related to ART adherence highlights substance abuse as a significant barrier to adherence [23••]. In addition, a previous review by Malta and colleagues [20] suggests that although active substance use is related to poor medication adherence, drug users with HIV can achieve high levels of adherence if receiving structured care and/or drug abuse treatment, possess positive psychological factors (eg, high self-esteem), and have access to mental health treatment. Their recent meta-analysis [24] also suggests that drug users and non-users may have similar rates of adherence (approximately 60%). However, several reviewed studies were limited to injection drug users and those in structured treatment, and there was considerable variation in the type of adherence assessments between studies. Nevertheless, there may well be important facilitators for medication adherence among substance users with HIV/AIDS. A recent study of 703 injection drug users with HIV/AIDS identified both structural (stable housing, medical coverage) and individual (patient-provider engagement, more HIV primary care visits, not currently using drugs, and a positive attitude about ART benefits) predictors of ART use at a 6-month follow-up. These results suggest that even within the context of substance use, there may be clinically relevant structural and individual level factors to consider as a means of facilitating HIV medication adherence. Future research is needed to examine the effects of addressing the observed facilitative adherence factors in relation to sustained ART adherence for drug users with HIV/AIDS.

In addition to HIV ART adherence, substance use also is related to nonadherence to other HIV-related medical treatment. For example, among 1666 patients with HIV/AIDS enrolled in the Supplement to HIV/AIDS Surveillance project and prescribed medication to prevent *Pneumocystis carinii* pneumonia (PCP), injection drug use, non-

injection drug use, and marijuana use were each related to nonadherence to PCP prophylaxis medications [25]. Similarly, among 140 individuals co-infected with both tuberculosis (TB) and HIV, alcohol use and cigarette smoking were related to non-adherence to anti-TB medications [26]. Thus, there may be multiple priority medication adherence targets among substance users with HIV/AIDS and co-occurring medical problems.

Comorbid Mental Health and Substance Use Disorders

Substance use and mental health disorders often co-occur in people with HIV/AIDS with recent estimates of up to 23% [8, 13]. Recent data from 1,138 adults with HIV/AIDS and comorbid mental and substance abuse disorders (assessed via a structured clinical interview) enrolled in the HIV/AIDS Treatment Adherence, Health Outcomes, and Cost Study suggest that costs of care for this population are approximately twice as high ($3880 per patient per month) as costs for people with HIV/AIDS in general [27]. Data from the same study indicated that nonadherence to medications was related to current alcohol and substance abuse, increased psychological distress, less attendance at medical appointments, nonadherence to psychiatric medication, and lower self-reported spirituality. Importantly, psychological distress was a significant predictor of non-adherence independent of substance abuse [28••]. Moreover, examination of data from the HIV Research Network (n=10,284) suggests that co-occurring mental illness and substance use are significantly related to the lower ART receipt and decreased odds of viral suppression as compared to individuals with either mental illness or substance use alone [29]. These results, collectively, highlight the clinical and cost significance of assessing and treating co-occurring mental illness and substance use among people with HIV/AIDS.

Access/Utilization/Retention in HIV Care

A recent meta-analysis examining the initiation of HIV medical care (eg, ART) suggests that early initiation of ART (at CD4 T-cell count >350) for persons with HIV/AIDS may contribute to slower clinical progression and better survival [30]. In addition, ongoing retention in care is also associated with better survival [31]. There is good recent evidence to suggest that substance use interferes with these treatment parameters. For example, among 3,722 patients with HIV/AIDS, a history of drug use (injection drug use [IDU] and non-IDU) was significantly related to decreased receipt of ART and less time on ART [9]. Similarly, in a large sample (n=1038) of inpatients with HIV/AIDS, crack cocaine use and heavy drinking was associated with never having had a HIV-care provider and not receiving ART [32].

Substance users with HIV/AIDS also tend to use emergency department (ED) services more often as a means for care [33, 34] and have worse early retention in HIV care [35]. For example, in a study of 951 patients from 14 HIV clinics, current or former substance use and social alcohol use was significantly related to using the ED to receive care in the previous 6 months [33]. In addition, recent data from 2,791 HIV-infected women enrolled in the Women's Interagency Study, a large prospective study, indicated that moderate alcohol use and use of crack/cocaine/heroin was significantly related to early (visits 2 and 3 out of 10) non-attendance [36].

Collectively, results suggest that substance users with HIV/AIDS may be less likely to initiate or access HIV-related medical treatment, may utilize ED services more often for care, and have greater problems with early retention in care. In addition, a recent study of 694 patients with HIV/AIDS suggests that those reporting drug use or heavy alcohol use may be significantly over-reporting utilization of care [37], suggesting that multiple methods of assessment may be warranted to accurately evaluate treatment utilization for this population. Moreover, identification of substance use and referral to substance use treatment at the early stage of HIV care may be particularly important for successful substance use and HIV management.

Specific Substances and Relations with ART and HIV Treatment Adherence

Alcohol

Harmful alcohol use is highly prevalent among people with HIV/AIDS [17••, 38]. HIV risk groups that may be most vulnerable for harmful use include men who have sex with men (MSM) using stimulants, polydrug users, and ex-substance users [38]. Alcohol use is related to poor health outcomes for persons with HIV/AIDS. For example, alcohol use is related to CD4 T-cell decline, independent of ART, and greater HIV viral load via ART nonadherence [39, 40]. A recent review of the literature suggests that alcohol use may play a causal role in terms of worsening disease state and is related to less support seeking and poor ART adherence [41]. In addition, alcohol use is significantly related to increased mortality, hepatitis C co-infection [42], developing lipodystrophy [43], and to never being on ART [44]. Moreover, consuming liquor only (compared to beer or wine only) is related to poor CD4 T-cell production and poor viral suppression [45•].

There is a large and growing body of research examining the relation between alcohol use and medication adherence and HIV disease markers. A recent review by Azar and colleagues [17••] suggests that alcohol use disorders are

related to decreased ART adherence and to poorer HIV treatment outcomes. In addition, a meta-analysis of 40 studies indicates that alcohol users are only 47–60% as likely to be adherent to ART than non-users, with no differences observed between problem drinking, moderate drinking, and global drinking stratifications based on the National Institute on Alcohol Abuse and Alcoholism criteria for at-risk drinking (>14 drinks/week or >4 drinks in a day or met diagnostic criteria for an alcohol use disorder) [19••]. In the Swiss HIV Cohort Study, among patients on ART (n=4519), alcohol use was significantly related to missed doses, and severe alcohol users (based on the World Health Organization classification [WHO]: >40 g for women and >60 g for men) were more likely to be off ART [46]. Results from the same cohort study suggest that increasing alcohol use independently predicts worsening adherence over time [47]. Moreover, low levels of alcohol use are related to better HIV appointment adherence over time, specifically among minority youth with HIV [48]. Finally, recent international studies consistently highlight a significant association between alcohol use and medication nonadherence [49–55].

Collectively, results indicate that alcohol use is indeed related to poor disease outcomes and medication non-adherence, and suggest that targeted alcohol interventions are needed for this population. Recent work suggests that patients with HIV have common beliefs that drinking alcohol is toxic when taking ART and as a result stop taking ART when drinking, which may lead to general ART nonadherence [56]. Other work highlights the significance of educating providers about the negative effects of alcohol and the importance of disconfirming beliefs and myths about the toxicity of alcohol use and ART [57].

Cognitive behavioral therapy (CBT)-based interventions have been shown to be effective in reducing alcohol use among people with HIV/AIDS [58], and related interventions can be effectively adapted for different cultures [59]. Previous work has effectively targeted ART adherence among harmful alcohol users with CBT and motivational interviewing skills; however, alcohol use was not significantly impacted [60]. A recent randomized clinical trial (n=253) evaluated the effectiveness of a manualized intervention to reduce alcohol use (and unprotected sexual behavior) [58]. The intervention included individual alcohol counseling, peer group education and support, and motivational interviewing compared to resource referrals. Results indicated that the active intervention significantly reduced drinking in a 30-day period and days on which heavy drinking and unprotected sex co-occurred. Future work is needed to build upon alcohol use-ART adherence interventions to target both health behaviors and interfering beliefs, and to develop novel interventions that may promote positive change over time [61].

Heroin

The use of heroin and other opioids, specifically via IDU, is associated with decreased ART receipt and adherence [9, 62], poor virologic and immunologic responses to ART [63], and may place individuals at risk for transmitting HIV [64, 65]. Opioid substitution therapy (OST), in particular methadone maintenance therapy (MMT) and buprenorphine-naloxone (BUP), has been shown to be effective in reducing opioid use, preventing relapse, and enhancing ART and HIV treatment adherence among people with HIV/AIDS [66–68]. Recent work suggests that the context and delivery of OST may affect HIV treatment attendance and drug use cessation rates. For example, data from a randomized trial indicate that providing BUP and case management at HIV medical clinics may be more successful in reducing opioid use and increasing HIV primary care visits than referral to opioid treatment programs; however, this method of treatment may not have an effect on ART adherence or CD4 T-cell count and HIV viral load [68].

In terms of ART adherence among heroin users, direct hands-on adherence interventions appear to be most effective. In a recent randomized study in China, active heroin users with HIV/AIDS that received nurse-delivered education and adherence skills training at home combined with telephone calls were more likely to report taking 100% of their ART medication and taking ART on time, compared to active users in routine care [69]. Treatment procedures that promote ART adherence that maintain over time in the context of heroin use and treatment have yet to be established. Comprehensive care models that intervene on IDU, ART adherence, and other comorbid problems (eg, depression/anxiety) may offer the best promise [70, 71].

Cocaine

Cocaine use has been linked to poor ART adherence and poor HIV-related health outcomes independent of ART use. Previous longitudinal work in 150 adults with HIV/AIDS identified that those who used cocaine in combination with methamphetamine were at greater risk for nonadherence than those using cocaine alone [72]. Similarly, in a large sample of black women (n=1196), crack cocaine users and users of other substances were less likely to take their medication as prescribed [73]. Furthermore, previous cocaine use has been associated with low CD4 T-cell counts [74] and weekly stimulant use, independent of ART nonadherence, and has been associated with elevated HIV viral load [75].

More recent research provides additional support for the association between cocaine use and markers of HIV disease progression. Baum and colleagues [76••] found that

crack-cocaine users were 2.14 times more likely to have a CD4 T-cell count decline to 200 cells/mL or below, and that viral load was significantly higher in crack cocaine users, also independent of ART use. Crack cocaine users not on ART showed greater risk for HIV disease progression than nonusers. These findings suggest that the association between cocaine use and HIV disease progression may operate though pathways other than adherence and may be mediated through biological pathways.

Investigating the relationship between cocaine use and medication nonadherence, Meade and colleagues [77] assessed the role of neurocognitive functioning in adherence among HIV-infected patients with and without current cocaine dependence. Results suggested that active users had greater neurocognitive impairment and worse medication adherence, and, that neurocognitive impairment partially mediated the relationship between cocaine dependence and adherence.

Recent research also highlights relations between cocaine use and HIV and substance-related treatment utilization. In a multisite study (n=355) investigating the characteristics of a sample of HIV-infected crack cocaine users, 21% reported never having been to a doctor for HIV-related treatment [78]. In addition, results showed that having no history of substance use treatment was associated with never having been in HIV care. Moreover, about half of the sample reported that they had put off going to HIV care due to being high on drugs and/or alcohol.

Collectively, these findings provide evidence for the need of effective inventions that address cocaine use in HIV-infected populations. This conclusion is further supported by recent reports that ongoing cocaine use was significantly associated with failure to maintain ART adherence gains acquired during an integrated depression-adherence CBT intervention [79]. A recent randomized trial tested a group coping intervention for the reduction of alcohol, cocaine, and marijuana use in a sample of 247 HIV-infected adults with a history of child sexual abuse [80]. The experimental condition utilized an intervention developed by Sikkema and colleagues [81] called "Living in the Face of Trauma" (LIFT), which uses CBT strategies for sexual trauma. When compared to those in the support group condition, those who received the LIFT group coping intervention demonstrated sustained reductions in alcohol use and cocaine use, in addition to trauma symptoms. These results suggest that CBT-based interventions may be effective in reducing cocaine use among persons with HIV and past trauma. Further research is needed to evaluate CBT-based interventions for cocaine use and medication adherence among active HIV-infected cocaine users, and to expand our understanding of factors underlying the relation between cocaine use and nonadherence and HIV disease management.

Marijuana

Prior research regarding marijuana use among persons with HIV/AIDS has examined marijuana as a medicinal agent and as a recreational drug [82, 83]. Similarly, empirical work examining the relation between marijuana and HIV treatment adherence suggests that this drug may serve as a potential barrier or facilitator for adherence, depending perhaps, on motivation for use [83–85]. However, research examining these associations is not consistent. For example, among HIV-infected individuals with moderate to severe nausea, marijuana users are more likely to report being adherent to HIV medication regimens than non-users, whereas among those with mild to no nausea, marijuana users are less likely to be adherent than non-users [84]. Conversely, Corless and colleagues [86] investigated the efficacy of marijuana use as a method of symptom management and its effect on adherence. The analyses involved data from a multisite randomized control trial with 775 participants in Kenya, South Africa, Puerto Rico, and the United States. When comparing marijuana users and non-users on four measures of adherence, marijuana users had more concerns and worries about their medications, more total reasons for missed medications, and more problems taking their medications than non-users, but, did not differ on "forgetfulness." Similarly, Deitz and colleagues [87] found that marijuana use is significantly associated with missed clinical appointments in a sample of HIV-infected adolescent and young adult women (n= 178, M age=20.6 years). The identification of the person-level, treatment, and other contextual variables that may moderate these disparate findings in the relationship between marijuana use and adherence will be particularly relevant for distinguishing barriers from facilitators, identifying those at most risk, and for developing functional interventions to promote both optimal medication and treatment adherence and symptom management.

Methamphetamines

The majority of research on methamphetamine (MA) use has focused primarily on HIV prevention and interrelated sexual risk-taking behaviors, and has involved mostly gay and bisexual men [88]. A recent study of 653 HIV-infected patients reported that lifetime MA use was common across different groups: 70% among MSM, 67% among transgender patients, 64% among heterosexual men, and 39% among women, and, that Caucasian MSM and heterosexual men report greater rates of MA use than other racial/ethnic groups [89].

Marquez and colleagues [89] also found that MA use in the past 4 weeks was significantly related to ART non-adherence and MA users in the past year were less likely to

be on ART than those who did not use. Considering the substantial prevalence of MA use, further study is imperative to examine specific aspects of MA use in regard to HIV treatment adherence. One earlier qualitative study has shed light on the MA-adherence relation. Here, Reback and colleagues [90] explored reasons for planned and unplanned nonadherence to ART among 23 HIV-infected, primarily Caucasian, gay and bisexual men diagnosed with MA abuse or dependence. Common reasons for planned nonadherence included taking "vacations" from the medication regimen and avoiding medication-MA interactions. Unplanned nonadherence was attributed to irregular schedules/routines while high, difficulty eating due to reduced appetite and dehydration, and irregular sleep patterns. Although these results cannot be generalized to all MA users with HIV/AIDS, these findings highlight specific barriers to adherence and potential targets that may be incorporated into tailored interventions for this population.

A recent pilot study by McElhiney and colleagues [91] tested a combined treatment for MA use in an HIV-infected sample. The 16-week treatment involved Provigil along with CBT. Findings suggest that CBT in combination with medication treatment may be effective in treating MA use among HIV-infected patients. Results also indicated that retention in the 16-week treatment was both feasible for participants and key to successful substance use treatment. This study provides an example of substance use treatment tailored for MA using HIV-infected participants. However, future research would benefit from integrated adherence-MA use treatments.

Tobacco

Significant rates of tobacco use have been observed among people with HIV/AIDS compared to the general population (40.5–70% vs 20.6%, respectively) [92–94]. These elevated rates are quite alarming given that cigarette smoking has been linked in HIV to a number of negative health outcomes including significantly higher rates of non-AIDS-defining cancers, cardiovascular disease, bacterial pneumonia, and all-cause mortality controlling for CD4 T-cell count and HIV viral load [95]. In addition, smoking is associated with a history of tuberculosis and lower CD4 T-cell count at the initiation of ART [96], and there is some suggestion that smoking may limit the effectiveness of ART by promoting HIV-1 gene expression [97••]. Collectively, these findings suggest smoking has a clinically significant effect on health-related outcomes for HIV-infected smokers, and thus, development of effective smoking cessation interventions is indeed warranted.

Recent findings suggest that HIV-infected smokers report a desire to quit smoking and may have difficulties quitting, perhaps due in part to comorbid psychiatric problems and social support networks comprised of other smokers [98] confirmed by recent reviews of the literature [99, 100]. Moreover, recent work, although limited, highlights significant relations between smoking, nicotine dependence, and ART nonadherence [101, 102]. Specifically, nicotine dependence appears to be related to nonadherence in the context of other substance use behavior [101], and depression may in part mediate the relation between smoking and ART nonadherence [102]. Given the rates of tobacco smoking in HIV-infected samples and the related adherence and health implications, more intervention development research is needed.

There are a few trials testing the efficacy of smoking cessation interventions in HIV-infected samples. First, Lloyd-Richardson and colleagues [103] compared the efficacy of standard care plus nicotine replacement therapy (NRT) and motivationally enhanced treatment plus NRT. In a sample of 444 HIV-infected participants, no significant differences in cessation rates were found between the two conditions. Second, Ingersoll et al. [104] found similar results in a smaller sample when comparing self-guided reading plus NRT and motivational interviewing plus NRT. The sample as a whole demonstrated a reduction in the number of cigarettes smoked per day and an increase in the number of abstinent participants; however, no significant group differences were observed. Findings from this study also suggest that adherence to NRT is key to treatment success, and thus future intervention work would benefit from including adherence-related skills. Last, Fuster and colleagues [93] evaluated rates and predictors of successful cessation following a nonrandomized group intervention that provided support, psychoeducation, and pharmacological treatment for smoking cessation. The sample included 368 HIV-infected participants; most were male (79.9%) and 64% were smokers. Thirty-three of these participants enrolled in the smoking cessation intervention. At 3-, 6-, and 12-month follow-up assessments 13, 10, and 8 patients, respectively, were abstinent. Smoking cessation was significantly related to higher motivation to quit pre-cessation.

While these intervention trials demonstrate the feasibility of smoking cessation programs, further research is necessary to develop more efficacious treatments. Future research would benefit from comprehensive cessation programs including adherence-related skills for NRT and ART, and taking into account the effects of comorbid psychiatric problems, specifically anxiety, in terms of smoking cessation [105, 106].

Substance Use and ART Adherence Interventions

Recent research suggests that substance abuse treatment alone may not promote improvements in immunity or viral load suppression [107••]. As such, it may be clinically

important to incorporate ART adherence-related skills to substance use interventions for substance users with HIV/AIDS. Several substance use-adherence interventions have been shown to be effective in reducing drug use and promoting ART adherence. First, directly administered ART (DAART) in conjunction with MMT (ie, taking ART when receiving MMT in methadone clinics) for opioid users with HIV/AIDS has been shown to be effective in reducing opioid use and improving ART adherence [108, 109]. A recent 24-week randomized controlled trial comparing DAART + MMT to MMT + self-administered ART also supports beneficial treatment gains in terms of ART adherence and HIV viral suppression [110••]. In addition, previous work suggests that active substance use and non-adherence to supervised dosing is significantly related to dropping out of DAART in persons with HIV/AIDS on MMT [111]. Collectively, these results suggest that DAART + MMT is effective in reducing substance use behavior, promoting ART adherence, and improving disease status, and that active substance use may be a barrier to remaining in this method of care. Future DAART + MMT interventions may benefit from additional treatment components aimed at retaining substance users in treatment (eg, motivational interviewing, problem-solving skills).

Second, a recent study tested the efficacy and feasibility of a motivational interviewing and skills building intervention compared to a video-information and debriefing intervention to address ART adherence and crack-cocaine use [112]. Results indicated that both interventions significantly reduced drug use and improved ART adherence at 3-month and 6-month follow-ups. These data suggest that motivational interviewing plus adherence and drug cessation skills and video-based information on ART adherence and substance use can be effective in reducing crack-cocaine use and promoting adherence. Future work is needed here to test the long-term sustainability of these effects and related associations with disease markers.

Third, Daughters and colleagues [113] tested the feasibility and initial effectiveness of a behavioral activation and adherence skills treatment called ACT HEALTHY among substance users with depression (n=3) and HIV who were receiving treatment in a residential substance abuse facility (one for alcohol dependence, one for crack/cocaine dependence, and one for heroin dependence). Results indicated that the intervention was effective in reducing depressive symptoms and improving ART initiation and adherence. Future work is needed to evaluate the intervention in a randomized control trial.

Most recently, a CBT intervention for adherence and depression (CBT-AD) was tested among depressed patients with HIV in treatment for opioid dependence [70]. Compared to an enhanced treatment as usual condition, the CBT-AD intervention was effective in reducing depression and improving ART adherence, and improving CD4 T-cell count over time; however, adherence treatment gains were not maintained at 6-month and 12-month follow-ups. As hypothesized, treatment-related reductions in depression mediated the positive effects of the intervention on ART adherence [114]. In addition, post hoc analysis found that ongoing cocaine use was significantly associated with failure to maintain treatment-related gains in adherence during the study follow-up period [79]. Future work is needed to continue to enhance CBT-based interventions to promote the maintenance of ART adherence gains. These results provide good evidence that addressing the mental health issues of HIV-infected patients in substance use treatment facilitates the acquisition of skills that increase ART adherence.

Conclusions

Substance use problems are common among people living with HIV/AIDS and significantly impact effective disease management. Substance use is related to accelerated disease course through poor medication and treatment adherence and through the direct effects of the substance. The frequent comorbid presentation of substance use with mental health problems, in particular, may interfere with patients' with HIV/AIDS ability to fully adhere to ART and other HIV treatment recommendations and may compromise HIV medical outcomes.

Based on the current state of the literature, several observations and recommendations are provided to further advance the field in terms of substance use and its effect on adherence to ART and HIV treatment, HIV medical outcomes, and HIV prevention efforts. First, it is necessary to improve the identification of substance use problems through screening methods within HIV primary care settings. To this end, educating primary care providers about screening for substance use problems and the effects of substance use on HIV medical care is an important first step. Here, there is evidence to support the use of the Alcohol Use Disorders Identification Test Consumption (AUDIT-C), a brief three-item indicator of risky drinking, alcohol abuse, and dependence [115–117], and the National Institute on Drug Abuse Modified Alcohol, Smoking, and Substance Involvement Screening Test (NMASSIST) [118]. The NMASSIST is a relatively brief screening instrument (available as a web-based interactive tool; ww1.drugabuse.gov/nmassist/) adapted from the WHO ASSIST [119] to assess for substance use behavior and related problems; it can be scored to indicate the level of intervention needed, and has links to resources for brief interventions and treatment referrals. Increasing access to substance use treatment through improved identification, referral, and

linkage to care within the context of primary HIV care, perhaps through integrative case management care models or health care navigation, may help facilitate successful substance use treatment and, in turn, improve HIV medical care.

Second, it is clinically important to develop methods to improve retention in care and coordination of health services for substance users with HIV. Care providers might consider utilizing different technological means for ongoing contact and communication with patients, such as use of text messaging and electronic mail notifications. In addition, given that substance users with HIV tend to overuse EDs for care, it is critical to improve communication between EDs and primary care providers for coordination and continuity of treatment [120]. Moreover, use of outreach initiatives and health care navigators may help address barriers to treatment and improve communication and relations with health care providers in order to improve engagement and retention in care [121, 122].

Third, there are both scientific and clinical imperatives to continue identifying basic mechanisms and pathways by which substance use affects ART adherence and HIV care. There are as yet many unknowns with respect to the pathways from specific substances of abuse to poor ART and treatment adherence particularly as these may manifest in specific HIV risk groups. For example, the relationship between methamphetamine use and ART adherence among MSM is poorly understood and there are no empirically supported treatment models to address it. Ongoing research is needed to identify the substance-specific barriers and facilitators to adherence to inform the development of targeted psychosocial interventions.

Fourth, there are several priorities for the development of ART adherence treatment models for application with people who are managing the dual challenges of HIV and substance use disorders. Emerging and confirmatory evidence suggests that substance use interferes dramatically with ART adherence, compromises the effectiveness of adherence interventions, and is associated with the failure to maintain adherence gains acquired during treatment. These findings correctly focus our attention on the development of integrated adherence treatment models. We identify three related priorities in this regard: 1) the development of efficacious and effective ART adherence interventions that specifically address co-occurring substance use and varying levels of substance use–related impairment; 2) the development of treatment models that can address ART and treatment adherence among those managing both substance use and mental health vulnerabilities; and 3) the development of adherence interventions that can be integrated into substance abuse treatment settings. Previous work in this area has had some success integrating adherence intervention into opiate substitution treatment settings [70, 108, 109]. We acknowledge the importance of emerging research that is developing adherence interventions in the context of other substance use treatment settings, such as in crack-cocaine use [112, 113].

Finally, recent prevention models suggest that effectively treating HIV early with ART can successfully decrease the risk of HIV transmission among serodiscordant couples [7••]. Given that substance use can interfere with ART adherence and HIV-related medical treatment, targeting substance use behavior in the context of adherence interventions will have important implications for secondary HIV prevention. Improving ART adherence among substance users with and without mental health problems through comprehensive, yet targeted, psychosocial interventions may also support primary HIV prevention by addressing substance use and mental health barriers to adherence to pre-exposure prophylaxis among those who are HIV-uninfected but may be at risk. The thoughtful development of integrated adherence/substance use treatment models has the potential then to support adaptive HIV disease management and HIV prevention.

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- • Of importance
- •• Of major importance

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