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Considerations for Antiretroviral Use in Special Populations

Substance Use Disorders and HIV

Key Considerations and Recommendations

Substance use disorders (SUDs) are prevalent among people with HIV and contribute to poor health outcomes; therefore, screening for SUDs should be a routine part of clinical care **(AII).**

The most commonly used substances among people with HIV include the following (listed in alphabetical order): alcohol, benzodiazepines, cannabinoids, club drugs, opioids, stimulants (cocaine and methamphetamines), and tobacco.

Health care providers should be nonjudgmental when addressing substance use with people with HIV **(AIII).**

People with HIV and SUDs should be screened for additional mental health disorders **(AII).**

People with HIV and SUDs should be offered evidence-based pharmacotherapy (e.g., opioid agonist therapy, tobacco cessation treatment, alcohol use disorder treatment; see Table 15 below) as part of comprehensive HIV care in clinical settings **(AI).**

Ongoing substance use is not a contraindication to antiretroviral therapy (ART). People who use substances can achieve and maintain viral suppression with ART.

Substance use may increase the likelihood of HIV transmission risk behaviors, the potential for drug–drug interactions, and the risk or severity of substance-associated adverse events (e.g., increased hepatotoxicity or an increased risk of overdose).

Selection of antiretroviral (ARV) regimens for individuals who practice unhealthy substance and alcohol use should take into account potential adherence barriers, comorbidities that could impact care (e.g., advanced liver disease from alcohol or hepatitis viruses), potential drug–drug interactions, and possible adverse events associated with the medications **(AII).**

For people with SUDs, ARV regimens with once-daily formulations (ideally as a single-tablet regimen), high barriers to resistance, low hepatotoxicity, and low potential for drug–drug interactions are preferred **(AIII).**

Rating of Recommendations: *A = Strong; B = Moderate; C = Weak*

Rating of Evidence: *I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion*

Background on Substance Use Disorders Among People With HIV

Ending the HIV epidemic requires addressing substance use among people with HIV, which poses a barrier to optimal engagement in the HIV care continuum. Ongoing substance use may prevent an individual from being tested for HIV, initiating antiretroviral therapy (ART), or adhering to ART. Substance use may also increase the likelihood of risk-taking behaviors (e.g., sexual transmission risk behaviors, needle sharing, injection of substances), the potential for drug–drug interactions, and the risk or severity of substance-related adverse events (e.g., increased hepatotoxicity and increased risk of overdose). In the United States, the death toll for drug overdose (102,123 deaths as of February 2024)[1] far exceeds the death toll for HIV (4,941 deaths in 2022).[2] As the drug overdose epidemic continues to expand, health care providers need a basic understanding of how to screen for and treat substance use disorders (SUDs) in people with HIV in clinical settings.[3]

Substance use exists on a continuum, from episodic use to an SUD with its concomitant negative consequences. Research on alcohol consumption has defined a threshold at which consumption does not reach a diagnosis of SUD, but where the level of consumption is nonetheless hazardous to the person. This level of consumption has been defined as at-risk or hazardous use. A comparable category does not exist for other substances. The prevalence of substance use and SUDs is higher among people with HIV than among the general public,[4] and polysubstance use is common. This section will focus on the most commonly used substances among people with HIV (listed in alphabetical order): alcohol, benzodiazepines, cannabinoids, club drugs,[5] opioids, stimulants (cocaine and methamphetamines), and tobacco. Additionally, xylazine, a non-opioid veterinary analgesic that is a common substance adulterant—a substance added to another substance that may lead to negative health consequences—is also discussed.

People with HIV may use more than one substance and may not be ready to consider reducing the use of substances or seeking treatment for SUDs. Polysubstance use occurs for multiple reasons, including to improve the euphoria associated with use (e.g., use of cocaine and heroin mixtures called "speedballs") and to reduce the adverse effects of a particular substance (e.g., the use of alcohol or benzodiazepines to reduce the anxiety caused by cocaine use).

Substance Use and Sexual Risk-Taking

A growing body of literature describes the intersection of substance use and sexual risk-taking, in which drugs are intentionally used to enhance sexual activity ("chemsex"). This research highlights the impact of substance use on sexual transmission risk behaviors; although no precise definition of "chemsex" exists, studies have investigated various substances used to enhance sexual pleasure, decrease inhibitions related to particular sexual acts, and combat low self-esteem. In a retrospective study in a London sexual health clinic, individuals who disclosed substance use (463 of 1,734 participants) had higher odds of acquiring new HIV infection, bacterial sexually transmitted infections (STIs), and/or hepatitis C virus (HCV).[6] A much larger analysis using the European Men Who Have Sex With Men (MSM) Internet Survey, which collected data from 16,065 United Kingdom-based respondents, found that MSM who reported using methamphetamines or gamma-hydroxybutyrate (GHB) during the previous year were more likely to have gonorrhea infection than MSM who did not use these drugs, with odds ratios of 1.92 and 2.23, respectively.[7] Between 2017 and 2020, the American Men's Internet Survey collected data on chemsex drug use among MSM in the United States over the preceding 12 months. Of 30,294 MSM respondents, 3,113 (10.3%) self-reported chemsex in the past 12 months, with 3,4-methylenedioxymethamphetamine (MDMA or "ecstasy") (65.1%), methamphetamine (42.5%), and GHB (21.7%) being the top drugs reported for use.[8] A recent study in Spain using an online, self-administered questionnaire found that 81.4% of 2,919 MSM attending four HIV/STI testing sites in Madrid and Barcelona had ever used any drug, and 50% had engaged in chemsex in the past 12 months. Of those engaging in chemsex, half engaged in condomless anal sex.[9] These data emphasize the need to screen people with HIV for substance use and STIs in clinical settings and to discuss strategies with these individuals to reduce potential harm.[10]

Substance Use and Unstable Housing

People with HIV who inject drugs are more likely to be unhoused.[11] Houselessness among people who inject drugs is associated with an increased risk of HIV acquisition.[12]

Among people with HIV and SUD, houselessness confers an increased risk for disruptions in the HIV care continuum independent of ongoing substance use. In a longitudinal study of people with HIV who used drugs, lack of housing was associated with a 44% decrease in the odds of progression through the HIV care continuum.[13] After adjusting for multiple intersecting risks, including unhealthy alcohol use, other substance use, incarceration, unemployment, education, age, sex, and race/ethnicity, unhoused people with HIV and SUD had significantly decreased odds of ART initiation and, adherence, and of viral suppression.

Interventions supporting housing among people with HIV and SUD can result in improved HIV treatment outcomes. A randomized controlled trial of a rapid rehousing intervention for people with HIV who were houseless (n = 236, 81% with substance use) found that clients in the Enhanced Housing Placement Assistance arm were more likely to be placed and, placed faster, and were twice as likely as the control group to reach or maintain viral suppression (95% confidence interval [CI], 1.1–4.0).[14,15] An observational study of applicants to a supportive housing program for low-income people with HIV and a mental health condition or SUD (n = 958; 86% with SUD) found that people who achieved stable housing were more likely to engage in HIV care and to achieve viral suppression.[16] These data reflect the importance of not only addressing SUD among people with HIV, but also understanding the co-occurring structural determinants that contribute to poorer outcomes among people with HIV and SUD.

Screening for Substance Use Disorders

Screening for SUDs should be incorporated into the routine clinical care of all people with HIV. The following questions can be used to screen for drug or alcohol use: "How many times in the past year have you used an illegal drug or used a prescription medication for nonmedical reasons?" and "How many times in the past year have you had X or more drinks in a day?" (X is five for men and four for women).[17] Individuals with liver disease, including active HCV infection, should not consume alcohol.

A positive response to either of the two questions above should prompt additional screening with other short screening tools (see the Screening and Assessment Tools Chart from the National Institute on Drug Abuse). These tools can identify substance use and guide decisions on appropriate treatment interventions. Currently, there are not enough data to determine how often people with HIV should be screened for SUDs; however, given the potential negative impact that SUDs may have on people with HIV, it is advisable to ask these questions during every clinical visit.

Health care providers should be nonjudgmental when discussing substance use with people who have HIV **(AIII).** People with HIV who experience stigma or judgment may lose trust in their health care provider's advice, avoid future visits, and consequently experience poorer health outcomes.[18] Language is one way in which stigma is communicated, and words such as "addict" and "dirty urine" convey a negative connotation. The Office of National Drug Control Policy (ONDCP), American Medical Association, American Society of Addiction Medicine, International Society of Addiction Journal Editors, and others have recommended the adoption of clinical, nonstigmatizing language for substance use, as described in the *Changing the Language of Addiction* report from ONDCP.

Co-occurring Mental Illness

Many people who use substances have co-occurring mental health disorders, including a history of trauma that may drive or exacerbate their substance use. Conversely, ongoing use of substances can place individuals at risk for trauma, such as sexual assault and sexual exploitation, which may further exacerbate their substance use.[6,19] People with SUDs should undergo evaluation and treatment for concurrent mental health disorders using standardized screening instruments (e.g., the Patient Health Questionnaire-2, or PHQ-2, for depression). Where applicable, clinicians should use available behavioral and pharmacological interventions to address mental health concerns, because recommending that people stop their substance use without providing treatment for underlying mental health conditions has very limited efficacy.[20]

Selecting, Initiating, and Maintaining Antiretroviral Therapy

Ongoing substance use is **not** a contraindication for prescribing ART. ART is recommended for all people with HIV to improve their health and to prevent transmission of HIV to others **(AI),** including sexual partners and individuals who share drug paraphernalia. These clinical, community, and individual benefits should encourage health care providers to initiate ART in all people with HIV who use substances. Although effective ART prevents sexual transmission of HIV, its effectiveness in preventing transmission through shared needles and shared use of other drug paraphernalia remains unknown.

For people actively injecting drugs, engagement in a syringe service program (SSP) can facilitate access and adherence to ART. SSPs primarily provide clean drug preparation and injection supplies to reduce transmission of HIV, HCV, and other bloodborne, skin, and soft tissue pathogens. As a regular point of contact for people with complex health and social challenges, SSPs also provide opportunities to offer other integrated health-related and social support services,[21] including those for treating SUDs.[22] For people with HIV, SSPs can be adapted to provide or link to rapid initiation[23,24] and maintenance of effective ART.[24]

When selecting ART regimens for individuals who use substances, clinicians should consider potential barriers to adherence (see Adherence to the Continuum of Care), comorbidities that could impact care (e.g., advanced liver disease from alcohol or HCV), potential drug–drug interactions, and possible adverse events that are associated with the medications. Providers and people with HIV should discuss adherence during multiple, nonjudgmental evaluations. In general, the use of simplified ART regimens should be considered to aid adherence. Regimens for people with SUDs should be easy to take, such as once-daily formulations, ideally as a single-tablet regimen,[25] and should have a high barrier to resistance and a low risk of hepatotoxicity **(AIII).** Adherence counseling should highlight the benefits of ART use, irrespective of concurrent substance use. While a reduction in substance use may improve adherence to ART,[26,27] ongoing use is not a contraindication to ART.

Long-Acting Antiretroviral Therapy

The development of long-acting (LA) injectable ART provides additional options for treatment. The combination of injectable cabotegravir (CAB) and rilpivirine (RPV) is an optimization option for people with HIV who demonstrate retention in HIV care and who are virologically suppressed on oral therapy (see Optimizing Antiretroviral Therapy in the Setting of Virologic Suppression). Current U.S. Food and Drug Administration (FDA) approval for LA CAB/RPV is limited to individuals with expected good adherence and an ability to achieve virologic suppression on oral therapy prior to starting LA ART. Limited data from a small, ongoing observational study found that LA CAB/RPV leads to high levels of viral suppression in people with HIV who have struggled with adherence to oral ART and those who are viremic at treatment initiation, including people who use stimulants.[28] Of note, the clinic in this study provided a significant amount of social support to ensure adherence to the LA CAB/RPV regimen (see Virologic Failure for additional details). It is not known if similar responses can be seen in clinics without the resources to provide a similar level of adherence support. Missing LA CAB/RPV doses or a delay in receiving scheduled injections may result in emergence of HIV drug resistance.[28]

The following factors should be considered when contemplating the use of LA CAB/RPV in people with HIV and SUDs:

- As with all treatment conversations, providers should discuss adherence with their patients during multiple, nonjudgmental evaluations.

Providers and people with HIV should consider the impact of using LA CAB/RPV in the context of current or past substance use behaviors. Although some people may welcome or even prefer LA CAB/RPV,[29] one qualitative study highlighted that using a needle for administering LA CAB/RPV could be a trigger for people with a history of injecting illicit substances.[30]

Studies utilizing LA CAB/RPV have included individuals with good adherence before starting the LA ART, but this should not exclude people with SUDs who are struggling with adherence from being considered for LA CAB/RPV. Rather, the clinical team should consider what additional support may be needed to help people with SUDs be successful with LA CAB/RPV and whether using LA ART without established viral suppression is warranted based on preliminary data (see Virologic Failure and Adherence to the Continuum of Care for additional details). Case management, patient navigators, and/or peer navigators should be considered to help people with HIV return for follow-up injections.

Given the often unpredictable lifestyles of people with SUDs, clinical care teams should be flexible in scheduling injections or accommodating walk-ins for injections. However, it should be stressed that the doses should be given within the mandatory 7 days before or after the scheduled LA CAB/RPV injection date.

As for all people with HIV, hepatitis B virus (HBV) status should be evaluated before the initiation of LA CAB/RPV (see HBV/HIV Coinfection and Optimizing Antiretroviral Therapy in the Setting of Virologic Suppression for additional details). If not already immune or infected, HBV vaccination should be initiated while considering LA CAB/RPV, including in those with isolated hepatitis B core antibody (HBcAb).

LA CAB/RPV is not recommended for people with HBV/HIV coinfection unless HBV-active drugs (i.e., tenofovir, entecavir) are included in the regimen.

As depressive disorders have been associated with LA CAB/RPV in all populations, people with SUD also should be screened for depressive disorders and treated for depression if indicated.[31] If depressive disorders worsen while on LA CAB/RPV, reevaluation should occur to determine whether continued therapy with this regimen is advisable.

Importantly, despite emerging observational data, multiple knowledge gaps exist regarding the use of LA ARVs among people with HIV and SUDs. The results from the ongoing Long-Acting Therapy to Improve Treatment Success in Daily LifE (LATITUDE) Study (NCT 03635788) will provide clinical trial results to help inform the use of LA CAB/RPV among people with HIV and SUDs who have struggled with ART adherence.[32] Additional research is also needed to determine optimal methods for supporting ART adherence (including to LA ARVs) among people with HIV and SUDs. These research studies will need to take into consideration the combination of various interventions (e.g., peer support, case management, pharmacotherapy for SUDs, housing) and the appropriate individual interventions needed to support overall ART adherence.

Commonly Used Substances and Their Impact on HIV and Antiretroviral Therapy

Health care providers should have a basic understanding of evidence-based pharmacologic and behavioral (e.g., cognitive behavioral therapy, motivational interviewing, motivational enhancement therapy, contingency management) treatments for different substances, including alcohol, benzodiazepines, cannabinoids, club drugs, opioids, stimulants (cocaine and methamphetamines), and tobacco. The sections below discuss the impact of these substances on people with HIV and how these substances affect ART use.

Alcohol

Epidemiology

Alcohol consumption is common among people with HIV. Recent estimates indicate that >50% of people with HIV in the United States consume any amount of alcohol (range, 54% to 67%).[33,34] Among a sample of people with HIV across seven university-based HIV clinics in the United States, 27% of people screened positive for unhealthy alcohol use as determined by the AUDIT-C.[34] Unhealthy alcohol use includes a spectrum of consumption, including at-risk or hazardous use, heavy episodic use (binge drinking), and alcohol use disorder (AUD).[35]

Risk-Taking Behaviors, the HIV Care Continuum, and Comorbidities

Unhealthy alcohol use has been linked to HIV acquisition because it can increase the frequency of behaviors that put a person at risk for sexual transmission of HIV.[36-38] In a meta-analysis of 27 studies, any alcohol use, unhealthy alcohol use, and alcohol use in sexual contexts all were associated with condomless sex among people with HIV.[37]

In addition, unhealthy alcohol use has been associated with interruptions in all steps of the HIV care continuum, including lower adherence to ART.[39,40] Studies have demonstrated both temporal and dose-related relationships between alcohol use and adherence, where ART is more likely to be missed on a given drinking day and the day after drinking, with a stronger association on heavy (binge) drinking days.[41-43] The negative impact of unhealthy alcohol use on ART adherence is likely multifactorial and driven by the effects of intoxication, ARV regimen complexity, and patient perceptions of adverse interactions between alcohol and ARV drugs.[44-46] Studies also have demonstrated an association between unhealthy alcohol use and the

loss of durable viral suppression,[47-49] greater time spent with a viral load >1,500 copies/mL after ART initiation,[50] increased risk of viral rebound, lower retention in care,[51,52] and increased mortality.[53-55] Unhealthy alcohol use alone (hazardous or AUD) and in combination with other common comorbidities, including viral hepatitis coinfection, can hasten liver fibrosis progression in people with HIV.[56,57] Finally, in general medical populations, unhealthy alcohol use complicates the management of diabetes mellitus, hypertension, mental health disorders, other substance use, and other chronic diseases, and it increases the risk for pneumonia, osteoporosis, a number of cancers (e.g., liver, head and neck, and breast cancers), and tuberculosis.

Management of Unhealthy Alcohol Use

Ongoing alcohol use is not a contraindication for a person to receive ART. However, treatment for unhealthy alcohol use may improve HIV treatment outcomes. Behavioral treatments for unhealthy alcohol use among people with HIV demonstrate a small but significant reduction in alcohol use[58,59] (see additional resources for alcohol management from the National Institute on Alcohol Abuse and Alcoholism and the Substance Abuse and Mental Health Services Administration [SAMHSA]). Pharmacotherapy also can reduce alcohol use among people with HIV. The FDA has approved three pharmacotherapies for AUD: naltrexone, disulfiram, and acamprosate (see Table 15 below).

Clinical trials have demonstrated the efficacy of naltrexone in reducing the number of heavy drinking days among those with HIV and among the general population. Naltrexone appears to be safe to use in people with HIV,[60,61] and it is not associated with significant drug–drug interactions or irreversible hepatotoxicity. However, it is not recommended for individuals with decompensated liver disease and should be used with caution in individuals with elevated transaminase levels. Use of naltrexone in people with HIV and AUD can improve HIV treatment outcomes.[62] In a randomized placebo-controlled trial of 100 prisoners with HIV who met the criteria for AUD, individuals who were provided depot naltrexone upon release from prison were more likely to achieve viral suppression at 6 months than the placebo group (56.7% vs. 30.3%).[61]

Data on the use of disulfiram and acamprosate among people with HIV are lacking. Notably, integrating treatment for AUD with treatment for HIV has been shown to increase the number of people who receive alcohol treatment medication, counseling, and formal outpatient alcohol treatment services. Integrating these treatments also may improve the likelihood that a person with HIV will achieve viral suppression on ART. A randomized controlled trial of 128 individuals with HIV and AUD compared an integrated stepped-care model of alcohol treatment in Veterans Administration HIV clinics to treatment as usual. At the end of treatment (24 weeks), integrated stepped-care resulted in more participants receiving pharmacotherapy for AUD and participating in counseling. Although differences in alcohol use and viral suppression were not seen at 24 weeks, at 52 weeks, integrated stepped-care was associated significantly with an increased number of alcohol-abstinent days, a decrease in the number of drinks per drinking day, and a decreased number of heavy drinking episodes. In addition, the participants in the stepped-care group had increased odds of achieving viral suppression (odds ratio [OR] 5.58; 95% CI, 1.11–27.99).[63]

Liver cirrhosis—whether related to chronic heavy alcohol use, viral hepatitis, or metabolic dysfunction–associated steatotic liver disease—can result in altered metabolism of ARV drugs. For those who have hepatic impairment due to alcohol-related liver disease, ART dosing should follow the recommendations in Appendix B, which are based on Child-Pugh classifications.

Benzodiazepines

Epidemiology

While the specific epidemiologic data on the prevalence of benzodiazepine use among people with HIV are limited, benzodiazepine misuse is a growing public health concern due to its impact on both morbidity and mortality.[64] Benzodiazepines cause anterograde amnesia, defined as difficulty recalling events after taking the medication. Individuals do not develop tolerance to this neurocognitive effect, and long-term use of benzodiazepines may result in impairment of neurocognitive functioning.[65]

Risk-Taking Behaviors and the HIV Care Continuum

People who inject drugs and who also use benzodiazepines engage in riskier behaviors than people who inject drugs but do not use benzodiazepines; these behaviors may include paying for sex, sharing injection equipment with more people, and performing more frequent injections.[66] A cohort of 2,802 people who injected drugs was followed from 1996 to 2013. During that time, benzodiazepines were the substances with the greatest association with mortality.[67] In a study of opioid and benzodiazepine use and all-cause mortality among 64,602 veterans (16,989 with HIV and 47,613 without) from the Veterans Aging Cohort Study (VACS) cohort (October 2008 to September 2009), long-term benzodiazepine receipt was associated with increased mortality regardless of long-term opioid receipt.[68] The long-term neurocognitive impact of benzodiazepines on ART adherence among people with HIV is unclear, but prescribing a memory-impairing medication to people with HIV who are prone to neurocognitive impairments from other causes may increase the risk of poor ART adherence.[69] Benzodiazepines also are used illicitly to counteract the negative side effects of stimulants, such as cocaine and methamphetamine.[70]

Management of Benzodiazepine Use

Repeated use of benzodiazepines can result in physiologic dependence and life-threatening withdrawal in some people. When feasible, individuals who chronically use benzodiazepines should be slowly tapered off the benzodiazepines under the supervision of an experienced clinician. Different benzodiazepines have different potencies (e.g., alprazolam is more potent

than diazepam) and, therefore, require different tapers in terms of length and graduated decrease in dosage.

Benzodiazepine and Antiretroviral Drug Interactions

Several pharmacological interactions between benzodiazepines and ARV drugs have also been described. For example, some benzodiazepines are cytochrome P450 (CYP) 3A4 substrates; thus, when these benzodiazepines are used with a ritonavir (RTV)-boosted or cobicistat (COBI)-boosted ARV drug, their half-lives and concentrations can increase significantly, leading to enhanced and prolonged sedating effects. See Drug–Drug Interactions for available data on benzodiazepine-related interactions.[71]

Cannabis and Cannabinoids

Epidemiology

Both medical and recreational cannabis (marijuana) use are prevalent among people with HIV.[72] Cannabis belongs to a class of compounds that activate cannabinoid receptors. This class, known as cannabinoids, also includes synthetic compounds, such as K2. In recent years, cannabinoids have become more popular. In 2009, two cannabinoids were reported to the National Forensic Laboratory Information System. By 2015, 84 compounds had been reported.[73] These compounds most commonly cause tachycardia, agitation, and nausea, but they have a wide range of psychiatric effects, including psychosis and paranoia.[74]

Risk-Taking Behaviors and the HIV Care Continuum

Cannabis has not been shown to negatively impact adherence to ART or a person's ability to achieve viral suppression. In one study, among 874 people with HIV, daily cannabis use did not predict lower odds of ART use or achieving an undetectable HIV RNA level, except when combined with binge drinking.[75] Data from the Multicenter AIDS Cohort Study have supported the idea that marijuana use does not predict problems with adherence to ART or achieving viral suppression.[76] In some cases, however, cannabinoids have been listed as the cause of death in overdoses. While data are lacking among adults with HIV, the nationally representative 2015 Youth Risk Behavior Survey (which includes data from 15,624 adolescent students in Grades 9 to 12) found that students who had ever used synthetic cannabinoids engaged in riskier activities, including sex, than students who only used marijuana.[77] While the available data suggest that the use of marijuana is not associated with decreased adherence to ART,[78] data are lacking on the impact of synthetic cannabinoids on ART adherence. Finally, with the growing use of synthetic cannabinoids, there is concern that fentanyl could be added to these products, which may increase the risk of opioid overdose.

Management of Cannabis and Cannabinoid Use

Because of the aforementioned concerns regarding cannabinoid use, particularly the variety of compounds and neuropsychiatric effects, people with HIV should be discouraged from using cannabinoids until more data are available. No pharmacological treatment exists for cannabinoid use disorder; however, behavioral health treatment may be effective for some people.[79-81]

Club Drugs

Epidemiology

Club drugs are recreational substances that have euphoric or hallucinogenic effects or that are used to enhance sexual experiences.[5] The use of multiple club drugs or other drugs simultaneously is common. Although these substances are used by many different people with HIV, the majority of data come from MSM with HIV. The use of club drugs in this population has been shown to negatively impact HIV treatment.[82] Club drugs include MDMA, GHB, ketamine, benzodiazepines (see the benzodiazepine section above), and other drugs that are used to enhance sexual experiences (e.g., mephedrone, inhaled nitrates [poppers], and phosphodiesterase-5 inhibitors [PDE5] for erectile dysfunction). Survey data from users of club drugs also have revealed that efavirenz is purchased by people without HIV for its intoxicating effects.[83]

Risk-Taking Behaviors and the HIV Care Continuum

Club drugs have disinhibitory effects. Using club drugs increases the likelihood that a person will engage in high-risk sexual practices, which can increase the risk of HIV transmission. In addition, these disinhibitory effects can lead to poor ART adherence.[71,82,84]

Management of Club Drug Use

Treatment strategies for club drug use have not been well studied in controlled trials.[85] No recommended pharmacotherapies exist at this time, and the most common strategy for treating people who use club drugs is to employ the behavioral interventions that are used for other drug use disorders.

Club Drug and Antiretroviral Drug Interactions

MDMA, GHB, ketamine, and methamphetamine all have the potential to interact with ARV drugs because they are metabolized, at least in part, by the CYP450 system.[71,84] Overdoses secondary to interactions between club drugs (i.e., MDMA or GHB) and protease inhibitor–based ART have been reported.[71,86] For instance, using PDE5 or ketamine concurrently with potent CYP3A4 inhibitors, such as RTV or COBI, can potentiate the effects of these substances.[82]

Cocaine

See the discussion in the section on stimulants below.

Opioids

Epidemiology

Opioids remain a significant concern for people with HIV, both for the acquisition of HIV and as major contributors to morbidity and mortality. Overdose involving opioids is the leading cause of accidental death in the United States.[87] The appropriate use of opioids while caring for people with HIV and chronic pain is an important component of combating the opioid epidemic, but this subject is beyond the scope of this section. Please refer to additional resources, such as those from the Centers for Disease Control and Prevention (CDC) and the Infectious Diseases Society of America.[88] To combat the opioid overdose epidemic, health care providers should prescribe naloxone for opioid overdose prevention for all people who are using opioids beyond the short-term treatment of acute pain.[3]

Risk-Taking Behaviors and the HIV Care Continuum

Many people who use opioids start by using opioid tablets (e.g., oxycodone) that are ingested orally or crushed and sniffed. Once tolerance develops, some individuals move from sniffing the crushed tablets to injecting heroin purchased on the streets. This transition from sniffing to injecting dramatically increases the risk of HIV and HCV infection.

Low-cost heroin is often a mix of heroin and higher-potency synthetic opioids, such as fentanyl.[87] Methamphetamines and cocaine also have been combined with fentanyl but at a lower rate than heroin.[89,90] With the growing use of synthetic cannabinoids, there is concern that fentanyl could be added to these as well. In all instances where fentanyl or other high-potency opioids are added to other drugs, the risk of overdose increases.

Although treatment for an opioid use disorder (OUD) can improve HIV treatment outcomes, it is not a prerequisite for treating HIV, as some people with HIV are able to adhere successfully to ART despite ongoing opioid use. Although ART coverage among people with HIV who injected drugs increased from 58% to 71% between 2009 and 2015, additional work is needed to improve ART coverage in this population.[91] Data from the Johns Hopkins HIV Clinical Cohort (2001–2012) demonstrated that in the early years of the cohort, people who injected drugs were less likely to be retained in care; however, this gap in retention had closed by 2012, and people who injected drugs and noninjectors had similar probabilities of being on ART and having a suppressed viral load during the later years of the cohort.[92]

Management of Opioid Use

FDA has approved three medications for the treatment of OUD that can help decrease or eliminate opioid use, reduce the risks of morbidity and mortality that are associated with opioid use, and improve HIV treatment success. These medications—collectively termed medications for opioid use disorder (MOUD)—include buprenorphine, methadone, and naltrexone (see Table 15 below). Buprenorphine and methadone are opioid agonists (the use of these drugs is termed opioid agonist therapy), whereas naltrexone is an opioid antagonist or "blocker." Both buprenorphine and naltrexone can be prescribed in the setting of routine HIV clinical care.[93] Prescribing buprenorphine requires specific training but no longer requires an X waiver (see the SAMHSA website for more information). Methadone must be prescribed through a licensed opioid treatment program (OTP). An OTP directory also can be found on the SAMHSA website.[94]

Use of buprenorphine or methadone can lead to reductions in risky behaviors associated with HIV transmission, psychosocial and medical morbidity related to OUD, and criminal behaviors. People who are receiving treatment for opioid use are already engaging with the health care system; therefore, they are more likely to initiate treatment for HIV and to be adherent to their ARV regimens. Both buprenorphine and methadone are cost-effective interventions at the societal level.[95] Methadone has better retention in SUD treatment than either buprenorphine or naltrexone, and it should be considered for individuals who do not achieve successful outcomes with buprenorphine or naltrexone.[96] Buprenorphine has a lower risk of overdose than methadone. In addition, it can be prescribed in primary care offices. People who are taking buprenorphine have significantly better retention in treatment than those who are taking daily oral naltrexone.[97] Although several randomized, controlled clinical trials have demonstrated efficacy for naltrexone when treating OUD, subsequent study results have been disappointing; one meta-analysis revealed that oral naltrexone was equivalent to placebo.[98] To address the adherence challenges with naltrexone, a depot formulation was created for monthly administration. This preparation has the potential to improve adherence; however, studies that compare opioid agonists (i.e., buprenorphine and methadone) to depot naltrexone as treatments for OUD have not been conducted. In a randomized, placebo-controlled trial in people with both HIV and OUD, participants who received at least three doses of depot naltrexone before discharge from prison achieved longer periods of continuous abstinence after transitioning from prison to the community than those who received either placebo or two or less doses of depot naltrexone.[61] On the basis of these data, methadone or buprenorphine generally are used as first-line agents for the treatment of OUD. Depot naltrexone is used as an alternative treatment for people who have been released recently from correctional facilities when other options are not available.

Important pharmacokinetic interactions between these medications (particularly methadone) and certain ARV drugs are listed in Drug–Drug Interactions.

Although medications remain the backbone of treatment for OUD, there is growing recognition of the critical importance of the social drivers of health and how they impact the willingness of people to engage in treatment with the medications discussed above. A recent randomized study of 114 people with HIV compared the effectiveness of different medications for the treatment of OUD to achieve viral suppression, finding that stable housing, high school–level education or greater, and income stability were associated with a greater reduction in opioid use.[94]

Xylazine and Opioids

Xylazine—a non-opioid analgesic utilized in veterinary medicine that is a commonly used adulterant in opioids and other substances—has become an emerging drug threat associated with the opioid epidemic.[99] The CDC has documented a 276% increase in the monthly percentage of illicitly manufactured fentanyl (IMF)–involved deaths where xylazine was detected.[100] Between 2020 and 2021, the Drug Enforcement Agency reported that xylazine-associated deaths increased by over 100% in all regions of the United States and over 1,000% in the South.[101] This growing body of data led the ONDCP to formally designate fentanyl adulterated with xylazine as an emerging drug threat.[102]

Xylazine is a substrate of CYP3A4 and, as such, when used with an ARV regimen including a CYP3A4 inhibitor, such as RTV or COBI, may lead to elevated levels and prolonged half-lives of xylazine.[103] For people with HIV who continuously use opioids in areas with high rates of xylazine-adulterated IMF, providers should weigh the risks and benefits of using ARV drugs with CYP3A4 inhibitors, given potential interactions and the increase in xylazine-associated adverse effects.

Opioid adulterants, such as xylazine, increase the risk of overdose. Although naloxone only reverses opioid effects, that alone may be sufficient to reverse the overdose. This highlights the need for universal access to naloxone and the active prescribing of naloxone by health care providers. The CDC maintains information about xylazine and how to reduce its harm on its website.[104]

Stimulants

Epidemiology

Cocaine and methamphetamine are powerful stimulants that have been associated with multiple detrimental effects among people with HIV, including accelerated disease progression, poor ART adherence, and lack of viral suppression. Cocaine powder is snorted or injected, whereas the free-base form (crack) is smoked. Methamphetamines can be taken orally or rectally, injected, or smoked. Cocaine and methamphetamine are commonly used with other substances, including alcohol, and can be combined with fentanyl, which increases the risk of overdose.[89,90] Individuals who use stimulants experience a sense of euphoria and may have heightened sexual desire and arousal. This can lead to disinhibited sexual behaviors, increasing the risk of HIV transmission.

The prevalence of stimulant use among people with HIV has been estimated to be 5% to 15% across multiple studies.[105-107] Methamphetamine use is more common among MSM,[108] and increased rates of cocaine use have been observed among ethnic and racial minorities and persons with a history of incarceration.[109]

Risk-Taking Behaviors and the HIV Care Continuum

People with HIV who use stimulants may experience multiple negative health consequences, including rapid development of dependence and adverse effects on multiple organ systems, particularly the central nervous and cardiovascular systems. Stimulant use is associated with neurocognitive impairment,[110] delirium, seizures, hemorrhagic strokes, and mental health disturbances, including anxiety, psychosis, and paranoia.

Stimulant use may independently lead to HIV disease progression even among people who are taking ART and have achieved viral suppression. Research to identify the cellular mechanisms responsible for this is ongoing, but increased viral replication, direct effects on the immune system that lead to declines in CD4 T lymphocyte cell count, enhanced immune activation, and disruption of the blood-brain barrier, facilitating HIV entry into the brain, have been implicated.[111-115] Stimulant use has been associated with poor HIV continuum of care outcomes, including suboptimal rates of ART adherence,[116] retention in care, and viral suppression.[117-119] Lack of viral suppression, combined with the increased likelihood of risky sexual behaviors that occur under the influence of stimulants, poses a threat to the HIV treatment-as-prevention paradigm.[120]

Management of Stimulant Use

Several pharmacologic and behavioral interventions for stimulant dependence have been investigated, and some trials have included people with HIV. The results of pharmacologic interventions generally have been disappointing. No FDA-approved pharmacotherapy for cocaine use disorder currently exists, despite research on multiple drug classes, including antidepressants, antipsychotics, anticonvulsants, and dopaminergic medications (e.g., disulfiram).[121,122] Among people with HIV who use crack and opioids, medication-assisted treatment for OUD may improve ART adherence and viral suppression.[123,124] Limited evidence indicates that some pharmacologic interventions (e.g., methylphenidate, modafinil, bupropion, naltrexone)[125] can reduce methamphetamine use or cravings. A double-blind, placebo-controlled trial of extended-release injectable naltrexone plus oral extended-release bupropion in adults with moderate or severe methamphetamine use disorder demonstrated a higher response of methamphetamine-free urine samples compared to placebo; however, the overall response rate was low.[126] A double-blind randomized clinical trial on people with methamphetamine use disorder evaluated

daily mirtazapine versus placebo in individuals who have sex with men. Over 36 weeks of follow-up, daily mirtazapine use led to reduced methamphetamine-positive urine drug tests and concurrent reductions in sexual risk behaviors.[127] No specific recommended pharmacotherapy exists to treat stimulant use disorder in people with HIV.

Several behavioral interventions have shown promise in randomized trials. People with HIV who received motivational interviewing sessions, cognitive behavioral therapy, or a combination of the two experienced decreased stimulant use, improved ART adherence, and were less likely to engage in sexual transmission risk behaviors.[128] Contingency management has been shown to be effective in decreasing stimulant use among people with HIV, but the sustained effects on the reduction of stimulant use and improvements in ART adherence are less clear.[106,129,130] The addition of a positive affect intervention to contingency management, compared with an attention control condition, decreased HIV viral load among gay, bisexual, and other MSM with HIV.[131] Technology-based interventions, such as text messaging, may have a role in supporting ART adherence and decreasing methamphetamine use among people with HIV, but further research is needed.[132] People with HIV who use stimulants benefit most from multidimensional interventions that target substance use, ART adherence, and risky sexual behaviors.[128]

Despite the challenges discussed above, people with HIV who use stimulants can achieve viral suppression with ART[119] and should be prescribed ART even if stimulant use is ongoing.

Tobacco

Epidemiology

The prevalence of tobacco smoking among people with HIV in the United States is approximately twice that of the general population (33.6% vs. 16.8%).[133] Prevalence is even higher among specific subgroups, including those who use alcohol and/or other drugs, those who have concurrent mental health disorders, and those of a lower socioeconomic status. Although smoking rates are declining overall in the United States, people with HIV are less likely to quit smoking than people in the general population.[133]

Associated Risks of Tobacco Use and HIV Infection

With respect to substance use and HIV, tobacco smoking is the biggest threat to health-related gains achieved through ART. Among individuals with viral suppression on ART, more years of life may be lost from continued smoking than from HIV infection itself.[134,135] Tobacco smoking among people with HIV is associated with an increased risk of numerous health conditions, including lung cancer and other smoking-related cancers, cardiovascular disease, and pulmonary disease. In a sample of 17,995 people with HIV on ART in Europe and North America, individuals who smoked had nearly twice the mortality of those who did not (mortality rate ratio 1.94; 95% CI, 1.56–2.41) with significant mortality attributed to cardiovascular disease and non-AIDS-related malignancy.[134] Importantly, tobacco cessation reduces the incidence of cardiovascular disease and smoking-related cancers (although definitive data on lung cancer are not available) and improves quality of life.[136-138]

Managing Tobacco Use

To maximize the survival benefits of ART, clinicians should consider using evidence-based behavioral and pharmacological[139-141] cessation strategies when treating people with HIV who smoke tobacco (see the tools and recommendations provided by the CDC and the U.S. Preventive Services Task Force and recent review).[142] These include (but are not limited to) advising the individual to quit smoking, using the five A's, employing motivational interviewing, and referring them to a tobacco quitline. Pharmacotherapies for smoking cessation (nicotine replacement therapy, bupropion, and varenicline) have few clinically significant interactions with ARV drugs and can lead to enormous reductions in morbidity and mortality if the person is able to stop smoking. Nicotine replacement is efficacious[143]; however, bupropion doubles rates of smoking cessation compared with nicotine replacement therapy.[144] Varenicline is a partial nicotine receptor agonist. In comparative studies, varenicline was more effective than bupropion in smoking cessation.[144,145] Clinical trials among people with HIV have found varenicline to be both effective and safe.[139,141] In a randomized controlled trial among 179 individuals with HIV who were assigned to receive 12 weeks of behavioral counseling and either varenicline or placebo, varenicline use led to an increase in the percentage of participants who achieved a 7-day abstinence period at 12 weeks (28.1% vs. 12.1%, OR 4.5; 95% CI, 1.83–11.2) and produced higher continuous abstinence between Weeks 9 and 12 (23.6% vs. 10%, OR 4.65; 95% CI, 1.71–12.67) compared to placebo.[141] Although significant between-group differences were not observed after 24 weeks, these data support the use of varenicline among people with HIV. Varenicline should be used in combination with relapse prevention strategies and other measures for long-term tobacco cessation.

Table 15. Medications for Treatment of Substance Use Disorders

Medication	Dose and Recommendations	Potential Interaction with ARV Drugs	Comments

Alcohol Use Disorder			
Acamprosate	666 mg PO three times a day *or* 333 mg PO three times a day for people with CrCl 30–50 mL/min	No significant interaction with ARV drugs expected.	**Contraindicated** in people with CrCl <30 mL/min
Disulfiram	250 mg PO once daily	Use with caution when prescribing an ARV oral solution that contains ethanol and/or propylene glycol (e.g., FPV, LPV/r, RTV).	Counsel people regarding disulfiram reaction when taken with alcohol; symptoms for the reaction may include flushing, tachycardia, nausea, vomiting, or hypotension.
Naltrexone	50–100 mg PO once daily Depot formulation is a fixed-dose monthly injection.	No significant interaction with ARV drugs expected.	Has the greatest efficacy of all FDA-approved medications for AUD.
Opioid Use Disorder			
Buprenorphine	Individualize buprenorphine dosing based on the person's opioid use. The dose range is 4–24 mg sublingually. Dosing is once daily or twice daily.	Potential interaction with ARV drugs that are CYP inhibitors or inducers. See Drug–Drug Interactions for further recommendations.	Buprenorphine has 90% first-pass hepatic metabolism. Verify that the person is using the appropriate technique for sublingual administration before adjusting the dose, because improper administration will result in poor absorption and low drug levels.
Methadone	Individualize the dose. People who receive higher doses (>100 mg) are more likely to remain in treatment.	Potential interaction with ARV drugs that are CYP inhibitors or inducers. See Drug–Drug Interactions for further recommendations.	QTc prolongation is a concern at higher doses. Methadone can be prescribed for OUD only by a licensed OTP.
Naltrexone	50–100 mg PO once daily Depot formulation is a fixed-dose monthly injection.	No significant interaction with ARV drugs expected.	Longer time of continuous abstinence in those who received depot formulation naltrexone compared with placebo after transition from prison to community.
Nicotine Use Disorder			
Nicotine Replacement	The FDA has approved a wide variety of nicotine	No significant interaction with ARV	Work with the person to identify the route of delivery that they will use and find most

Therapy	replacement products. All formulations are effective.	drugs expected.	helpful.
Bupropion	Start at 150 mg PO daily for 3 days, then increase to either 150 mg twice daily or 300 mg once daily (use only formulations that are approved for once-daily dosing).	Concentration may be reduced when used with ARV drugs that are CYP2D6 inducers. See Drug–Drug Interactions for further recommendations.	For optimal results, tobacco quit date should occur 1 week after starting therapy.
Varenicline	Titrate the dose based on tolerability until the desired effect is achieved. The goal is to reach a dose of 1 mg PO twice daily. Requires dose adjustment in people with CrCl <30 mL/min.	No significant interaction with ARV drugs expected.	For optimal results, tobacco quit date should occur 1 week after starting therapy.

Key: ARV = antiretroviral; AUD = alcohol use disorder; CrCl = creatinine clearance; CYP = cytochrome P450; FDA = U.S. Food and Drug Administration; FPV = fosamprenavir; LPV/r = lopinavir/ritonavir; OTP = opioid treatment program; OUD = opioid use disorder; PO = orally; QTc = QT corrected for heart rate; RTV = ritonavir

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