Optimizing Care for HIV-Infected People Who Use Drugs: Evidence-Based Approaches to Overcoming Healthcare Disparities

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Substance use disorders (SUDs) and human immunodeficiency virus (HIV) are pervasive epidemics that synergize, resulting in negative outcomes for HIV-infected people who use drugs (PWUDs). The expanding epidemiology of substance use demands a parallel evolution of the HIV specialist—beyond HIV to diagnosis and management of comorbid SUDs. The purpose of this paper is to describe healthcare disparities for HIV-infected PWUDs along each point of a continuum of care, and to suggest evidence-based strategies for overcoming these healthcare disparities. Despite extensive dedicated resources and availability of antiretroviral therapy (ART) in the United States, PWUDs continue to experience delayed HIV diagnosis, reduced entry into and retention in HIV care, delayed initiation of ART, and inferior HIV treatment outcomes. Overcoming these healthcare disparities requires integrated packages of clinical, pharmacological, behavioral, and social services, delivered in ways that are cost-effective and convenient and include, at a minimum, screening for and treatment of underlying SUDs.

Keywords. HIV; substance use disorders; healthcare disparities; treatment; engagement in care.

Substance use disorders (SUDs) and human immunodeficiency virus (HIV) are pervasive overlapping epidemics with a vast array of social and health consequences at individual and societal levels [1]. SUDs are chronic relapsing medical conditions that, if left untreated, result in negative medical, psychological, and social consequences. People who inject drugs (PWIDs) contribute to the HIV epidemic by simultaneously needing care and potentially transmitting HIV to their injecting and sex partners [2]. Despite significant attention to injecting behaviors since the dawn of the HIV epidemic, >175 000 PWIDs in the United States have died of AIDS, including 4759 in 2009 [3, 4]. The proportion of incident HIV cases directly attributable to injecting has declined to 8% [5], but the prevalence of injecting among people living with HIV/AIDS (PLWHA) continues to rise [3]. The most recent US national strategy named PWIDs as a key target population for high-impact HIV prevention [6]. People who use drugs (PWUDs), including more ubiquitous alcohol and noninjection drugs, contribute to HIV transmission through behavioral disinhibition, associated with high-risk and transactional sex. The National Survey on Drug Use and Health estimates that 20.6 million people in the US, or 8% of adults, have SUDs, meeting criteria for substance dependence or abuse [7]; however, >25% of PLWHA in the United States have SUDs that required treatment last year [8]. The substances most frequently used and abused by PLWHA include cocaine, alcohol, cannabis, tobacco, and opioids, with differing effects on HIV-related healthcare utilization and health outcomes, and polysubstance abuse is common [8, 9]. Evidence-based treatment options for SUDs are discussed below.

HIV-infected PWUDs experience increased age-adjusted non-HIV-associated comorbidities [10]. The
Evidence supports medication-assisted therapies (MATs) for opioid and alcohol dependence. When given alone or with counseling, MATs are physiologically and psychologically beneficial and can secondarily improve HIV treatment engagement [18]. Evidence-based MAT options for opioid and alcohol dependence and their relationship to HIV are presented in Table 1. Nicotine dependence is also highly prevalent: >40% of all PLWHA [19, 20] and >90% of HIV-infected PWUD are current smokers [21], contributing to non-HIV-related morbidity and mortality. Smoking cessation strategies that use MAT with behavioral counseling are recommended for PWUDs (Table 1) to address cardiovascular and overall health, although no empiric studies have specifically documented benefits of smoking cessation on HIV treatment outcomes [22, 23].

Despite widespread use of cocaine and amphetamine-type substances worldwide, psychosocial interventions remain the only evidence-based treatment modality for stimulant users [24], but evidence for naltrexone [25] and mirtazapine [26] treatments is emerging. Healthcare provider recognition of patients’ amphetamine-type substance use and other club drugs (MDMA, ketamine) is critical because they are often used in sexual contexts to facilitate disinhibition and are associated with high-risk sex and HIV transmission, especially among men who have sex with men [27, 28].

The lives of PWUDs are often chaotically organized around substance use, replacing even the most basic subsistence needs. To realize benefits of drug treatment on substance use and HIV treatment outcomes, clinical and social services are most effectively offered in ways that are flexible, convenient, and socially meaningful to PWUDs [16, 29, 30]. Historically, highly regulated methadone maintenance therapy and HIV clinical services have been offered in separate sites, creating a potential barrier for PWUDs [31]. Buprenorphine, an alternative MAT for treating opioid dependence, may be prescribed in office-based settings by any physician who completes an 8-hour course, allowing “1-stop shopping” models for eligible HIV-infected patients, and is discussed further below.

**STRATEGIES TO OVERCOME HEALTHCARE DISPARITIES FOR PWUDS**

**HIV Diagnosis**

Beyond the 50 000 HIV cases diagnosed annually in the United States [3], one-fifth of PLWHA in the United States remain undiagnosed, many of whom have comorbid SUDs [14]. Being undiagnosed is associated with delayed entry into care and increased risk-taking behaviors, during which HIV may be transmitted to others [32, 33]. Among PWIDs and men who have sex with men, SUDs are associated with decreased access to and utilization of medical care [13], but routine and targeted testing improves HIV identification. Risk assessments with practical...
opt-out HIV testing can be performed at sites that serve PWUDs. In a large randomized controlled trial, on-site rapid HIV testing in drug treatment programs increased the likelihood of HIV testing compared to off-site referrals [38]. Nonetheless, less than half of these programs provide on-site HIV testing [38, 39] and, combined with the fact that <15%–20% of PWUDs

<table>
<thead>
<tr>
<th>Type of Therapy</th>
<th>Administration Issues</th>
<th>Important Pharmacokinetic Interactions</th>
<th>Effectiveness as Drug Treatment</th>
<th>Impact on HIV Prevention and Treatment</th>
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<tr>
<td><strong>Opioid dependence</strong></td>
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<tr>
<td>Methadone&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Oral daily Highly regulated and available only in structured drug treatment programs Longest track record Lowest cost for medication Cost-effective</td>
<td>↑ ZDV toxicity (monitor) ETR, EFV, NVP ↑ opioid withdrawal (adjust methadone dose as needed) All boosted PIs may ↑ opioid withdrawal (monitor) Rifampin ↑ opioid withdrawal (change to rifabutin or ↑ methadone substantially) Fluconazole ↑ methadone levels</td>
<td>↓ relapse to opioids &amp; duration of use</td>
<td>↓ injecting and needle-sharing (transmission) behaviors ↑ retention in HIV care ↑ ART adherence</td>
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<tr>
<td>Buprenorphine&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Sublingual daily or 3×/wk May be given in less structured settings Physicians must be licensed to prescribe Excellent safety profile ↓ abuse potential Cost-effective</td>
<td>Contraindicated with unboosted ATV ATV/r ↑ sedation ↓ buprenorphine dose as needed Naloxone contraindicated in pregnancy</td>
<td>↓ relapse to opioids &amp; duration of use</td>
<td>↓ injecting (transmission) behaviors ↑ retention in HIV care ↑ ART adherence</td>
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<tr>
<td>Naltrexone XR</td>
<td>Intramuscular monthly ↓ abuse potential Cost-effective</td>
<td>Not studied but none anticipated</td>
<td>Effective in highly motivated patients</td>
<td>Not studied</td>
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<td><strong>Alcohol dependence</strong></td>
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<td>Naltrexone tablet&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Oral daily or every other day Intramuscular monthly XR formulation costly but has excellent adherence Excellent safety profile No abuse potential Does not require specialized licensure</td>
<td>Not studied but none anticipated</td>
<td>↑ time to relapse ↓ number of heavy drinking days</td>
<td>Not studied</td>
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<td>Naltrexone XR</td>
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<td>Not studied</td>
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<td>Acamprosate</td>
<td>Oral 3×/d Adherence problematic</td>
<td>Not studied</td>
<td>↑ abstinence No benefit in preventing relapse</td>
<td>Not studied</td>
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<tr>
<td>Disulfiram&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Oral daily Aversion therapy: nausea/vomiting if alcohol ingested Should not be coadministered with APV or metronidazole</td>
<td>Not studied</td>
<td>May be useful in motivated patients, in combination with other therapies</td>
<td>Not studied</td>
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<td><strong>Nicotine dependence</strong></td>
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<tr>
<td>Varenicline</td>
<td>Oral twice daily Black box warning for suicidality Relatively expensive</td>
<td>None reported in preliminary studies</td>
<td>Highest rates of abstinence from and reductions in smoking</td>
<td>↑ CD4 count in single pilot open-label study</td>
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<tr>
<td>Nicotine replacement therapy</td>
<td>Transdermal, oral, sublingual, or inhaled</td>
<td>Not studied</td>
<td>May be useful when combined with other therapies</td>
<td>Not studied</td>
</tr>
<tr>
<td>Bupropriona</td>
<td>Oral Rare but serious neuropsychiatric side effects EFV and LPV moderately ↓ bupropion concentrations</td>
<td>Superior outcomes when combined with other therapies</td>
<td>Not studied</td>
<td></td>
</tr>
</tbody>
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Source: Adapted from [13, 15, 34-36] with permission from authors; and [37].

Abbreviations: ↑, increase; ↓, decrease; APV, amprenavir; ART, antiretroviral therapy; ATV, atazanavir; EFV, efavirenz; ETR, etravirine; HIV, human immunodeficiency virus; LPV, lopinavir; NVP, nevirapine; PI, protease inhibitor; r, ritonavir-boosted; XR, extended release; ZDV, zidovudine.

<sup>a</sup> Generics available.
PWUDs are a core component of Ryan White Program significantly increased linkage to care [55], and ICM services for detainees, most of whom had SUDs, found that ICM significantly more effective than passive referrals in facilitating linkage to HIV care [54]. International guidelines recommend integrating treatment for HIV and SUDs to improve retention in care and other health outcomes. HIV care was first successfully integrated into methadone maintenance programs [63]. Integration of drug treatment within a HIV clinic, however, may imply co-location of an “addiction specialist,” which often requires access and resources, or complete “primary care” integration where each clinician simultaneously treats both conditions [31, 64–66]. For opioid-dependent patients, integrating buprenorphine and HIV treatment is feasible and cost-effective, and successfully improves both substance use and HIV outcomes [17, 67, 68]. Barriers to integrating MAT into HIV care, however, may include low prioritization of MAT on AIDS Drug Assistance Program formularies [69].

For HIV providers reluctant to integrate MAT into routine care, they can alternatively screen regularly for problematic drug or alcohol use, provide a brief intervention, and refer to available drug treatment (SBIRT; Figure 2). SBIRT uses an evidence-based algorithm to reduce negative consequences of alcohol or drug use and may be delivered in diverse clinical settings by treating clinicians or case managers, or as computer modules [70, 71]. SBIRT facilitates both routine screening for problematic substance use and linkages between primary care and addiction specialty care, but has not yet been effective at improving HIV treatment outcomes [70]. As HIV and SUD large cohort and cross-sectional studies confirm that SUDs, especially injection drug use, independently contribute to poor HIV treatment retention [55, 59–61]. Strengths-based case management enables clients to identify and apply personal strengths to acquire needed resources and is recommended for improving treatment entry and retention for PLWHA [16, 54], but among PWUDs, it is not effective in reducing drug use or improving psychosocial functioning [62].

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Entry Into HIV Care
After HIV diagnosis, entry into care requires an initial clinic visit with an HIV provider. Delayed entry into care results in increased morbidity and mortality [51], and HIV-infected PWUDs, compared to non-drug users, consistently experience longer delays to healthcare entry. In one study, time to entry into care was 14 months and 19 months for “problematic drinkers” and PWUDs, respectively [52], while another documented that both groups were significantly less likely to enter care within 6 months [53]. Crack cocaine use was specifically correlated with delayed entry in the large multisite Antiretroviral Treatment and Access Study [54].

Targeted outreach strategies effectively use nonphysician staff members, including nurses, paraprofessionals, and/or peer navigators to successfully connect with and retain HIV-infected PWUDs in primary care, but are often challenging to implement in practice. Intensive case management (ICM) is significantly more effective than passive referrals in facilitating linkage to HIV care [54] and international guidelines recommend ICM for all newly diagnosed PLWHA, including those with SUDs [16]. A national multisite study of HIV-infected jail detainees, most of whom had SUDs, found that ICM significantly increased linkage to care [55], and ICM services for PWUDs are a core component of Ryan White Program-funded Early Intervention Services.

Retention in HIV Care
National guidelines define retention in HIV care as attending clinic visits with laboratory monitoring at least quarterly [56, 57]. Attrition from care contributes to poor outcomes along the HIV treatment cascade, with only half of PLWHA being retained in longitudinal HIV care [58]. Treatment retention is requisite for timely ART initiation with its attendant benefits on overall health, mortality, and secondary transmission prevention, but remains prohibitively challenging for PWUDs [13]. Multiple

![Figure 2. Screening, brief intervention, and referral to treatment (SBIRT) algorithm [72, 73].](https://academic.oup.com/cid/article-abstract/57/9/1309/486741)
epidemics expand and converge, the role of the HIV specialist is expanding in tandem. To maximize opportunities to intervene on the health of PWUDs, providers can, at a minimum, screen for SUDs and provide evidence-based, brief, nonjudgmental counseling sessions with referrals to care. Beyond managing ART and opportunistic infections, today’s HIV specialist can be a key provider of secondary HIV prevention, ART adherence counseling, and, when needed, treatment for SUDs.

Initiation of Antiretroviral Therapy

Once HIV-infected PWUDs establish HIV care, timely ART initiation is imperative, especially with recommended ART initiation at any CD4 threshold, to effectively decrease morbidity, mortality, and secondary HIV transmission [74]. A 47-country survey found that, tragically, only 4% of HIV-infected PWIDs received ART [75]. Older studies in the United States similarly found low levels of ART initiation among PWUDs and PWIDs [76], yet more recent models suggest similar ART uptake by reason of similar proportion of PWIDs achieving viral suppression compared to people who do not inject drugs [77].

Reasons for delayed ART initiation among PWUDs are multifactorial. Specific structural barriers to ART access may prove insurmountable for PWUDs, including lower health literacy and socioeconomic status, lack of healthcare insurance, unstable housing, and disjointed healthcare systems [78]. Patient-level indicators of not taking ART despite clinical indication include nonmodifiable (female sex and younger age) and modifiable (not being enrolled in drug treatment) factors [79]. Other potentially modifiable factors include personal attitudes and patient preference to defer ART because of religious beliefs, confidentiality concerns, lack of HIV-associated symptoms, or concerns about nonadherence during periods of active substance use [80]. Patient–provider relationships also impact ART initiation: ART-naive PWIDs reporting “perfect engagement” with their healthcare provider were 45% more likely to initiate ART within months [81]. Overcoming these modifiable patient-level barriers to ART uptake requires a combination of proactive outreach programs, public health education campaigns, organizational change, and improved patient–provider communication that align PWUDs with their providers.

Clinicians also contribute to ART nonprescription and delays because of nonadherence concerns relating to SUDs, despite current evidence and treatment guidelines recommending otherwise [74, 82]. ART delays may be influenced by clinician lack of experience with HIV-infected PWUDs and heavier clinical workloads that reduce clinical time to address SUDs [82]. Negative attitudes toward HIV-infected PWIDs persist, with 14% of US providers agreeing that their treatment seemed “futile” and 9% stating that they would rather not treat HIV-infected PWIDs at all [83]. Negative attitudes toward PWIDs translate directly into suboptimal and potentially life-threatening prescribing practices. Among 662 HIV-treating clinicians surveyed, those who agreed that “providers are not professionally obligated to care” for HIV-infected PWIDs were 5 times more likely to defer ART for PWIDs, irrespective of CD4 count [82].

Culturally conditioned and provider-perpetuated stigma against PWUDs may deter some individuals from disclosing their HIV status, accessing care, or initiating ART [84]. HIV-related stigma remains high among people marginalized from mainstream medical care by their substance use, sex, sexual orientation, racial/ethnic affiliation, or commercial sex work [85, 86]. Stigmatization, together with a prevailing mistrust of healthcare establishments, may compound fear of criminalization, preventing PWUDs from seeking treatment for either HIV or SUDs.

In the United States, where the “war on drugs” has devolved into a “war on drug users,” PWUDs often cycle through the CJS, and incarceration disrupts HIV care continuity and ART treatment persistence [87, 88]. Once people are incarcerated, the CJS can effectively identify and treat HIV and SUDs if adequate services are available to optimize treatment [89]. Benefits are rarely sustained after release [87, 89–91], suggesting that there are insufficient transitional services to engage PWUDs in longitudinal care [47, 87, 90, 91]. Although no single simple solution will reduce stigmatization of HIV-infected PWUDs and effectively retain them in care, multipronged systemic reform involves cultural change, drug policy and healthcare reform, creation of sustainable linkages between CJS- and community-based care, and public health campaigns that do not demonize PWUDs.

To promote care for HIV-infected PWUDs in practice and to counter ignorance, clinicians can be empowered through education about HIV and substance use, and training about SUDs can be incorporated into medical school curricula [92, 93]. Postgraduate medical education on SUDs and their treatment is also free and available as online modules (eg, see www.pcss-o.org). Specifically, providers can prescribe take-home naloxone for administration by laypeople to prevent opioid-related overdose and deaths that disproportionately affect PLWHA (see www.prescribetoprevent.com) [94], with further adaptation for PWUDs transitioning from the CJS [95]. Furthermore, given that SUDs are chronic medical conditions, providers can employ evidence-based practices for early relapse detection and referral to treatment [96, 97]. Addiction experts can, in turn, play a key role in integrating SUD treatment with HIV risk reduction, identifying HIV, and linking PWUDs to HIV care. Directed training about HIV and comorbid SUDs equips healthcare providers with tools to comprehensively manage HIV-infected PWUDs.

Adherence to ART With Viral Suppression

High-level ART adherence is required to achieve the ultimate goal, viral suppression [14]. PWUDs are misperceived as
noncompliant with ART and thus at risk of developing drug resistance, which has been discredited by scientific evidence [15]. A meta-analysis of 9055 patients (23% PWIDs) in 12 studies found that ART resistance developed similarly between PWIDs and people who do not inject drugs [98]. Overall, simplified ART regimens successfully promote ART adherence and persistence among PWIDs, and minimizing pill burden, side effects, and drug interactions remain guiding principles for ART selection.

HIV-infected PWUDs are heterogeneous in their substance use and its effects on ART adherence. Treatment of underlying SUDs, however, consistently facilitates ART adherence [99] and secondarily promotes parity in achieving viral suppression between PWUDs and non-drug users [100]. Opioid substitution therapy using methadone or buprenorphine provides the best evidence for promoting ART adherence [17]; however, 2 longitudinal studies found that any drug treatment, irrespective of modality, confers an ART adherence advantage over no drug treatment [101, 102]. Drug treatment is especially important for promoting ART adherence among PWUDs because otherwise recommended self-management tools (eg, pillboxes, alarms) are often insufficient in the context of chaotic lifestyles, neurocognitive impairment, and intoxication experienced by PWUDs [103, 104].

The best randomized controlled trial evidence for promoting ART adherence among PWUDs is with directly administered antiretroviral therapy (DAART) [105], effectively delivered on a mobile healthcare van [106], during home visits [107], and in methadone programs [108]. Though not recommended in non-drug users [109], DAART consistently increases ART adherence and viral suppression. DAART implementation, however, may be limited by required human resources, expense, and waning benefits during the postintervention period [110]. Recent data support retention on buprenorphine over DAART for PLWHA with opioid dependence [111], yet DAART was superior over methadone alone, particularly with individuals also using stimulants [108]. Beneficial effects of DAART and drug treatment on ART adherence are enhanced by comprehensively addressing other barriers to adherence for PWUDs that include diagnosis and treatment of underlying mental disorders, housing instability, limited access to transportation, and poor social support [99].

CONCLUSIONS

Despite a number of available resources for PLWHA in the United States, HIV-infected PWUDs experience health-related disparities due to delayed HIV diagnosis, entry into and retention in HIV care, ART initiation, and viral suppression compared to non–drug users. Risk-taking behaviors, in the absence of suppressive ART, facilitate HIV transmission, particularly among people with undiagnosed HIV infection. HIV-infected PWUDs represent a key target population for secondary HIV prevention efforts, requiring proactive screening and treatment. Denying PWUDs access to comprehensive treatment and prevention services by continued stigmatization only contributes to the 50,000 new HIV infections annually in the United States. Successful drug treatment implementation requires fundamental healthcare system reorganization to deliver comprehensive and cost-effective care, as espoused by the Affordable Care Act, that is convenient and useful to patients (eg, integrating clinical services for HIV, viral hepatitis, SUDs, sexually transmitted infections, and mental disorders with social services for housing, insurance, and transportation). The Affordable Care Act will also further efforts to reduce healthcare disparities for HIV-infected PWUDs by eliminating HIV/AIDS as a “preexisting condition” and requiring that substance abuse and mental health treatment options be offered through state-based marketplace exchanges [112, 113].

Although this paper focuses on the United States, healthcare disparities for PWUDs, especially in eastern Europe and Asia, have fueled an explosion in HIV incidence and prevalence [30]. Police-enforced criminalization of PWUDs, name-based registries, insufficient availability of evidence-based MATs, and reduced ART access result in undertreatment of HIV among PWUDs [114, 115]. The most recent World Health Organization global health strategy on HIV calls for the provision of “comprehensive, integrated services for key populations” including for PWUDs [116]. Resources can be effectively harnessed to engage PWUDs in care and to sustain their engagement at each point along the HIV continuum of care for both individual and public health [14].

Notes

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