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Synthetic Opioid Use and Common Injection-associated Viruses: Expanding the Translational Research Agenda

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Abstract

The US is in the midst of a major epidemic of opioid addiction and related comorbidities. People with opioid use disorder (OUD) are at significant risk for transmission of several blood-borne pathogens including the human immunodeficiency virus (HIV), hepatitis B virus (HBV), and hepatitis C virus (HCV). Commonly abused opioids and their receptors promote viral replication and virus-mediated pathology. However, most studies demonstrating an adverse effect of drugs of abuse have been conducted *in vitro*, the specific effects of synthetic opioids on viral replication have been poorly characterized, and the evaluation of opioid-virus interactions in clinically relevant populations is rare. Rigorous characterization of the interactions among synthetic opioids, host cells, and common injection-associated viral infections will require an interdisciplinary research approach and translational studies conducted on humans. Such research promises to improve clinical management paradigms for difficult-to-treat populations, facilitate rational public health policies given severely strained resources, and reveal additional pathways for novel target-specific therapeutic interventions. This mini-review examines the published literature on the effects of opioids on HIV, HBV, and HCV pathogenesis and proposes a series of scientific questions and considerations to establish a translational research agenda focused on opioid-virus interactions.

Keywords

HIV; hepatitis B virus (HBV); hepatitis C virus (HCV); drug use; opioid; pathogenesis

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CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

1. THE OPIOID CRISIS

The US is in the midst of a major opioid crisis [1], and adverse outcomes from opioid use disorder (OUD) continue despite prevention and harm reduction strategies. Drug overdose deaths tripled from 1999 to 2014, and deaths involving synthetic opioids other than methadone and heroin increased further from 2014 to 2015 [2, 3]. The synthetic opioid fentanyl is now involved in >60% of overdose deaths [1, 2]. Nationally, hospitalizations after fentanyl overdose and synthetic opioid deaths increased by 426% and 79%, respectively, during 2013–2014 [4, 5]. 2017 data found that ~90% of unintentional overdoses involved fentanyl or fentanyl analogs (FA) [5, 6].

Persons with OUD are at significant risk for transmission of viral infections such as the human immunodeficiency virus (HIV), hepatitis B virus (HBV), and hepatitis C virus (HCV) both from high-risk sexual activity and the sharing of injection equipment. Persons who inject drugs (PWID) account for 8% of new HIV infections and 15% of those living with HIV in the US [7]. An association between fentanyl use and HIV infection has been reported in other settings as well [8, 9]. People living with HIV who also inject drugs have higher age-matched morbidity and mortality compared to people living with HIV who do not inject [10]. Moreover, the proportion of PWID with HBV has increased in recent years [11–14], and increased numbers of acute HBV infections have been reported in Florida, Kentucky, West Virginia, and Tennessee [15, 16]. Globally, HCV prevalence rates range from 60% to 80% in PWID [17], and the number of acute HCV infections has risen steadily across the United States with just twelve states accounting for 68.6% of cases [7].

Currently, translational/interdisciplinary research related to this opioid-centered epidemic relies heavily on *in vitro* studies of other non-opioid drugs of abuse and studies of opioid-virus interactions in clinically relevant populations are rare. A robust understanding of opioid-host and opioid-virus interactions in patient populations is limited to date but remains essential for the development of new and optimized treatment and harm reduction strategies.

2. TREATMENT CHALLENGES

Medications approved for the treatment of OUD are underutilized by those most affected ones and are not offered in many settings. Community-based treatment programs do not always offer medication-assisted treatment (MAT), the gold-standard OUD treatment. Moreover, specific data on the efficacy of different MAT options and the outcomes for patients with synthetic opioid addiction are lacking. Service gaps remain across the substance use care continuum from initial screening through engagement and retention in appropriate treatment. There are also significant gaps existing in testing, linking, and retaining patients with OUD to HIV, HBV, and HCV prevention and care services. The US Centers for Disease Control and Prevention, the Preventive Services Task Force, and the Institute of Medicine, all recommend routine HIV and HCV testing for high-risk individuals, including those with a history of injection drug use [18–23]. Testing addresses the first step in the treatment care cascade by identifying patients (potentially at an earlier disease stage), and may facilitate earlier treatment initiation [24]. Despite being at increased risk, HIV testing rates have declined among opioid users in the US in recent years [25, 26]. While

sustained viral suppression is effective at reducing transmission to others, linkage and retention in HIV and HCV care are often poor, with lower retention in HIV care among individuals using illicit substances [27, 28]. Indeed, recent meta-analyses examining the HIV and HCV care cascades highlight significant gaps in the care continuums from initial testing, confirmatory testing, and linkage to care to initiation of treatment, and optimal virologic response, particularly among individuals who use opioids [24, 28]. Nonetheless, results from a randomized, placebo-controlled trial demonstrate that extended-release naltrexone improves or extends HIV viral suppression and provides encouraging data for treatment of patients with OUD and viral infection [29]. Among HCV-infected PWIDs, high rates of viral clearance were achieved when treatment with direct-acting antivirals and opioid agonist therapy were given [30].

3. OPIOIDS

Opioids include both endogenous and exogenous (synthetic) compounds that function through activation of several opioid receptors. Opioid receptors are abundantly expressed on various immune cells including lymphocytes, macrophages, neutrophils, and monocytes [31]. Opioid receptors are also present in the liver [31, 32]. Opioid receptors are classified as μ -opioid receptors (MORs), δ -opioid receptors (DORs), κ -opioid receptors (KORs), and opioid-like receptors (OLR) and are encoded by the *OPRM1*, *OPRD1*, *OPRK1*, and *OLR* genes, respectively [33]. Upon receptor activation, adenylyl cyclase is inhibited, which activates K^+ channels and diminishes conductance of voltage-sensitive Ca^{2+} channels. Opioid receptors also activate mitogen-activated protein kinases and phospholipase C-mediated signaling, leading to the formation of IP3 and diacylglycerol. These effects activate or inhibit multiple downstream signals that mediate the intrinsic effects of opioids [34, 35]. Importantly, opioid receptors are abundantly expressed on various immune cells [31, 36] and in the liver, where they are important mediators of liver disease progression [37–43].

Underappreciated is the fact that commonly abused substances antagonize innate immune responses and promote viral replication (Table 1). However, the vast majority of data on how drugs of abuse, including opioids, regulate viral pathogenesis are derived from *in vitro* studies or *ex vivo* infections in the presence of the drug. Patient studies are rare, and the clinical relevance of many of the findings reported to date remain largely speculative in the absence of longitudinal studies conducted in persons with OUD. Nonetheless, because viral replication is a major predictor of disease progression, transmission, and treatment response, the interactions between drugs of abuse and viral pathogenesis require thorough investigation.

4. HIV AND SUBSTANCE ABUSE

Much of our current mechanistic understanding of how drugs of abuse impact viral pathogenesis is derived from *in vitro* and *ex vivo* studies, and the specific effects of synthetic opioids on viral replication have not been reported. Initial studies with non-opioid drugs of abuse showed increased viral replication in peripheral blood mononuclear cells (PBMCs) from healthy individuals that were infected *ex vivo* with clinical isolates of HIV in the presence of cocaine or morphine [44–46]. Antibodies to transforming growth factor beta

blocked cocaine-enhanced HIV replication [46]. Cocaine also downregulates chemokines such as MIP-1 α while upregulating CCR5 co-receptor expression [47], suggesting that it may contribute to increased susceptibility to infection, as well as disease progression. Cocaine also promotes HIV gene transcription through NF κ B and mitogen- and stress-activated kinase 1 (MSK1) signaling, phosphorylation of histone H3, and phosphorylation of p38 mitogen-activated protein kinase [48–50]. In the simian HIV model, cocaine treatment of macrophages similarly increases viral replication, activation of the HIV long terminal repeat (LTR) through NF κ B, and increased IL-10 expression [51]. Cocaine has also been shown to inhibit microRNA-155 in monocyte-derived dendritic cells and increase their susceptibility to HIV infection [52]. A recent study demonstrated that cocaine induces overexpression of DC-SIGN and facilitates virus transfer from dendritic cells to T-cells [53].

As with other drugs of abuse, morphine-induced transactivation of the HIV LTR has been demonstrated [54]. Morphine increases replication of HIV in PBMCs [44, 55], as well as in purified blood-derived macrophages [56, 57], by enhanced CCR5 – but not CXCR4 – receptor mRNA expression and inhibition of β chemokines. In neonatal macrophages, morphine upregulates CCR5 co-receptor expression, inhibits MIP-1 β , and enhances HIV replication [57]. This effect may not be limited to the periphery, as β chemokine expression is also downregulated and chemokine co-receptor is upregulated in a morphine-treated astrocytoma/ glioblastoma cell line [58]. Furthermore, morphine-treated cells express lower levels of cellular anti-HIV miRNA than untreated cells and compromise IFN-induced anti-HIV microRNA expression [59]. Similarly, morphine is also associated with decreased RNase L activity in PBMCs [60]. In latently-infected T lymphoblasts, reactivation of HIV was triggered by morphine in a dose-dependent manner [61]. A μ -opioid receptor agonist increases CXCR4 and CCR5 co-receptor expression, permitting enhanced replication of HIV [55]. Methadone – an opioid frequently used in the treatment of opioid use disorder – enhances HIV infection in several cell types by increased expression of CCR5 coreceptor [62, 63]. Similarly, endogenous opioid peptides such as β endorphin, endomorphin-1, and dynorphin enhance HIV expression [64–67]. Multiple studies have shown that opioid receptor antagonists can reverse the proviral effects of morphine, methadone, heroin, or opioid peptides [44, 59, 61, 62, 64, 65, 68–70]. Unfortunately, many drugs of abuse – including synthetic opioids – have not been evaluated thoroughly.

Other commonly abused substances also impact HIV replication. For instance, methamphetamine (meth) causes a dose-dependent increase of HIV reverse transcriptase activity in macrophages by upregulating CCR5 co-receptor expression and inhibiting endogenous IFN α [71]. Dopamine D1 receptor antagonists can block meth-induced virus replication. Similarly, meth enhances HIV infection and decreases chemokine production in dendritic cells [72, 73]. Subsequent studies reported that meth inhibits the anti-HIV activity of toll-like receptor 9 and suppresses several innate restriction factors associated with reduced type I IFN production [74, 75]. A recent study showed that meth induced transactivation of the LTR through NF κ B and Sp1 and increased infection of neuronal progenitor cells [76]. These data are supported by higher HIV viral loads and lower CD4 cell counts observed in meth users *in vivo* [77, 78]. In non-viral systems, synthetic opioids such as fentanyl induce apoptosis, alter NF κ B signaling, and can exert immunosuppressive effects [79–82]. However, similar studies on the cell targets of HIV infection have not been

conducted nor have gene expression patterns been analyzed in individuals with HIV and synthetic opioid exposure.

The ability of opioids to modulate epigenetic changes – particularly microRNA expression – highlights another mechanism by which opioids impact viral infection. For example, morphine and heroin inhibit the expression of anti-HIV microRNAs that target the 3'UTR of viral transcripts [59, 61, 70]. Similarly, opioids inhibit anti-HIV microRNAs that stimulate replication of latent HIV in resting CD4⁺ T cells and monocytes [61, 83]. Expression analysis indicated downregulation of several anti-HIV microRNAs – particularly microRNA-125b – in primary CD4⁺ T cells treated with cocaine [84]. While these findings are intriguing, different drugs of abuse may differentially regulate microRNAs, and no studies have evaluated the impact of synthetic opioids on microRNA expression to date.

5. VIRAL HEPATITIS AND SUBSTANCE ABUSE

Several opioid receptors are expressed in the liver and – along with endogenous and exogenous opioids – may contribute to liver disease [37–43]. As HCV is commonly transmitted via injection drug use, understanding the impact of commonly abused substances on HCV replication and liver pathogenesis is important. Zhou *et al.* reported that HCV-infected heroin users had significantly higher HCV RNA levels compared to non-heroin users [85]. Levels of microRNAs known to promote HCV replication were also increased in heroin users with HCV infection. *In vitro* morphine treatment inhibits endogenous and recombinant IFN α and increases HCV expression in a dose-dependent manner. This induction requires NF κ B and can be inhibited by opioid receptor antagonism [86, 87]. Interestingly, morphine withdrawal is also associated with increased HCV replication *in vitro* [88]. Methamphetamine inhibits endogenous IFN α , antagonizes the antiviral effects of recombinant IFN α , and enhances HCV replication in hepatocytes *in vitro* [89]. Multiple microRNAs stimulate or suppress HCV replication as reviewed elsewhere [90]. While opioids can regulate microRNA expression and alter HIV replication as outlined above, similar studies of opioid-HCV-microRNA interactions are absent from the literature. Moreover, the impact of individual synthetic opioids on HCV expression has not been evaluated to date. As well, despite its transmissibility by IDU, surprisingly little is known about the effects of any drug of abuse – including synthetic opioids – on HBV replication *in vitro* or in HBV-infected individuals with OUD.

6. RESEARCH PRIORITIES

The National Institute on Drug Abuse (NIDA) set forth several research priorities in its 2016 – 2020 Strategic Plan, including bridging the gap between research discovery and clinical and community practice and utilizing research to inform clinical practice [91]. While acknowledged as a complex challenge, it is one that is absolutely necessary to maximize benefits to the most impacted populations. NIDA also included the goal of “accelerating development of treatments” which requires repurposing medications already approved for other indications that may benefit people with substance use disorders and translating basic research on molecular pathways involved in substance abuse to develop new approaches that

modulate specific pathways. Essential to achieving these goals is the robust characterization of opioid-host and opioid-virus interactions.

While several studies demonstrate an adverse effect of drugs of abuse – including opioids – on virus replication *in vitro*, confirmation of these findings in clinically relevant populations is rare. Despite a profound proviral effect caused by many commonly abused substances, the specific effects of synthetic opioids such as fentanyl or its analogs, on viral replication have not been evaluated in detail. We recently reported preliminary *in vitro* data showing that fentanyl causes increased expression of HIV, HBV, and HCV [92], although the mechanism(s) underlying this observation has yet to be determined and confirmatory studies in individuals with OUD are now required. Nonetheless, these findings and the larger landscape of interactions between viruses, substances of abuse, and a variety of cell pathways highlight the need to carefully study these interactions for each drug. For instance, if human studies confirm that fentanyl is associated with higher HCV RNA levels, then its therapeutic use in settings with limited knowledge of the patient's HCV status (such as emergency rooms, resource constrained treatment centers, and/or private practice) might be limited or suggests that point-of-care viral testing is required. Similarly, increased viral replication in the presence of fentanyl could prompt physicians to prescribe more potent antivirals or to initiate treatment for OUD first. In addition, possible fentanyl-antiviral interactions could shift prescribers away from certain drug combinations. Finally, with increased availability of opioid antagonists, recreational users survive overdoses. Yet, their risk of co-morbid conditions such as HCV remains due to OUD relapse and HCV reinfection and could fuel secondary transmission events.

Prescription opioid use is common in individuals living with HIV [93, 94], and there is growing recreational use of synthetic opioids in individuals with or at risk for viral infections. Research related to this opioid-centered epidemic is lacking but is crucial to the development of new and optimized treatment and harm reduction strategies. For example, there is evidence that the linkage to treatment services is improved when provided within the same healthcare system [95]. This highlights the need for a coordinated, multi-faceted approach to improve substance use, HIV, and HCV outcomes among individuals with OUD that can be integrated more seamlessly within clinical care. Research to evaluate different care models to address the OUD and HCV, HIV care cascades is urgently needed [96]. An implementation of a scientific framework may be particularly useful to study alternative health care delivery approaches and the associated impact on OUD and injection-associated viral outcomes. Additionally, synthetic opioids may impact viral disease progression indirectly through drug-drug interactions and/or by reduced antiviral activity, although this remains to be explored in detail. Importantly, opioids can modulate epigenetic changes such as microRNA expression that impact viral infection [59, 61, 70, 83, 97]. However, the cellular pathways altered by synthetic opioid use have not been explored *in vivo*, thereby hindering the development of novel therapeutic strategies to treat complex virus-opioid interactions and the life-threatening comorbidities associated with recreational opioid use. Thus, a number of unanswered questions remain, such as:

Do synthetic opioids influence viral pathogenesis as documented for other commonly abused substances? Do individual synthetic opioids differ in their proviral or antiviral

activities? Recreational use of synthetic opioids has risen dramatically in recent years. While fentanyl is perhaps the most widely known synthetic opioid, its structural scaffold has been modified periodically by illicit drug manufacturers to produce novel analogs [98]. Even as multiple synthetic opioids continue to adulterate the drug supply, there are no published data evaluating the impact of these agents on replication of any viruses, although our preliminary in vitro studies suggest that fentanyl causes increased expression of HIV, HBV, and HCV [92]. These findings require rigorous examination in vivo as well. Importantly, the mechanisms described thus far for how other drugs of abuse alter HIV or HCV replication are quite diverse. Thus, mechanistic studies are required for each drug of abuse (*i.e.*, individual synthetic opioids may alter virus replication in a drug-specific manner).

Does opioid receptor antagonism counteract the effects of synthetic opioids on viral replication, thereby providing an added benefit to individuals with continued synthetic opioid use? Opioid antagonists such as naloxone and naltrexone are known to reverse the enhancement of viral replication by several drugs of abuse [44, 56, 60, 63, 68–70, 86, 87]. However, the potential effects of these agents on synthetic opioid-mediated virus replication have not been reported to date and must be evaluated in at-risk patient populations.

What role does polysubstance use play in viral pathogenesis?

Polysubstance use is the norm in most individuals with OUD. Moreover, current NIDA research priorities highlight polysubstance use and the need to broaden the research focus to include complex interactions (*e.g.* multiple substances, comorbidities, and coinfections), the inherent variability in substance use, and the need to develop treatments and delivery strategies that simultaneously address substance use and comorbidities [91]. Nonetheless, whether multiple drugs of abuse have additive, synergistic, or antagonist effects on viral replication and pathogenesis remains unexplored and requires careful evaluation.

Are there drug-drug interactions between synthetic opioids and currently prescribed antiviral medications for HIV, HBV, or HCV that must be considered in high-risk patient populations? Very little is known about the possible interactions between synthetic opioids and antiviral agents. While a single study has shown that ritonavir is associated with increased fentanyl concentrations in plasma [99], other antiretroviral (ART) medications were not evaluated. Similarly, there are no data on whether synthetic opioids counteract the antiviral effects of direct-acting agents (DAAs) for the treatment of HCV. Nonetheless, drug-drug interactions between synthetic opioids and currently prescribed DAAs and/or ARTs must be carefully evaluated in high-risk individuals.

What cellular pathways and microRNAs are regulated by synthetic opioids that could be exploited to control viral replication in virally-infected individuals with substance use disorders? Commonly abused substances and their receptors affect viral replication and virus-mediated pathology through the multiple mechanisms outlined above and elsewhere [32], although surprisingly little is known about how synthetic opioids shape the cellular transcriptome, contribute to cell dysfunction, or regulate disease progression. Different drugs of abuse are likely to have distinct effects on a particular signaling pathway and/or cell type; yet, robust mechanistic evaluations of opioid-virus and opioid cell interactions are lacking and represent a significant gap in the available literature. Detecting transcriptional changes

using unbiased high-throughput next-generation sequencing (NGS) would expedite the discovery of novel mRNA and microRNA species that are critical for virus-cell-opioid interactions and/or define dominant gene expression signatures that are altered in response to individual synthetic opioids. Such investigations would also serve as the basis for biomarker discovery and could reveal additional pathways for novel target-specific therapeutic interventions.

CONCLUSION

There is an urgent public health need to address the linked opioid, HIV, and HBV/HCV epidemics, particularly in regions with a high prevalence of opioid use disorder. This review summarizes the existing research regarding the relationship between opioid use and viral replication and identifies gaps in the literature. Given the current national opioid crisis, an interdisciplinary research approach that addresses the intersection of opioid use and infectious diseases requires an immediate coordinated approach by investigators with complementary expertise across the translational research spectrum. For example, research to establish a cohort study of individuals with OUD at-risk or infected with viral infections could facilitate research across the translational continuum. Ultimately, such research offers the potential to inform treatment decisions regarding optimal treatment approaches for opioid use disorder and co-occurring HIV, HCV, and/or HBV.

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Table 1.

Effects of substance abuse on viral replication.

Substance	Effect	Virus	Cell Types
Methadone	Increases	HIV	Monocyte-derived macrophages [62]; fetal microglia [62]
Methadone	---	HCV	No published data
Methamphetamine	Increases	HIV	Monocyte-derived macrophages [71, 74, 75, 100]; neural progenitor cells [76]; dendritic cells [52, 72, 73]; HIV-infected patients [77, 78, 101]
Methamphetamine	Increases	HCV	Hepatocytes [89]
Cocaine	Increases	HIV	Monocyte-derived macrophages [48, 49]; T cells (84); dendritic cells [52, 53]; PBMCs [45, 46]
Cocaine	---	HCV	No published data
Morphine	Increases	HIV	Monocyte-derived macrophages [56, 59, 68]; neonatal macrophages [57]; latently-infected T lymphoblasts (61); PBMCs [44, 60]
Morphine	Increases	HCV	Hepatocyte cell lines [86-88]
Heroin	Increases	HIV	Monocyte-derived macrophages (59, 70); latently-infected T lymphoblasts (61)
Heroin	Increases	HCV	HCV-infected patients [85]
Opioid peptides	Increase	HIV	Fetal perivascular microglia [65]; fetal brain tissue [64]; monocyte cell lines [66, 67]
Opioid peptides	---	HCV	No published data