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Drugs of abuse and HIV infection/replication: implications for mother-fetus transmission

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Abstract

Human immunodeficiency virus (HIV) infection and progression of acquired immunodeficiency syndrome (AIDS) can be modulated by a number of cofactors, including drugs of abuse. Opioids, cocaine, cannabinoids, methamphetamine (METH), alcohol, and other substances of abuse have been implicated as risk factors for HIV infection, as they all have the potential to compromise host immunity and facilitate viral replication. Although epidemiologic evidence regarding the impact of drugs of abuse on HIV disease progression is mixed, in vitro studies as well as studies using in vivo animal models have indicated that drugs of abuse have the ability to enhance HIV infection/replication. Drugs of abuse may also be a risk factor for perinatal transmission of HIV. Because high levels of viral load in maternal blood are associated with increased risk of HIV vertical transmission, it is likely that drugs of abuse play an important role in promoting mother-fetus transmission. Furthermore, because the neonatal immune system differs qualitatively from the adult system, it is possible that maternal exposure to drugs of abuse would exacerbate neonatal immunity defects, facilitating HIV infection of neonate immune cells and promoting HIV vertical transmission. The availability and use of antiretroviral therapy for women infected with HIV increase, there is an increasing interest in determining the impact of drug abuse on efficacy of AIDS Clinical Trials Group (ACTG) -standardized treatment regimens for woman infected with HIV in the context of HIV vertical transmission.

Keywords

Opioids; Methamphetamine; Cocaine; Marjuana/Cannabinoid; Alcohol; HIV

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CONFLICT Of INTEREST STATEMENT

The authors declare that there are no conflicts of interest.

INTRODUCTION

Since the beginning of the global acquired immunodeficiency syndrome (AIDS) epidemic, almost 60 million people have been infected with human immunodeficiency virus (HIV) and 25 million people have died of HIV-related causes. As of 2008, the approximate number of people living with HIV or AIDS was 33.4 million, among them 50% women and 2.1 million children under 15 years of age. In year of 2009, around 2.7 million new HIV infections, including 430,000 newborn children was reported (UNAIDS 2008, 2009). HIV/AIDS is now the third leading cause of death among women aged 25 to 44 years and the leading cause of death among African women in this age group. HIV infection and progression of AIDS are affected by a number of cofactors, including drugs of abuse. HIV epidemic has been driven by drug abusers in the United States and other regions in the world. Injection drug users (IDUs) are at a significant risk for acquiring HIV infection, representing one of the largest reservoirs of HIV infection in the United States and contributes to the fastest spread of the virus (Alcabes and Friedland 1995; Risdahl et al. 1998). One third of HIV-infected individuals in the United States are intravenous drug abusers. In addition to collective use of injecting equipment and drug solution, the negative impact of drug abuse on host immune system is another factor for promoting HIV infection. Thus, drugs of abuse have been suggested to have a cofactor role in the immunopathogenesis of HIV disease. In the following sections, we discuss the effects of some of popularly used drugs including alcohol on HIV infection/replication and their implication in HIV progression and vertical transmission.

OPIOIDS AND HIV

Opioids are agents that bind opioid receptors principally found in the central nervous system (CNS) and gastrointestinal tract, but they 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 (Cabral 2006). Because many of opiate abusers (> 90%) use injection as the primary route of administration, opiate abuse contributes significantly to HIV transmission among drug users (Martin et al. 2010). In addition, clinical and epidemiological evidence from early, pre-AIDS studies indicates that opiates have a cofactor role in the pathogenesis of AIDS (Alcabes and Friedland 1995; Donahoe et al. 1993; Ronald et al. 1994; Specter 1994). Furthermore, laboratory studies have demonstrated that morphine enhances susceptibility of the immune cells to HIV infection (Guo et al. 2002; Ho et al. 2003; Li et al. 2003; Nair et al. 1997a; Wang et al. 2005) and increase viral titers in the brain (Stefano et al. 1996). The expression of HIV in co-cultures of chronically infected promonocytes and human brain cells was increased following exposure to morphine (Peterson et al. 1994). Morphine enhances HIV replication in human PBMC co-culture assay (Peterson et al. 1990) and Simian immunodeficiency viruses (SIV) replication in monkey peripheral blood mononuclear cell (PBMC) (Suzuki et al. 2002). Morphine enhances HIV replication in human macrophages (Guo et al. 2002; Ho et al. 2003; Li et al. 2003; Li et al. 2002), T lymphocytes (Chuang et al. 1993; Peterson et al. 2004; Steele et al. 2003), kuffer cells (Schweitzer et al. 1991), human neuroblastoma cells (Squinto et al. 1990) and human brain cells (Chao et al. 1995; Peterson et al. 1999). A study by Nair's group (Reynolds et al. 2006) found that heroin potentiates HIV replication in normal human astrocytes. With 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). Although these in vitro data clearly demonstrate that opioids such as morphine or heroin enhance HIV infection/replication (Table 1), the animal and clinical studies have yielded contradictory data with regard to the role of opioid use in the progression of SIV or HIV disease (Donahoe

and Falek 1988; Rothenberg et al. 1987) (Table 2). The studies conducted by Donahoe et al. (Donahoe et al. 1993; Donahoe et al. 2009) showed that long -term opiate dependency seemed to retard the rate of progression to AIDS in the SIVsmm9 monkey model, but Chuang et al. (Chuang et al. 1995) and Kumar et al. (Kumar et al. 2004) observed greater SIV disease progression after opiate injection (Table 2).

Although the role of opioid use in promoting the progress of HIV disease is still debatable, it is well known that opioids exert a profound influence on immunomodulatory activity. Opioid abusers have higher incidence of infectious disease, which may be directly related to impaired immune functions (McCarthy et al. 2001; Nair et al. 1997b; Novick et al. 1989; Ochshorn et al. 1990; Peterson et al. 1993; Risdahl et al. 1998). 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 polymorphonuclear leukocytes (Bayer et al. 1990). Opioids also inhibits antibody (Lockwood et al. 1994) and cytokine release by the immune cells (Hung et al. 1973; Wang et al. 2003). Morphine suppressed the production of interferon–alpha (IFN-α (Peterson et al. 1989; Wang et al. 2002a), a cytokine that modulates all phases of immune processes and has a central role in host innate immunity against viral infections. We recently showed that morphine, through the suppression of interferon-gamma (IFN-γ), compromised $CD8^+$ T cell-mediated anti-HIV activity in both acute and latently infected cells (Wang et al. 2005). Opioids modulates immune functions via pharmacological activation of endogenous opioid receptors in the immune cells (Bayer et al. 1990; Fecho et al. 1996; Hernandez et al. 1993).

In summary, although the biological impact of opioid use on the progression of HIV disease remains to be determined, opioid use has profound effects on host immune systems, which may form not only HIV transmission, but also viral replication. Certainly, more studies with well-characterized opioid-using population will be needed to definitely establish the role of opioid use in HIV disease progression.

COCAINE AND HIV

Crack cocaine has been identified as an independent risk factor for HIV infection and AIDS epidemic. As a non-injection drug use, cocaine contributes to the spread of HIV through risky sexual behaviors including multiple sex partners, inconsistent condom use, and exchanging sex for drugs or money (Booth et al. 1993; Pechansky et al. 2006). In the earlier cohort studies (Caiaffa et al. 1994; Chaisson et al. 1989; Chiasson et al. 1991; Nelson et al. 2002) different groups found that both intravenous cocaine use and smoking illicit drugs (marijuana, cocaine, crack) were associated with HIV and bacteria infection. Studies that distinguished among the types of drugs used by people positive for HIV found that cocaine, and particularly crack-cocaine, increased the risk of progression to AIDS (Cook et al. 2008; Duncan et al. 2007; Webber et al. 1999). In a more recently cohort study, Baum et al. reported that crack–cocaine use facilitates HIV disease progression by reducing adherence in those on highly active antiretroviral therapy (HAART) and by accelerating disease progression independently of HAART (Baum et al. 2009).

The role of cocaine in promoting HIV disease is also supported by the laboratory investigations (Table 1). In vitro studies indicate that cocaine increases replication of HIV in both stimulated (Bagasra and Pomerantz 1993) and unstimulated human peripheral blood cells (Peterson et al. 1991;Peterson et al. 1992). Cocaine alters both cytokine production and HIV expression in mononuclear phagocytes, including microglia cells (Gekker et al. 2006;Gekker et al. 2004). Cocaine markedly enhanced virus production in simian human immunodeficiency virus (SHIV)-infected macrophages and in a chronically infected promonocytic cell line (Dhillon et al. 2007). Nair et al reported that cocaine exacerbates HIV infection by up-regulating Dendritic Cell-Specific Intercellular adhesion molecule-3-

grabbing non-integrin (DC-SIGN) on dendritic cells and these effects are mediated via dysregulation of mitogen-activated protein kinases (MAPKs) (Nair et al. 2005). In addition to the in vitro findings described above, in vivo animal studies also support the role of cocaine in promoting HIV replication. Using the human peripheral blood mononuclear leukocyte (huPBL) severe combined immunodeficiency (SCID) mouse model, Roth et al demonstrated that systemic exposure to cocaine leads to increase in HIV replication and spread in vivo (Roth et al. 2002;Roth et al. 2005b).

Taken together, findings from laboratory and epidemiological studies indicate that cocaine use has a significant impact on the pathogenesis/progression of HIV disease. This impact maybe mediated by immunological and viralogical factors that influence host susceptibility, use of antiretroviral therapies and underlying corruptibility. This information should be used to guide future research on the mechanism (s) involved in the cocaine action on HIV infection.

METHAMPHETAMINE (METH) AND HIV

Because of the alarming prevalence of HIV infection among METH users (Boddiger 2005), it is becoming increasingly important to investigate the association between psychotropic drug use and HIV infection. METH use is associated with risky sexual behavior, increasing the potential of users to become infected with HIV and hepatitis B virus and hepatitis C virus (Letendre et al. 2005). METH-type substances can be used percutaneously and a high correlation has been reported for injection frequency and HIV transmission (Bruneau et al. 2001). A strong connection between METH dependence and HIV infection has been observed for METH-dependent men who have sex with men (Morin et al. 2005; Peck et al. 2005; Plankey et al. 2007; Shoptaw and Reback 2006, 2007), men who have sex with women (Wohl et al. 2002) and female sex workers (Patterson et al. 2008). More importantly, METH use has been correlated with more rapid progression to AIDS in HIV-infected people (Moore et al. 2004). METH exposure increases virus load in the CNS of HIV-infected patients (Maragos et al. 2002; Marcondes et al. 2010). Active METH users displayed higher levels of HIV loads than non-users (Ellis et al. 2003), which may be attributable to increased viral replication. The effect of METH on HIV may be at the viral entry or integration into host genome levels, but not at the translation level (Gavrilin et al. 2002). We and other have shown METH has the ability to enhance HIV replication in macrophages (Liang et al. 2008) and dendritic cells (Nair et al. 2009).

Similar to other drugs of abuse, METH abuse has immunosuppressive effects and consequently has the potential to increase susceptibility of host immune cells to HIV infection. METH has been shown to exert immunomodulatory effects (Yu et al. 2003). There is the immunosuppressive effect of METH on the T cell-mediated immune response (House et al. 1994; Iwasa et al. 1996). In vivo studies have shown that METH significantly suppressed interlukin-2 (IL-2) and IFN-γ expression (Gavrilin et al. 2002). METH stimulates secretion of Tumor Necrosis Factor-alpha (TNF-α) in splenocytes from retrovirus-infected mice (Yu et al. 2002). METH exposure inhibited macrophage-mediated antiviral and cytotoxic activities and reduced their ability to produce nitric oxide (NO)/TNF-α (In et al. 2004). METH treatment induced an increase in the percentage of $CD4^+$ cells with simultaneous decrease in the percentages of $CD8^+$ and double-positive $CD4^+$ $CD8^+$ in thymus (In et al. 2005). Microarray analysis of human brain tissue from HIV-infected METH users showed significant up-regulation of genes associated with inflammation (Everall et al. 2005), which contributes to enhancement of HIV expression in vivo (Ellis et al. 2003). Taken together, investigations from in vivo and in vitro studies provide evidence to support the possibility that METH may have a cofactor in the immunopathogenesis of HIV infection and progression to AIDS.

MARIJUANA, CANABINOID AND HIV

There have been a limited number of studies that have addressed the impact of marijuana or cannabinoids on HIV infection and AIDS. It remains to be determined whether the use of marijuana or administration of cannabinoids in a therapeutic mode has potential risks and/or hazards associated with HIV infection. Earlier epidemiologic studies suggested marijuana as a potential cofactor in the development and progression of HIV infection. Using univariant and multivariant analyses, Tindall et al reported there was an association between marijuana use and progression of HIV seropositivity to development of symptomatic AIDS (Tindall et al. 1988). In contrast, a number of studies have documented that marijuana or cannabinoid pro ducts have little impact on the immune system or on HIV infection (Bredt et al. 2002; Coates et al. 1990; Di Franco et al. 1996; Kaslow et al. 1989; Miller and Goodridge 2000; Persaud et al. 1999; Struwe et al. 1993; Wallace et al. 1998). Marijuana use was found to have little effect on non-AIDS mortality in men and on total mortality in women (Cabral 2006). It was reported that antenatal marijuana use was unrelated to sexually transmitted infections during pregnancy (Miller and Goodridge 2000). Smoked and oral cannabinoids did not appear to be a risk in individuals with HIV infection with respect to HIV RNA levels, $CD4^+$and $CD8^+$cell counts, or protease inhibitor levels (Abrams et al. 2003). In vitro studies also showed contradictory effect of cannabinoid receptor agonist on HIV infection. Klein's team found that cannabimimetic drugs may enhance HIV infection of human T cell line (Noe et al. 1998). However, Peterson's group showed that the synthetic cannabinoid WIN 55,212-2 was found to potently inhibit HIV expression in a concentration-and time-dependent manner in $CD4^+$lymphocyte and microglial cell cultures (Peterson et al. 2004; Rock et al. 2007). Using the huPBL SCID mouse model, Roth et al demonstrated that exposure to Tetrahydrocannabinol (THC) in vivo could suppress immune function, increase HIV coreceptor expression, and act as a cofactor to significantly enhance HIV replication (Roth et al. 2005a). Clearly, more in vitro and in vivo studies are needed in order to establish the association between marijuana or cannabinoids and HIV infection/replication. Particularly, it is necessary to develop in vitro model and systems that resemble to human and real-world HIV infection. At the same time, there is a need for longitudinal epidemiological studies on human populations.

ALCOHOL AND HIV

Alcohol is the most commonly used and abused drug in the United States. Approximately 14 million American meet criteria for alcohol abuse or dependence (Bryant 2001). The adverse effects of alcohol abuse are directly associated with induction of immune deficiencies and with increased incidence and prevalence of infectious diseases, including HIV. Since alcohol abuse is widespread and often heavy among HIV-infected individuals and among the most sexually-active age groups at risk of HIV infection, it has been a great interest to investigate the role of alcohol abuse in promoting HIV transmission and infection. It was suggested that alcohol use, both acute and chronic, may increase host susceptibility to HIV infection (Szabo 1997, 1999). Alcohol consumption, especially heavy consumption and abuse, was strongly related to incidence of HIV infection (O'Leary and Hatzenbuehler 2009). Alcohol consumption and alcohol abuse have been identified as potential behavioral risk factors for the transmission of HIV/AIDS, in the form of drinking before risky sexual events or frequent binge drinking as associated with HIV incidence (Erbelding et al. 2004; Fisher et al. 2007; Kalichman et al. 2007). Alcohol consumption, particularly high consumption, has been shown to have a direct influence on adherence to medication in general (Weiss 2004) and specifically to HIV medication (Cook et al. 2001; Hendershot et al. 2009; Meyerhoff 2001; Petry 1999). Chander et al found that hazardous levels of alcohol use were associated with decreased antiretroviral utilization, adherence, and viral suppression independent of active drug use. Combined alcohol and drug use was associated with lower odds of adherence and viral suppression than either drugs or alcohol alone (Chander et al. 2006).

Several lines of evidence has demonstrated there is a strong associations between alcohol consumption and worsening HIV disease. In a cross-sectional study of HIV disease in intravenous drug users, the relative risk of AIDS was 3.8 times higher in heavier drinkers than moderate drinkers (Lake-Bakaar and Grimson 1996). Pol *et al*. showed that HIV-infected alcohol abusers had a 41% increase in the number of $CD4^+$ T cells after cessation of alcohol use, whereas only a 15% increase was seen in uninfected control subjects who stopped drinking (Pol et al. 1998). Among patients who have a history of alcohol problems and are receiving antiretroviral treatment, alcohol consumption was associated with higher HIV RNA levels and lower $CD4^+$T cell counts (Samet et al. 2003). In a prospective study of HIV-infected drug abusers, alcohol abuse did not correlate with changes in the percentage of $CD4^+$ T cells, however, the percentage of $CD8^+$T cells significantly increased among the heaviest drinkers (Crum et al. 1996).

The findings from the epidemiological studies are supported by several in vitro studies indicating that alcohol augmented HIV replication in PBMC (Table 1) (Bagasra et al. 1996;Bagasra et al. 1989;Bagasra et al. 1993;Saravolatz et al. 1990). Our group demonstrated that alcohol potentiates HIV infection of human blood mononuclear phagocytes (Wang et al. 2002b), T lymphocytes (Wang et al. 2006). Liu et al. showed that alcohol enhanced the entry of CXCR4-tropic HIV into peripheral blood lymphocytes (PBLs) ten-fold compared to untreated cells (Liu et al. 2003). Alcohol enhances HIV infection of normal human oral keratinocytes by up-regulating CXCR4 expression (Chen et al. 2004). These *in vitro* findings are validated in the animal studies. Bagby et al. found that alcohol could promote SIV infection and replication in both PBMC and alveolar macrophages from rhesus monkeys (Bagby et al. 1998). Several recent reports also showed that under physiologic conditions, chronic alcohol consumption accelerates progression of SIV disease (Bagby et al. 2003;Marcondes et al. 2008;Molina et al. 2008;Poonia et al. 2006).

It is apparent that alcohol consumption has an association with HIV infection/replication. This impact of alcohol on HIV may be a consequence of immunesuppression on immune cells such as T cells and macrophages, the tragets for HIV. However, the mechanism(s) by which alcohol increases suscesitibility of the immune cells to HIV infection are not been fully deliberated. It is difficult to extrapolate results from in vitro and in vivo animal studies to the human conditions. Nevertheless, the studies that have been reviewed suggest that alcohol act, at least as a cofactor that can increase the severity of HIV infection.

IMPACT OF DRUG ABUSE ON MOTHER-TO-FETUS TRANSMISSION OF HIV

Although rates of vertical transmission of HIV in the U.S. and other resource rich areas of the world have declined dramatically since the introduction of antiretroviral therapy, vertical transmission remains a very serious problem in resource poor nations and among poor populations in resource rich countries. Perinatal HIV transmission rates range from 5 ~ 8% to as high as 25 ~ 40%, particularly in settings where little to no prenatal care is available, and in resource-poor countries where there is no access to or no resources for ACTG-standardized treatment regimens (Abrams et al. 1995; Fowler et al. 2000). In order to develop effective strategies to prevent mother to infant transmission of HIV and to prevent disease progression in HIV-infected children, it is essential to understand the host and environment factors that influence perinatal transmission. Although drugs of abuse have been identified as a risk factor for HIV transmission, we know little about the role of drug abuse in vertical transmission of HIV.

Earlier studies demonstrated that HIV-infected women who used illicit drugs during pregnancy had a higher risk of transmitting HIV to their infants than did HIV-infected pregnant women who did not use drugs (Keegan et al. 2010; Shankaran et al. 2007). There is a strong association between the abuse of alcohol, other substances and acquisition,

progression of HIV/AIDS among women. Increased levels of alcohol consumption are associated with diminished immune function, as evidenced by reduced levels of $CD4^+$and $CD8^+$ T cell activity. In addition to the pathological relationship between alcohol use and increased susceptibility to HIV infection, the effects of alcohol on accelerated progression to AIDS among infected women are unknown. Although the mechanisms for the role of substance abuse in perinatal transmission of HIV are yet to be determined, it has been demonstrated that such drugs of abuse as opioid, cocaine, and METH have the ability to enhance HIV replication in the target cells (Table 1). In addition, systemic exposure of several drugs of abuse (morphine, cocaine, METH, and alcohol) enhances HIV replication and spread in vivo (Table 2).

The enhancing effect of these abused substances on HIV infectivity/replication could diminish the effectiveness of the anti-HIV drugs (Arnsten et al. 2002; Chander et al. 2006; Golin et al. 2002; Kapadia et al. 2005; Lucas et al. 2002; Lucas et al. 2006). As the availability and use of antiretroviral therapy increase, it is becoming extremely important to determine the impact of drug abuse on efficacy of ACTG-standardized treatment regimens used for treating HIV-infected pregnant women. It is known that high levels of viral load in maternal blood are associated with increased risk of HIV vertical transmission. Increased risk of perinatal HIV transmission may also result from neonatal factors. The neonatal immune system differs qualitatively from the adult system (Merkerova et al. 2009; Millet et al. 1999). It is highly possible that exposure to drugs of abuse would exacerbate neonatal immunity defects, facilitating HIV infection of neonate immune cells and promoting HIV vertical transmission. We and others have shown that neonatal macrophages are more susceptible to HIV infection than paired maternal macrophages (Ho et al. 1992; Reinhardt et al. 1995; Sundaravaradan et al. 2006; Wellensiek et al. 2009). Morphine treatment of placental cord blood monocyte-derived macrophages enhanced HIV infection (Li et al, 2003). In animal models, alcohol administration to a mother during pregnancy affects the fetal immune system (Jacobson et al. 1993; Seelig et al. 1996). It was demonstrated that alcohol also modulates cytokine secretion and synthesis in the human fetus (Ahluwalia et al. 2000).

The mechanism(s) of HIV transmission in utero is poorly understood. In addition to the fact that the placental transmission of HIV is influenced by maternal viral load and maternal/ neonatal immunity, placenta itself also has a fundamental role in the vertical HIV transmission from the mothers to the fetus. It is likely that environment factors such as drugs of abuse affect HIV transmission through their detrimental effects on placenta. Abused drugs taken by a pregnant woman reach the fetus primarily by crossing the placenta, the same route taken by oxygen and nutrients, which are needed for fetus's growth and development. It is known that alcohol exposure is associated with placental dysfunction, decreased placental size, impaired blood flow and nutrient transport, endocrine changes, increased rates of stillbirth and abruption, umbilical cord vasoconstriction, and low birth weight (Burd et al. 2007). There is strong supporting evidence to indicate that the placental transport systems are either direct or indirect targets for the drugs of abuse, including cocaine, amphetamines, nicotine, and cannabinoids (Ganapathy et al. 1999; Malek et al. 2009; Paakki et al. 2000). A recent study using placenta perfusion system demonstrated that maternal use of cocaine and heroin increased the permeability of the placenta (Malek et al. 2009). In spite of advance of our knowledge about the interaction of drugs of abuse with placenta, there are still many unaddressed questions about the impact of drug abuse on placenta structure and function changes. Particularly, we need to know whether drugs of abuse impair innate immunity of placenta such as function of macrophages (Hofbauer cells) and T cells in the placenta. Placental cells produce large quantities of cytokines and chemokines that participate in the anti-HIV activity. Therefore, it is of importance to

determine whether drugs of abuse modulate the expression of these cytokines and chemokines.

CONCLUSIONS

Overall, this review has provided evidence that there is a strong association between drugs of abuse and HIV infection/replication. Although the role of drugs of abuse in promoting HIV disease progression is still debatable, it is known that many of abused drugs exert a profound and detrimental effort on host immunity that has a critical role in restricting HIV replication. It is likely that exposure to drugs of abuse directly or indirectly impairs maternal/neonatal/placental immunity, that facilitating perinatal HIV transmission (Figure 1). However, much remains to be learned about the role of drugs of abuse in vertical HIV transmission. Apparently, more extensive studies are needed in order to determine the specific impact of drugs of abuse on maternal/neonatal/placental immunity and on HIV infection of neonatal/placental immune cells. In addition, it is necessary to determine the effects of drugs of abuse on efficacy of HAART in the context of perinatal transmission.

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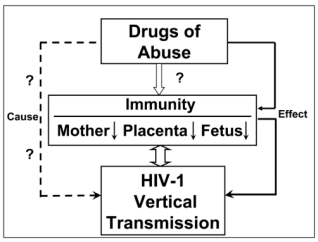

Figure 1.
The impact of drug abuse on maternal/neonatal/placental immunity and HIV vertical transmission.

Table 1

In vitro Studies on Impact of Drug Abuse on HIV

Substance	Effect	Target Cells	Type of Study	Refecrences
Heroin	↑	Human Astrocytes	*in vitro*	Reynolds et al. (2006)
	↑	Human MT-4 T cell line	*in vitro*	Selimova et al. (2002)
Morphine	↑	Human Macrophages	*in vitro*	Guo et al. (2002), Ho et al. (2003)
				Li et al. (2003)
	↑	Human PBMC	*in vitro*	Peterson et al. (1990), Li et al. (2003)
	↑	Monkey PBMC	*in vitro*	Suzuki et al. (2002)a
	↑	Human CEMX174 cell line	*in vitro*	Chuang et al. (1993)
	↑	Human lymphocytes	*in vitro*	Steele et al. (2003)
	↑	Human promonocyes and human brain cells	*in vitro*	Peterson et al. (1994)
	↑	Human CD4+ T lymphocytes and microglial cells	*in vitro*	Peterson et al. (2004)
	↑	Human Kuffer cells	*in vitro*	Schweitzer et al. (1991)
	↑	Human Brain cells	*in vitro*	Peterson et al. (1999)
	↓	Human macrophages and T lymphocytes	*in vitro*	Szabo et al. (2003), Peterson et al. (2004)
Cocaine	↑	Human PBMC	*in vitro*	Peterson et al. (1991), (1992),
	↑	Human microglia cells	*in vitro*	Gekker et al. (2004), (2006)
	↑	Human macrophages	*in vitro*	Dhillon et al. (2007)
	↑	Human dendritic cells	*in vitro*	Nair et al (2005)
METH	↑	Human macrophages	*in vitro*	Liang et al. (2008)
	↑	Human dendritic cells	*in vitro*	Nair et al. (2009)
Marijuana or Cannabinoid	↑	Human MT-2 T cell line	*in vitro*	Noe et al. (1998)
	↓	Human CD4+ T cells and microglia cells	*in vitro*	Peterson et al. (2004), Rock et al. (2007)
Alcohol	↑	Human macrophgaes	*in vitro*	Wang et al. (2002)
	↑	Human PBMCs	*in vitro*	Saravolatz et al. (1990), Bagasra et al. (1993)
	No effect	Human Lymphocytes	*ex vivo*	Cook et al. (1997)
	↑	Human T Lymphocytes	*in vitro*	Liu et al. (2003), Wang et al. (2006)
	↑	Human Oral Keratinocytes	*in vitro*	Chen et al. (2004)
	↑	Monkey PBMC and alveolar macrophages	*in vitro*	Bagby et al. (1998)

Table 2

In vivo Studies on Impact of Drug Abuse on HIV

	Effect	Type of Study	Refecrences
Heroin	↑	Human	Martin et al (2010)
	↓	Human	Margolick et al. (1992)
Morphine	↑	Monkey	Chuang et al. (1997)
	↑	Monkey	Kumar et al. (2004)
	↓	Monkey	Donahoe et al (1993)
Cocaine	↑	Human	Chaisson et at (1989), Nelson et al (2002)
			Baum et al. (2009)
	↑	Mouse	Roth et al (2002), (2005)
METH	↑	Monkey	Burdo et al. (2006), Marcondes et al (2010)
	↑	Human	Kall and Olin (1990), Maragos et al. (2002)
			Ellis et al. (2003), Morin et al. (2005),
			Peck et al. (2005), Martin et al (2010)
Marijuana or Cannabinoid	↑	Mouse	Roth et al (2005)
	↑	Human	Tindall et al (1988), Kaslow et al. (1989)
	No effect	Human	Abrams et al. (2003), Simbayi et at (2005)
Alcohol	↑	Monkey	Bagby et al. (2003), Poonia et al. (2006)
			Marcondes et al. (2008), Molina et al. (2008)
	↑	Human	Szabo et al. (1999), Fisher et al. (2007),
			Kalichman et al. (2008), Baliunas et al. (2009)