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Opioids and HIV/HCV Infection

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Abstract

Since human immunodeficiency virus (HIV) and hepatitis C virus (HCV) share the same modes of transmission and common risk factors for infection, co-infections with HIV and HCV are frequently found in injection drug users (IDUs). IDUs represent one of the largest reservoirs of HIV as well as HCV in the United States. These two pathogens are also likely to be responsible for the highest infectious disease morbidity and mortality rates among IDUs. IDUs frequently involve the abuse of heroin, the most common abused opiate. Opiates have been suggested to have a cofactor role in the immunopathogenesis of HIV disease, as they have the potential to compromise host immune responses and enhances microbial infections. Although in vitro studies have yielded relatively agreeable data that morphine, the active metabolite of heroin, exacerbate HIV infection/replication, epidemiologic studies as well as in vivo non-human primate investigations on the impact of opiate abuse on HIV disease progression have yielded the conflicting data. Given immunomodulation and immunocompromising effect as well as demonstrated impact to enhance HIV replication in vitro, it is reasonable to believe that opiate abuse is a facilitator in HIV and/or HCV disease progression. However, much remain to be learned about the mechanisms of opiate-mediated broad influence on host immunity and viral expression. Thus, more extensive studies are needed in order to determine the effects of different conditions of opiate abuse and to define the understanding of the role of opiate in modulating HIV and/ or HCV disease progression.

Keywords

Opioids; Heroin; Morphine; Methadone; HIV; HCV

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Introduction

HIV and HCV share the same transmission routes and risk factors for infection. Thus, injection drug users (IDUs) are at a significant high risk for acquiring both HIV and HCV. In the United States and other regions of the world, HIV and HCV epidemics have been driven by drugs of abuse. IDUs are representing one of the largest reservoirs of HIV infection in the United States, contributing to the fastest spread of the virus (Alcabes and Friedland 1995; Risdahl et al. 1998). IDUs also comprise the largest risk group for HCV infection (Alter et al. 1999; Lauer and Walker 2001; Mathei et al. 2002), and are the primary source of new HCV infection. Rates of HCV infection among past and current IDUs are extremely high, generally ranging from 70% to over 90% in the United States (Diaz et al. 2001; Thomas et al. 1995). Coinfection with HIV and HCV is becoming a major global problem. In the United States, about 300,000 individuals are coinfecting with HIV and HCV (Sherman et al. 2002), representing 25–30% of all HIV-infected people and 5–10% of all HCV-infected individuals (Sherman et al. 2002). As patients with HIV infection are living longer in the era of highly active antiretroviral therapy (HAART), the clinical significance of HCV coinfection is becoming more prominent. HIV/HCV infections appear to affect the clinical course of each infection adversely (Sulkowski and Thomas 2003). There is increasing evidence that co-infected subjects have higher morbidity and mortality of liver disease. The deleterious effects of HIV on the pathogenesis of HCV infection include a higher rate of viral persistence, increased viral loads, a faster rate of fibrosis progression, and higher rates of hepatic decompensation (Sulkowski and Thomas 2003). In addition, HIV/HCV-coinfected individuals have lower treatment response rates following interferon-alpha (IFN- α)-based therapies compared with those HCV-monoinfected subjects (Chung et al. 2004; Perez-Olmeda et al. 2003; Torriani et al. 2004). We, however, know little about the mechanisms by which HIV and HCV directly interact at cellular and molecular levels. No direct virus-virus interactions have been shown to date.

Opioids bind opioid receptors principally found in the central nervous system (CNS) and gastrointestinal tract, but opioid receptors are also found on immune cells. Four classes of opioids have been categorized: endogenous opioid peptides; opium alkaloids, such as morphine and codeine; semisynthetic opioids that include heroin and oxycodone; and fully synthetic opioids such as pethidine and methadone that have structures unrelated to the opium alkaloids. IDUs frequently involve abuse of heroin, the most commonly abused opiate. In fact, most heroin addicts are stereotypic IDUs. As many as 2.4 million Americans are heroin users. In addition to collective use of injecting equipment and drug solution, which contributes to HIV and/or HCV transmission, the negative impact of opiate abuse on host immune system is another key factor to facilitate HIV and/or HCV replication. Thus, opiate abuse has been suggested to have a cofactor role in the immunopathogenesis of HIV disease. In the following sections, we discuss the impact of opiates (heroin, morphine, and methadone) on host immunity and HIV/HCV expression as well as the implication in the disease progression.

Opiates and HIV

Because many of opiate abusers use injection as the primary route of administration, opiate abuse contributes significantly to HIV transmission among drug users (Ronald et al. 1994; Specter 1994). Several early studies indicated that intravenous use of opiates influences the outcome of HIV infection (Alcabes and Friedland 1995; Battjes et al. 1988; Risdahl et al. 1998; Ronald et al. 1994; Specter 1994). Heroin injection increased the risk of acquiring HIV (Friedman et al. 2003) and progression to AIDS (Ronald et al. 1994). However, because of the extreme complexity of opiate addiction and/or HIV infection, it has been extremely difficult to compare different clinical and epidemiological findings in studying the

impact of opiate abuse on HIV disease progression (Donahoe et al. 2009). In contrast, laboratory in vitro studies have yielded relatively agreeable data, showing that morphine, the active metabolite of heroin, enhances susceptibility of the immune cells to HIV infection. Peterson et al. first reported that morphine enhances HIV replication in human PBMC co-culture system (Peterson et al. 1990). They also showed that the expression of HIV in cocultures of chronically infected promonocytic clone U1 and human fetal brain cells was increased following exposure to morphine (Peterson et al. 1994). Morphine also facilitated simian immunodeficiency viruses (SIV) replication in monkey peripheral blood mononuclear cell (PBMC) (Suzuki et al. 2002a). Morphine enhances HIV replication in human macrophages (Guo et al. 2002; Ho et al. 2003; Li et al. 2002, 2003a), T lymphocytes (Chuang et al. 1993a; Peterson et al. 2004; Steele et al. 2003), Kupffer cells (Schweitzer et al. 1991), human neuroblastoma cells (Squinto et al. 1990) and human brain cells (Chao et al. 1995; Peterson et al. 1999), microglia (Peterson et al. 2004). A study by Nair's group (Reynolds et al. 2006) found that heroin potentiates HIV replication in human astrocytes. Using human T lymphoid cell line, Selimova et al. demonstrated that heroin increased HIV replication at the early stages of its life cycle (Bobkov et al. 2005; Selimova et al. 2002).

Opiates and SIV

Although the in vitro studies (Table 1) clearly demonstrated that opioids such as morphine or heroin enhance HIV expression, the non-human primate studies (Chuang et al. 1993b, 1995, 2005; Kumar et al. 2004, 2006) have produced the contradictory data with regard to the role of opiate use in the progression of SIV disease (Donahoe et al. 1993, 2009; Donahoe and Vlahov 1998) (Table 1). The studies conducted by Donahoe et al. (Donahoe et al. 1993, 2009; Donahoe and Vlahov 1998) showed that long-term opiate dependency retarded the rate of progression to AIDS in the SIV_{smm9}-infected monkey model, but Chuang et al. (Chuang et al. 1993b, 1995, 2005) and Kumar et al. (Kumar et al. 2004, 2006) observed a greater SIV disease progression after opiate injection. The variability of opiate effects on SIV infection of monkey model could be due to the differences in study designs and methodological limitations including type of opiate treatment and dose of opiates (Friedman et al. 2003; Kapadia et al. 2005; Lucas et al. 2006). In the studies of Chuang et al., the investigators used a fairly virulent SIV strain (mac239) and limited numbers of rhesus macaques chronically injected with morphine (opiate dependency). In contrast, Donahoe et al. who reported AIDS progression was retarded in their study used a relatively weak SIV strain (smm9) and 37 Indian rhesus macaques. In addition, compared with Donahoe's model, the Chuang study administered about one-half of the amount of opiate per injection cycle, causing withdrawal-like conditions. In Kumar's studies, a three virus combination (SIV/17E-Fr, SHIV_{89.6P} and SHIV_{KU}) was used to infect the monkeys (Kumar et al. 2004, 2006), which produced very rapid disease and death in 50% of the morphine-addicted monkeys. Clearly, these differences in the study design of these studies described above should contribute to the variability of opiate effects on SIV infection of monkeys.

Opiates and immunity

Although the role of opiates in promoting HIV disease is still debatable, overwhelming evidence indicates that heroin and other opiate-derived substances affect both innate and adaptive immunity (Donahoe and Vlahov 1998; McCarthy et al. 2001; Wang et al. 2008b; Zhang et al. 2006). Opiate abusers have higher incidence of infectious diseases, which may be directly related to impaired immune functions (Alonzo and Bayer 2002; Nair et al. 1997; Novick et al. 1989; Ochshorn et al. 1990; Peterson et al. 1993; Wang et al. 2008b). The administration of morphine to rodents suppresses a variety of immune responses that involve the major cell types in the immune system, including natural killer cells, T cells, B cells, macrophages and polymorpho-nuclear leukocytes (Bayer et al. 1990). Morphine also

inhibits in vivo antibody responses (Lockwood et al. 1994). Morphine suppressed the production of antiviral cytokines, such as interferon-alpha (IFN- α) and IFN-gamma (IFN- γ) by immune cells (Hung et al. 1973; Peterson et al. 1989; Wang et al. 2002, 2003). Both type I IFNs (IFN- α , β) and type II IFN (IFN- γ) are involved in all phases of immune processes and have a central role in host innate immunity against viral infections. We showed that morphine, through the suppression of IFN- γ production, compromised CD8⁺ T cell-mediated anti-HIV activity in both acute and latently infected cells (Wang et al. 2005c). Opioids modulate immune functions via pharmacological activation of endogenous opioid receptors in the immune cells (Bayer et al. 1990; Bidlack 2000; Fecho et al. 1996; Hernandez et al. 1993; McCarthy et al. 2001; Mellon and Bayer 1998) and/or in the cells in the CNS (El-Hage et al. 2006a, b, 2008, 2011; Wan et al. 2008). Several studies (Guo et al. 2002; Li et al. 2003a; Mahajan et al. 2005; Mahajan et al. 2002; Miyagi et al. 2000; Suzuki et al. 2002a, b) showed that morphine could activate mu opioid receptors of human immune cells (macrophages, T lymphocytes, microglia) and up-regulate the expression of CCR5 and CXCR4, the key HIV entry coreceptors. Morphine-mediated induction of CCR5 and CXCR4 was associated with increased HIV infection of macrophages (Li et al. 2003a; Steele et al. 2003). In recent years, it has become clear that intracellular restriction factors play a crucial role in determining the host range of HIV infection. Some cellular miRNAs have been identified to inhibit or promote viral replications (Han and Siliciano 2007). Computational analyses of miRNAs in T cells have identified five miRNAs (miR28, miR125b, miR150, miR223 and miR382) that can target highly conserved regions in HIV (Hariharan et al. 2005). These miRNAs are more highly expressed in resting CD4⁺ T cells than activated T cells (Huang et al. 2007). We recently showed that monocytes express significantly higher levels of these miRNAs than donor-matched macrophages (Wang et al. 2009). We also demonstrated that morphine has the ability to inhibit the expression of these anti-HIV miRNAs in monocytes, enhancing the susceptibility of cells to HIV infection (Wang et al. 2011).

Clearly, opiates have immunomodulatory and immunocompromising effects as well as a demonstrated potential to modulate HIV-1 production in vitro. However, different state of opiate dependency included maintenance (Metzger et al. 1993; Selwyn et al. 1993; Sullivan et al. 2008; Zaric et al. 2000), tolerance (DeLeo et al. 2004; Donahoe 1993; Eisenstein et al. 2006; Umbricht et al. 2003) and opiate withdrawal (Donahoe 2004; Feng et al. 2005, 2006b; Rahim et al. 2002, 2003, 2005; Wang et al. 2006) has the potentially differential effects on immune function and HIV infection. Because of the complexities of variable and conditional dependence of opiate effects, a consideration should be given to opiate use conditions (maintenance, tolerance, and opiate withdrawal) and stages (acute v.s. chronic use) in explaining data collected with regard to the role of opiates in immunomodulation and HIV infection/AIDS.

Opiates and microtranslocation

Opiate abusers are a high-risk population for bacteria infection (El-Sharif and Ashour 2008; Friedman et al. 2003; Kapadia et al. 2005). Numerous clinical studies have shown that immunocompromise resulting from prolonged drug use contributes to the increased risk of respiratory tract infection (El-Sharif and Ashour 2008). There is actually a 10-fold increase in the risk of community-acquired pneumonia in drug users (Boschini et al. 1996). Overall, respiratory tract infections caused by *S. pneumoniae*, *S. aureus*, *K. pneumoniae*, *Mycobacterium*, *Staphylococcus*, *Haemophilus*, and other bacteria are among the most common diagnoses of this IDUs (Hind 1990; Perlman et al. 1995). The data from animal model showed that opioid treatment causes increased susceptibility and mortality to various bacterial infections, including *S. pneumoniae* (Wang et al. 2005b, 2008a), *K. pneumoniae* (Tubaro et al. 1983), acute *Toxoplasma gondii* (Chao et al. 1990), oral *Salmonella*

typhimurium (Feng et al. 2006a), *Candida albicans* (Szabo et al. 1993), *Acinetobacter baumannii* (Lee et al. 2007), *S. aureus* (Koyuncuoglu et al. 1988), and *Listeria monocytogenes* (Asakura et al. 2006). Although opiate addiction has been identified as a risk factor for clinical tuberculosis (Durante et al. 1998), an in vitro infection study (Peterson et al. 1995; Rock et al. 2004), contrary to other bacterial infection studies, showed that morphine stimulated the phagocytosis of *M. tuberculosis* by human microglial cells, the resident macrophages of the brain.

Recently, the bacterial product-mediated immune activation has been suggested as a strong predictor of HIV disease progression (Brenchley et al. 2006a; Grossman et al. 2006). Elevated plasma endotoxin (lipopolysaccharide, LPS, a component of gram-negative bacteria), a consequence of translocation of bacterial products from a leaky gut, is likely responsible for the systemic immune activation in chronic HIV infection (Brenchley et al. 2006b). The level of microbial translocation was correlated with immune activation and CD4⁺ T cell depletion in HIV-infected subjects (Ancuta et al. 2008; Brenchley et al. 2004, 2006a, b). Evidence that circulating LPS translocated from gut was also provided by studies using SIV-infected rhesus macaques (Brenchley and Douek 2008a, b; Brenchley et al. 2006b), which showed that plasma LPS levels were reduced following treatment with antibiotics. A recent study (Ancuta et al. 2008) reported that substance abuse and HCV infection are associated with high plasma levels of LPS. Opiate-mediated immunosuppression may be a factor that enhances microbial infections (Friedman et al. 2003; Kapadia et al. 2005; Wang et al. 2008b). Experimental animal studies showed that opioid treatment causes increased susceptibility and mortality to various bacterial infections (Wang et al. 2008b). Mouse model studies (Feng et al. 2006b; Peng et al. 2001) suggested that chronic morphine exposure inhibited mucosal antibody responses in gut-associated lymphoid tissue, suggesting the possibility of specific defects in IgA-mediated responses, to enteric bacteria. Morphine induced sepsis in mice, as morphine-treated mice had a spontaneous increase in the number of enteric organisms in liver and spleen and were sensitized to endotoxic shock (Hilburger et al. 1997). It is likely that morphine synergizes with LPS to amplify its suppressive effect on host immunity, which was shown in a chronic endotoxemia model (Roy et al. 1999). Thus, the involvement of opioids (heroin, morphine) and/or LPS in the modulations of immune cell functions is likely to have in vivo relevance to the immunopathogenesis of HIV disease.

Opiates and HCV

HCV is five times as widespread as infection with HIV nationwide. It is estimated that 130–170 million persons are infected with HCV globally. Although generally asymptomatic, around 2.7 million people in the United States are chronically infected with HCV with persistent viremia (Scott et al. 2006). Heroin addicts are a high-risk group for HCV infection and development of chronic HCV disease (Backmund et al. 2003; Bassani et al. 2004; Day et al. 2003; Garten et al. 2004; Quaglio et al. 2003; Smyth et al. 2005). HCV infection is highly prevalent among IDUs and rapidly acquired after drug users first inject drugs (Garfein et al. 1998). Because of the HCV epidemic, interest in studying the impact of drug abuse on HCV infection has increased greatly. Although IDUs contribute significantly to viral transmission, it is difficult to determine whether the cause of the increased exposure to infectious agents is due to transmission through contaminated needles, or whether contact with the drugs themselves, through suppression of immune function in the host, results in greater susceptibility to viruses (McCarthy et al. 2001). Unlike the research on opioids and HIV, there has been little information about the relationship between opiate abuse and HCV disease progression, which is a major barrier to fundamental understanding of the immunopathogenesis of HCV disease. It remains to be determined whether opiate abuse promotes HCV disease progression in HCV-infected IDUs or enhances susceptibility to

HCV infection in HCV seronegative individuals exposed to opiates. Our in vitro study (Li et al. 2003b) demonstrated that morphine significantly increases HCV replicon expression in human hepatocytes, which could be abolished by the opioid receptor antagonists, naltrexone or β -funaltrexamine. In addition, we reported that in vitro morphine withdrawal, a crucial and recurrent event during the course of opioid abuse, facilitates HCV infection of hepatocytes (Wang et al. 2005a). These data suggest that continued, intermittent use of opiates with or without acute withdrawal leads to a greater risk of increased HCV replication. Although these observations raise concerns about the cofactor role of opioids in facilitating HCV disease, clinical studies are needed to confirm these in vitro findings.

The interaction between HCV and host immunity is an important determinant of outcome of HCV infection (Chisari 2005; Thimme et al. 2002). Therefore, the negative impact of opiates of abuse on host immunity should be considered as an important factor in increasing the likelihood of HCV infection and the development of chronic HCV disease. Peterson and colleagues (Peterson et al. 1987a, b) showed that morphine suppressed the production of IFN- γ in cultured PBMC, which could be blocked by naloxone. Our earlier work (Li et al. 2007; Wang et al. 2005a) showed that morphine has the ability to suppress endogenous IFN- α expression in human hepatocytes which was coupled with enhanced HCV replication (Li et al. 2007). These data suggest that elevated levels of HCV replication, caused by opiates and their withdrawal, may impair host responses to IFN- α treatment. This assumption was confirmed in our studies, showing that morphine compromises the in vitro anti-HCV effect of IFN- α (Li et al. 2007), the only antiviral cytokine approved for clinical treatment of chronic HCV infection. This in vitro finding is highly significant, as for a long time, IDUs were considered a contraindication for antiviral treatment of chronic HCV infection on the assumption of poor compliance, substantial treatment side-effects, high re-infection rates, and relevant co-morbidity (Aitken et al. 2008; Reimer et al. 2005). Taken together, these important in vitro findings, although need to be confirmed in vivo, support the notion that opioid abusers may be immunocompromized, which may contribute to the chronicity of HCV infection and HCV disease progression. This speculation is supported by our recent in vivo observation that although there was no significant difference in frequency of CD56⁺ T cells (a major T cell population in liver) among three study groups, CD56⁺ T cells from the heroin users had significantly lower levels of constitutive IFN- γ expression than those from the normal subjects (Ye et al. 2010). In addition, when stimulated by IL-12, CD56⁺ T cells from HCV-infected heroin users produced lower levels of IFN- γ than those from the normal subjects (Ye et al. 2010). This diminished ability to produce IFN- γ by CD56⁺ T cells was associated with increased plasma HCV viral loads in HCV-infected heroin users (Ye et al. 2010).

Methadone and HCV

Because methadone is widely used for the maintenance treatment of drug users with opiate dependence (Kreek 1992) and proven to be safe for long time use (Novick et al. 1993), it is essential to understand the impact of methadone treatment on HCV seroconversion, HCV treatment, and related disease progression. High HCV seroprevalence exists at methadone maintenance (MM) programs, ranging from 67% to 96% (Chamot et al. 1992; Chetwynd et al. 1995; Crofts et al. 1997; McCarthy and Flynn 2001; Novick et al. 1997; Piccolo et al. 2002; Selvey et al. 1997). Research confirms the feasibility, efficacy, safety and tolerability of HCV therapy for HCV-monoinfected MM patients (Bonkovsky et al. 2008; Litwin et al. 2009; Mauss et al. 2004; Sylvestre and Clements 2007; Zanini et al. 2010). Methadone treatment has been shown to reduce risk behavior that can spread HCV (Novick 2000). The factors contributing to HCV seroconversion during MM treatment include an inadequate methadone dose (Bell et al. 1995; Dole 1988; Strain et al. 1999). Many studies have shown that higher doses of methadone lead to less ongoing heroin use during treatment and to

greater treatment retention (Bell et al. 1995; Dole 1988; Strain et al. 1999). IDUs not infected with HCV, who enter a methadone program and do not use other drugs or alcohol, are very likely to remain HCV-negative. Thus, expansion of MM treatment would undoubtedly prevent some new cases of HCV infection.

While the beneficial impact of methadone therapy on HCV seroconversion has been demonstrated, there is no clinical evidence suggested that HCV treatment with IFN- α should be limited to IDUs or methadone substituted patients (Schaefer et al. 2004). In addition, there have been no studies investigating whether methadone treatment interferes with the anti-HCV ability of both exogenous and endogenous IFN- α . The effect of methadone on both local and systemic immune system is largely unknown, although methadone therapy is associated with normalization of cellular immunity, which had become abnormal during injection drug use (Novick et al. 1989). This information is particularly important for patients who are receiving daily methadone. As an opioid agonist, methadone may share the direct and indirect immunoregulatory effects of other opioids such as morphine. Therefore, both in vitro and clinical studies are essential to further illustrate the effect of methadone on the anti-HCV activity of IFN- α , as well as on full-cycle HCV replication in the target cells. Given the high prevalence of HCV infection among IDUs, it is important to evaluate the impact of antiviral therapy on the pharmacokinetics of methadone to ensure that the treatment of HCV infection could not alter risk-benefit profile in this population. It has been shown that peginterferon alfa-2b was well tolerated in patients with HCV infection undergoing MM therapy (Gupta et al. 2007). Other studies indicated that methadone did not influence the effect of IFN and ribavirin during the treatment of patients with chronic HCV infection (Schaefer and Mauss 2008; Verrando et al. 2005).

HIV and HCV interaction

Coinfection with HIV and HCV is a major global problem, leading to increased morbidity and mortality in developed countries. This is especially important in populations of IDUs, as they are at a significant high risk for acquiring both HIV and HCV. HCV coinfection is becoming more significant, as HIV-infected people are living longer with HAART. Coinfected subjects have higher morbidity and mortality of liver disease. It has been suggested that HIV and HCV modify one another's disease course, and cause immune dysfunctions, potentiating the viral replication of the both viruses. Since the liver is also an immune organ with the ability to generate anti-inflammatory proteins such as cytokines via the immune cells such as Kupffer cells, the liver provides a central regulatory role in inflammation. The liver harbors several types of immune cells including NK cells, NKT cells, and CD4⁺ T cells, the primary target for HIV. The most prominent immune cells in the liver are Kupffer cells, the unique resident macrophages of the liver. They represent the largest fixed population of macrophages in the body. Nearly 80% of all the macrophages in the body are Kupffer cells (Sheth and Bankey 2001). Kupffer cells represent an important arm of the innate immune response, and when activated, can produce IFNs and other inflammatory cytokines involved in immunomodulation (Sheth and Bankey 2001). Kupffer cells also are the targets for HIV infection (Hufert et al. 1993; Schmitt et al. 1990). It remains to be determined whether Kupffer cells are permissive for HCV, although a study showed that primary human Kupffer cells were not susceptible to HCV infection (Royer et al. 2003). Nevertheless, the liver is an organ where both HIV and HCV can find their host cells (Kupffer cells and hepatocytes, respectively) to infect.

HIV→HCV

HCV replication is enhanced by HIV infection, either by HIV-induced immunosuppression or by HIV-HCV interactions (Beld et al. 1998; Cribier et al. 1995; Thomas et al. 1996). HCV viral load is higher in the individuals who are co-infected with HIV than those without

HIV coinfection (Cribier et al. 1995; Matthews-Greer et al. 2001), both in plasma (Cribier et al. 1995; Sherman et al. 2002) and liver tissue (Bonacini et al. 1999). This relationship has been shown both in cross-sectional and longitudinal studies (Eyster et al. 1993; Ghany et al. 1996; Matthews-Greer et al. 2001; Thomas et al. 1994, 1996). Spontaneous clearance of HCV occurs in 20% of cases in HCV-monoinfected patients compared to 5 to 10% for HIV/HCV coinfecting subjects (Sulkowski and Thomas 2003).

HIV-coinfection was an independent risk factor for the development of cirrhosis in a study population of HCV-infected drug users (Pol et al. 1998). HIV and HCV coinfection leads to accelerated hepatic fibrosis progression. HIV/HCV-coinfecting individuals with ongoing HIV viremia have a faster rate of HCV-related liver fibrosis progression and a more rapid progression of liver failure or hepatocellular carcinoma than HCV-monoinfected persons (Benhamou et al. 1999; Martinez-Sierra et al. 2003; Mohsen et al. 2003; Poynard et al. 2003; Soto et al. 1997). However, the reasons for the accelerated chronic HCV disease in HCV/HIV coinfection are largely unknown. One possible explanation is enhanced hepatocyte apoptosis. Hepatocyte apoptosis was increased in the presence of HCV and HIV compared to HCV or HIV alone (Jang et al. 2010). It has been documented that Fas system-mediated apoptosis is involved in the pathogenesis of chronic HCV disease (Hayashi and Mita 1999; Yoon and Gores 2002). Apoptosis of primary hepatocytes and hepatoma (HepG2) cells was enhanced by exposure to surface proteins of both HIV and HCV (Munshi et al. 2003). This in vitro observation is supported by the in vivo report showing that HCV/HIV-coinfecting patients had higher percentage of hepatocytes expressing Fas and undergoing irreversible apoptosis than HCV-monoinfected patients (Macias et al. 2005). Hepatocyte apoptosis was associated with the presence of liver fibrosis in HCV/HIV-coinfecting patients (Macias et al. 2005). HIV and HCV coinfection induced expression of TGF- β 1, a central mediator of liver fibrogenesis, in the liver and serum of patient (Blackard et al. 2006; Bruno et al. 2010; Choi and Ou 2006; Choi and Hwang 2006; Lin et al. 2008; Rotman and Liang 2009). HCV infection could increase TGF- β 1 expression in HCV replicon cells (Schulze-Krebs et al. 2005) through the enhanced production of reactive oxygen species (ROS) in infected hepatocytes (Bruno et al. 2010; Lin et al. 2010). Furthermore, HIV or HCV independently regulates hepatic fibrosis progression through the generation of ROS in an NF- κ B-dependent fashion (Lin et al. 2011).

HCV→HIV

In contrast to the deleterious effect of HIV on HCV disease, the influence of HCV infection on HIV disease remains to be determined. Conflicting results have been reported about the effect of chronic HCV on progression of the natural history of HIV infection. In the Swiss Cohort, the presence of HCV was independently associated with an increased risk of progression to AIDS and death (Tenner-Racz et al. 1998). Similar findings were reported in an Italian study (De Luca et al. 2002). Clinical progression is more rapid in HIV/HCV co-infected patients than HIV-infected patients without HCV infection (Piroth et al. 1998). Although HCV serostatus did not affect the risk of HIV disease progression, the risk of liver disease-related death was markedly increased in HCV-seropositive patients (Rockstroh et al. 2005). Piroth et al. (Piroth et al. 1998) found a more rapid progression of HIV in 119 HCV-co-infected patients compared to control subjects who were infected only with HIV. They also showed more rapid CD4⁺ lymphocyte decline as well as clinical progression of HIV in HCV-coinfecting patients. In contrast, Sulkowski et al. (Sulkowski et al. 2002) reported that there was no evidence that HCV infection substantially alters the risk of dying, developing AIDS, or responding immunologically to HAART, especially after accounting for differences in its administration and effectiveness. Three more studies, in European and American also showed no difference in increased progression to an AIDS-defining illness or death between HCV positive or negative patients (Haydon et al. 1998; Llibre et al. 1993;

Staples et al. 1999). These discrepancies are difficult to determine, particularly as the cohorts and their respective controls varied in demographics and epidemiological background (Laskus et al. 2005). Thus, there is need for further in vitro and in vivo studies to understand the direct pathological relationships between HIV and HCV.

Conclusions

Taken together, although great progress has been made in studying the effects of opioids on immune function and HIV/HCV disease progression, often inconsistent information is produced and the real clinical relevance of opiate effects is unclear. This review has provided evidence that there is a strong association between opiate use, impaired immune functions and HIV or HCV infection/replication. Because opiates exert a profound and detrimental effects on host innate immunity that has a critical role in restricting HIV or HCV replication in target cells, it is likely that opiate abuse has the ability to alter the course of HIV and/or HCV disease progression. However, much remain to be learned about the mechanism(s) of opiate-mediated immunomodulation and immunocompromising effects as well as a demonstrated potential to facilitate HIV and/or HCV infection/replication in vitro. Given the current high incidence and prevalence, both opiate abuse and HIV/HCV infection are expected to remain a public health problem. Thus, more extensive research is needed to determine the specific impact of opiates on host immunity directly related to viral infections, particularly HIV and/or HCV. It is still worthy of future studies to determine whether opiates affect rates of development of HIV and/or HCV infection-related outcomes. In addition, it is interesting and necessary to determine the effects of opiates on efficacy of current HAART or IFN- α based therapy for HIV and/or HCV infection in opiate-abusing population.

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Table 1

Effects of opioids on HIV/SIV

	In vitro effect	Target cells	Host	References
Heroin	↑	Astrocyte	Human	(Reynolds et al. 2006)
	↑	MT-4T lymphoid cell	Human	(Selimova et al. 2002; Bobkov et al. 2005)
	↑	Macrophage	Human	(Guo et al. 2002; Ho et al. 2003; Li et al. 2003b)
	↑	Monocyte	Human	(Wang et al. 2011)
	↑	PBMC	Human	(Peterson et al. 1990; Li et al. 2003b)
	↑	PBMC	Monkey	(Suzuki et al. 2002a)
	↑	CEMX174 line	Human	(Chuang et al. 1993a)
Morphine	↑	CD3 ⁺ lymphoblast, CD14 ⁺ monocyte	Human	(Steele et al. 2003)
	↑	Promonocytic clone U1 cocultured with human fetal brain cells	Human	(Peterson et al. 1994)
	↑	CD4 ⁺ T cell and microglial	Human	(Peterson et al. 2004)
	↑	Kuffer cell	Human	(Schweitzer et al. 1991)
	↑	Microglial	Human	(Peterson et al. 1999)
	↑	Neuroblastoma cells	Human	(Squinto et al. 1990)
	↓	CD4 ⁺ T cell, PBMCs, macrophage	Human	(Szabo et al. 2003; Peterson et al. 2004)
	↑	PBMC	Human	(Li et al. 2002)
	↑	Microglia	Human	(Peterson et al. 1993; Li et al. 2002)
	↑	Macrophage	Human	(Li et al. 2002)
Methadone	↑	CD4 ⁺ T cell	Human	(Rodriguez et al. 2007)
	↑	CEMX174 cell	Human	(Suzuki et al. 2002c)
	In vivo Effect	Study Materials	Host	References
Morphine	↑	Peripheral mononuclear cell	Monkey	(Chuang et al. 1993b, 2005)
	↑	CD4 ⁺ T cell, plasma, CSF	Monkey	(Kumar et al. 2004)
	↑	Cerebral compartment	Monkey	(Kumar et al. 2006)
	↓	CD4 ⁺ T cell, plasma	Monkey	(Donahoe et al. 1993; Donahoe and Vlahov 1998; Donahoe et al. 2009)