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Substance abuse, HIV-1 and hepatitis

Nirzari Parikh[1,2], **Michael R. Nonnemacher**[1,2], **Vanessa Pirrone**[1,2], **Timothy Block**[1,3,4], **Anand Mehta**[1,3,4], and **Brian Wigdahl**[1,2,*]

[1]Department of Microbiology and Immunology Drexel University College of Medicine Philadelphia, Pennsylvania 19102, USA

[2]Center for Molecular Virology and Translational Neuroscience, Institute for Molecular Medicine and Infectious Disease, Drexel University College of Medicine Philadelphia, Pennsylvania 19102, USA

[3]Drexel Institute for Biotechnology and Virology 3805 Old Easton Avenue, Doylestown, Pennsylvania 18901, USA

[4]Institute for Hepatitis and Virus Research 3805 Old Easton Avenue, Doylestown, Pennsylvania 18901, USA

Abstract

During the course of human immunodeficiency virus type 1 (HIV-1) disease, the virus has been shown to effectively escape the immune response with the subsequent establishment of latent viral reservoirs in specific cell populations within the peripheral blood (PB) and associated lymphoid tissues, bone marrow (BM), brain, and potentially other end organs. HIV-1, along with hepatitis B and C viruses (HBV and HCV), are known to share similar routes of transmission, including intravenous drug use, blood transfusions, sexual intercourse, and perinatal exposure. Substance abuse, including the use of opioids and cocaine, is a significant risk factor for exposure to HIV-1 and the development of acquired immune deficiency syndrome, as well as HBV and HCV exposure, infection, and disease. Thus, coinfection with HIV-1 and HBV or HCV is common and may be impacted by chronic substance abuse during the course of disease. HIV-1 impacts the natural course of HBV and HCV infection by accelerating the progression of HBV/HCV-associated liver disease toward end-stage cirrhosis and quantitative depletion of the $CD4^+$ T-cell compartment. HBV or HCV coinfection with HIV-1 is also associated with increased mortality when compared to either infection alone. This review focuses on the impact of substance abuse and coinfection with HBV and HCV in the PB, BM, and brain on the HIV-1 pathogenic process as it relates to viral pathogenesis, disease progression, and the associated immune response during the course of this complex interplay. The impact of HIV-1 and substance abuse on hepatitis virus-induced disease is also a focal point.

Keywords

bone marrow; brain; cocaine; HBV; HCV; HIV-1; opioids

*Corresponding author Mailing address: Department of Microbiology and Immunology Drexel University College of Medicine 245 North 15th Street, MS # 1013A Philadelphia, PA 19102 Telephone: (215) 762-7598 Fax: (215) 762-1955 bwigdahl@drexelmed.edu.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest to report.

INTRODUCTION

HIV Disease and Its Relationship with Coinfection and Substance Abuse

According to the 2010 UNAIDS report, approximately 1.5 million people in the United States are infected with the human immunodeficiency virus type 1 (HIV-1), whereas globally, an estimated 33.3 million people are living with HIV infection or the acquired immune deficiency syndrome (AIDS) [1]. During initial acute infection with HIV-1, the resultant innate immune response and the eventual adaptive immune response ultimately curb the primary infection, leading to the establishment of a basal viral load or "viral set point." After acute infection, the patient undergoes a period of clinical latency that involves intermittent bursts of viral replication in the regional lymph nodes with small amounts of virus periodically being shed into the peripheral blood (PB) compartment and elsewhere [2]. During the acute phase of HIV-1 infection, the virus is likely seeded into a number of tissues and associated cellular reservoirs that may include the brain [3], lung, gastrointestinal tract [4], kidney [5], genital tract [6], bone marrow (BM) [7], and other tissues, with at least one of the cellular reservoirs including cells of the monocyte-macrophage lineage [8] or resting memory $CD4^+$ T cells [9] present within the PB compartment and regional lymph nodes [10]. Although a number of therapeutic strategies have resulted in some success regarding the long-term control of HIV-1 infection and disease progression, eradicating latent virus from these cellular reservoirs has proven to be a major obstacle not yet overcome by antiretroviral therapy strategies used to date. Nevertheless, these reservoirs can be considered reasonable and important targets for therapeutic intervention [11, 12]. In addition to the cells of the monocyte-macrophage lineage, progenitor cell populations within the BM (Fig. 1A) have also been shown to harbor HIV-1 proviral DNA (Fig. 1B). This infected cellular reservoir may be a critical factor in the etiology of disease within the central nervous system (CNS) and perhaps other end organs [13-15]. The BM consists of many different cell types, one of them being $CD34^+$ hematopoietic progenitor cells (HPCs) (Fig. 1A). Certain subpopulations of HPCs express CD4, CCR5, and/or CXCR4, the HIV-1 receptor and coreceptors, respectively [13, 16]. An in vivo study has shown that $CD34^+$ HPCs were infected with HIV-1 in a subset of seropositive individuals [17]. Because the progenitor cell population has a substantial proliferative capacity, these cells could generate infected cell lineages that can disseminate the infection to the brain and other end organs [13, 15]. The BM is also the site of hematopoiesis, and HIV-1-infected patients are often diagnosed with a wide variety of hematologic abnormalities [13]. Thus, the BM likely plays a pivotal role in HIV-1 pathogenesis and disease.

Hepatitis B virus (HBV), hepatitis C virus (HCV), and HIV-1 are known to share similar routes of transmission and can be transmitted via parenteral intravenous drug use (IVDU) and blood transfusions and sexual and perinatal exposure. Thus, coinfection with HIV-1 and HBV and/or HCV is commonly encountered [18, 19]. In fact, about 2 billion people worldwide have been infected with HBV, a DNA virus; of that number, 350 million remain chronically infected, which is the cause of approximately 30% of all cases of liver cirrhosis and 53% of the cases of hepatocellular carcinoma (HCC) [20]. Meanwhile, HCV, an RNA virus, has a slightly lower global prevalence, with more than 170 million people with chronic infections [21]. HCV has been shown to be responsible for 27% of the cases of liver cirrhosis and 25% of the HCC cases [20]. The burden of HIV/HCV coinfection has been estimated at 4 to 5 million people worldwide, whereas the prevalence of HIV/HBV coinfection is estimated to be 5% to 7% among HIV-infected individuals (approximately 2 million) [22]. These rates are lower than the rates of 10% to 20% found in highly endemic areas [23-25].

Substance abuse is a significant risk factor for exposure to HIV-1 due to increased high-risk sexual behavior and direct inoculation of the virus into the bloodstream through the sharing

of virus-contaminated needles [26]. In addition to enhancing susceptibility to HIV-1 through biological and behavioral means, IVDU that continues once a person is infected has been responsible for more than 36% of AIDS cases; of the 34,233 new AIDS cases in 2009, 6,522 were associated with IVDU [27]. One of the consequences of chronic substance abuse, important in the context of this review, is coinfection with hepatitis. Although opiates are known to modulate the immune system and may augment susceptibility to HIV-1 infection by increasing the number of chemokine receptors present on the cell surface [28] or by increasing viral replication [29], cocaine can facilitate HIV-1 disease progression by impairing macrophage and $CD4^+$ T-cell function and activating HIV-1 gene expression in these cell types as previously reviewed [30], modulating the levels of cytokines and increasing the level of viral replication.

This review examines the effects exerted on the BM by HIV-1 infection and relates these events to the pathogenesis of HIV in the PB and brain. The impact of coinfection with HBV and/or HCV on these interactions and subsequent viral interplay during the course of disease are also reviewed and analyzed. Finally, the impact on HIV-1 infection alone or after coinfection with HCV or HBV within and outside the BM of persistent substance abuse, primarily opiates and cocaine, is discussed.

BM as an Important Reservoir of HIV Infection

HIV-1 likely establishes a number of cellular reservoirs despite the host immune response and therapeutic strategies aimed at decreasing viral load during the primary infection. The BM is one such long-standing reservoir of HIV-1 and has proven to be one of a number of obstacles complicating strategies to eradicate HIV-1 infection. The BM environment consists of HPCs, which are a mixture of fibroblasts, endothelial cells, adipocytes, and myeloid cells [31-33] (Fig 1). HIV-1-infected individuals exhibit many hematologic abnormalities such as anemia, neutropenia, and thrombocytopenia [34, 35] that increase as the disease progresses [36]. These cytopenic conditions may be associated with deficient HPC growth and differentiation [37].

Infection of HPCs [38] and BM stromal cells [39] can lead to altered cytokine profiles and altered differentiation and growth due to the viral proteins gp120, Tat, and Nef [40-42] (Fig. 1B). Many studies have shown that specific lineages of $CD34^+$ HPCs express CD4, CCR5, and/or CXCR4 and that expression of these receptors and coreceptors is required for susceptibility to HIV-1 infection as previously summarized [13]. In an in vitro study, normal human $CD34^+$ HPCs, when incubated with HIV-1 for 24 h, resulted in a noncytopathic infection of the progenitor cells [43]. Similarly, an in vivo study showed that $CD34^+$ HPCs were infected in a subset of seropositive individuals, indicating that these cells may serve as a reservoir within infected individuals [17]. Despite evidence from many studies, the controversy still exists as to whether HPCs can be infected with HIV-1. In this regard, one report has demonstrated that $CD34^+$ HPCs isolated from 10 asymptomatic HIV-1-seropositive individuals were not infected with HIV-1 when tested using conventional and nested polymerase chain reaction techniques [44]. However, it appears that with advanced HIV-1 disease, $CD34^+$ progenitor cells may become more prone to HIV-1 infection. Because this study used asymptomatic patients, the question of susceptibility and permissivity of $CD34^+$ progenitor cells may need to be reevaluated. It has also been reported that the process of reverse transcription is defective in resting cells [45]. Hence it would be difficult to productively infect quiescent progenitor cells [44]. Despite the debate concerning infection of BM progenitor cells, it is believed that even a limited infection of these cells could establish a viral reservoir within this important cellular compartment, particularly over a long period. In this regard, studies have reported the detection of latent HIV-1 genomes present within HPCs isolated from patients who had been treated with highly active antiretroviral therapy (HAART) [46]. These studies have indicated that HPCs are

susceptible to HIV-1 infection. Since the infected HPCs have been shown to be long-lived, the virus can be harbored for prolonged periods of time. These studies also demonstrated that HIV-1 gene expression could be activated from latently infected HPCs by treatment with differentiation factors such as phorbol 2-myristate 13-acetate [46] even when patients had been on HAART for more than 6 months prior to isolation of infected HPCs. This observation has suggested that productive viral replication in this cell population could be targeted for elimination by antiretroviral therapy or other therapeutic strategies currently in development. In addition to HPCs, other cell populations found within the stroma of the BM, such as myeloid cells [47] and stromal fibroblasts [39], are also capable of being infected by HIV-1 (Fig. 1B); however, their role in maintaining a latent viral reservoir in the BM is not as well documented. Limited infection of myeloid cells was confirmed by p24 assays as well as by an HIV-1-specific DNA polymerase chain reaction assay. However, no integrated HIV-1 proviral DNA was detected in this cell population, which was devoid of all cellular components found within the BM microenvironment [47]. With respect to HIV infection of BM stromal fibroblasts, the one study that has been performed to date indicated that this subset of cells is also susceptible to infection with HIV-1 and HIV-2 [39]. Consequently, HIV-1 infection of the cells of the BM stroma may facilitate transmission of the virus to HPCs and may also damage the BM microenvironment by dysregulation of the cytokine milieu especially due to an increase in the proinflammatory cytokines within the BM, thereby contributing to abnormal hematopoiesis.

Role of HIV-1-infected BM in HIV-1 CNS Infection and Neurological Dysfunction

HIV-1 infection of the CNS may result in a range of HIV-associated neurocognitive disorders. HIV-1-infected monocytes and lymphocytes can cross the blood-brain barrier (BBB) and transmit virus to target cells within the brain that include perivascular macrophages, microglial cells, and astrocytes [48][49] (Fig. 2). Investigations concerning the etiology of HIV-1-associated dementia (HIVD) have involved sequencing and comparison of HIV-1 gp160 sequences from autopsied bone marrow, lymph node, lung, and four different regions of the brain from a patient suffering from HIVD (44). The comparisons of the sequences demonstrated a closer relationship between viral sequences obtained from the deep white matter of the brain and those derived from the BM than from any other peripheral sources [50]. This observation has suggested that HIV-1-infected cells in the BM (most likely cells within the monocyte-macrophage lineage) migrate out of the BM, enter PB circulation, and traverse the BBB, seeding HIV-1 infection in the brain (Fig. 2). The authors also proposed that trafficking of cells from the infected BM into the brain could accelerate during late stage disease and that this process could probably explain the occurrence of dementia during that time [50]. Changes were also observed in the biological makeup of the BM that may also affect the course of HIV-1 infection in the brain and the process of hematopoiesis and cell departure from the BM [50]. The clival and calvarial regions of the BM (important sites of hematopoiesis), found within the cranium [51], were compared between uninfected and HIV-1-infected individuals. Magnetic resonance imaging analyses were performed to determine if changes within the BM could affect the severity of HIVD. These studies were designed to identify alterations in membranes, membrane permeability, morphological structure, and volume of extracellular spaces within the BM. Variations were found within the clival and calvarial regions that could be a reflection of altered hematopoiesis within the HIV-1-infected BM compartment. These changes correlated with the severity of HIVD observed in the infected individuals [52]. Furthermore, investigations performed in individuals with HIVD have shown that specific subsets of monocytes, the CD14/CD16 subset, were found in increased numbers in AIDS patients [53], and CD69 (monocyte activation marker) was found to be especially increased in individuals with AIDS and dementia [54]. BM-derived macrophages are known to express CD14 [55]; in fact, CD14 and CD16 have been used to identify heterogeneous populations of cells that

are trafficking from the BM to various peripheral organs [56, 57]. In an interesting study, HIV-1-infected $CD14^+CD16^+$ macrophages were found to accumulate in the CNS of infected individuals with HIV encephalopathy [58], thus strengthening the argument that trafficking of HIV-1-infected cells can enhance the spread of infection. Another recent study identified 5-bromo-2'-deoxyuridine–labeled monocytes originating in the BM that migrated to the CNS in a simian immunodeficiency virus (SIV)-infected $CD8^+$ T-lymphocyte-depleted macaque model. Increased numbers of 5-bromo-2'-deoxyuridine+ monocytes were found in animals that had rapidly progressed to AIDS; this finding was also correlated with soluble CD163, a marker of activated monocytes-macrophages and innate immune activation [59]. This result reinforces the fact that there is increased trafficking of cells from the BM to the brain and that activation of monocytes plays an important role in HIV/SIV neuropathogenesis [15]. It has also been suggested that changes within the cytokine environment of the BM, due to activation of inflammatory responses resulting from HIV-1 infection, can result in an increase of this particular subset of cells and activate the migratory potential of these cells [60]. These alterations could lead to changes in monocyte production and migration from the BM, which can influence the activation state of these cells in circulation. In fact, an increase in the number of activated monocytes has been correlated with HIVD [54].

Impact of HBV and/or HCV on BM

The primary site of the pathogenic impact of HBV occurs in the liver with secondary effects observed in other organs such as pancreas, kidney, skin, spleen, and cells of the BM [61-68]. HBV has also been detected in peripheral blood mononuclear cells (PBMCs) and polymorphonuclear leukocytes [69, 70]. With regard to the BM, acute HBV infection can lead to mild depression in a number of physiological properties, such as hematopoiesis [71]. One such study demonstrated that serum containing HBV DNA inhibited the differentiation process and proliferation of BM progenitor cells such as colony forming unit-granulocytes, erythrocytes, monocytes, and megakaryocytes, colony-forming unit-granulocytes/macrophages, burst forming unit-erythroids, and colony-forming unit-erythroids [72] (Fig. 1C). The inhibition of colony formation was reversed under conditions in which the serum was devoid of viral particles. HBV-induced inhibition of colony formation was also neutralized by anti-HBV murine monoclonal antibodies, indicating that the presence of HBV virions was responsible for the suppression of the differentiation process. An additional study confirmed that the degree to which differentiation and proliferation were inhibited was proportional to the multiplicity of infection of HBV used in the study [73].

HCV is considered to be an important factor to consider for the development of hematologic abnormalities, which can range from immune thrombocytopenia to lymphoma [74]. In fact, thrombocytopenia has often been associated with chronic liver disease and has also been identified in patients infected with HCV [75], possibly involving BM suppression with decreased platelet production and diminished levels of the hematopoietic growth factor thrombopoietin (Fig. 1D). Thrombopoietin is produced in the liver, BM, and kidney and has been shown to be responsible for regulating megakaryocyte development and maturation, along with platelet production and release [76, 77], thereby playing an important role in the process of hematopoiesis.

Impact of HBV and/or HCV on Peripheral Immune Function

Although HBV and HCV can affect BM development, they demonstrate a direct effect on peripheral immune cells, immune activation, and immunoregulatory pathways, suggesting a comprehensive impact on the immune system. In an interesting study, DNA microarray analysis was performed on PBMCs in groups of individuals who were infected either with HIV or HCV or coinfected to delineate the differential gene expression patterns in PBMCs

[78]. HCV exhibited a distinct immunologic profile with an increase in the proinflammatory immune response in non-T cells, which was in contrast to HIV, which induced an immune profile with activation of $CD4^+$ and $CD8^+$ T cells. Expression levels of genes associated with various receptors on natural killer cells, B cells, and plasmacytoid dendritic cells were increased in HCV-infected individuals when compared to levels in HIV-1-infected individuals. Expression of the proinflammatory cytokine, fractalkine, was also elevated in the PB in the HCV-infected group, suggestive of liver fibrosis or injury in contrast to levels found in the HIV-1-infected group. This study presented an in-depth comparison of the different ways host immune responses resulting from chronic HCV and HIV infections [78] are regulated. Similarly, efforts are under way to determine the effects of chronic HBV infection on the function of the peripheral immune system. A study involving 206 individuals with chronic HBV infection demonstrated that T-cell dysfunction in these individuals was extensive and persisted with a significant decrease in $CD3^+$ T cells, which translated into a loss of competent cells that were immunologically capable of challenging the infection [79]. In fact, there have been reports that antiviral treatment can increase $CD4^+$ [80] and $CD8^+$ [81, 82] T-cell responsiveness to chronic HBV infection, suggesting that these cell populations were present but suppressed by HBV infection. Thus, HBV-induced T-cell loss will facilitate viral persistence and continued chronic viral infection.

Impact of HIV-1 Infection on Hepatitis Virus Pathogenesis

The natural history of infections is often altered in people coinfected with HIV and HBV and/or HCV. Indeed, in individuals undergoing long-term effective management of HIV disease, it is often the viral-induced hepatitis in a coinfected individual that becomes the dominant disease [83]. In fact, similar studies for HIV and HBV/HCV coinfections have shown the risk of liver-related deaths to be 2 to 3 times higher in individuals coinfected with HIV-HBV/HCV compared with those monoinfected with HBV/HCV [84]. Taken together, however, it appears that HIV has more of an effect on HBV disease than HBV does in modifying HIV pathogenesis, although some studies report an increase in the progression of HIV to AIDS in people with serological markers of HBV [85].

Although icteric disease may follow a more moderate course, individuals coinfected with HIV and HBV or HCV often experience a more aggressive chronic liver disease, with accelerated development of fibrosis and cirrhosis [86] (Fig. 3). HIV-1 can impact the natural course of HBV infection and leave the HIV-1-infected population vulnerable to development of chronic hepatitis B compared to those individuals who have not been infected with HIV-1 [87, 88]. Hadler et al. observed a threefold increase in the risk of developing chronic HBV infection in unvaccinated individuals who were infected with HIV-1 before being infected with HBV; they also did not observe any subsequent effect on liver enzymes or even on the severity of clinical illness [88]. The increase in HBV carriage could have been due to the fact that clearance of HBV infection was dependent on normal functioning of the T helper cells, which was affected during HIV-1 infection [88]. Thus, the detrimental impact of HIV-1 on the immune system could lead to a defect in the resolution of acute HBV infection, enabling chronic HBV infection to develop more readily.

HIV-1 accelerates the progression of HBV-associated liver disease toward cirrhosis and is usually associated with a decrease in the size and quality of the $CD4^+$ T-cell compartment [89]. Lower $CD4^+$ T-cell counts are often associated with increased risk for HCC in HIV-HBV coinfected individuals (Fig. 3). However, it remains unclear as to whether HIV-1 mono-infection can increase the risk of HCC [90]. Also, HBV-induced liver disease, which is an immune-mediated process, is accelerated by HIV-1. This event may be due to the cytopathic effects induced by the HIV-1-encoded proteins rather than by the immune system itself. One such form of liver disease is known as fibrosing cholestatic hepatitis [91]. HBV has been shown to exist in at least eight different genotypes (A – H), and many studies have

shown that specific HBV genotypes correlate with disease severity, development of acute versus chronic infection, and progression to HCC as previously reviewed [92]. A recent study has shown the prevalence of dual infection of HBV genotypes A+G in 17.6% of HIV-1/HBV coinfected individuals [93]. In this study, A+G dual genotype infections correlated with increased HIV viral load [93]. The effect of A+G dual genotype infections within the context of HIV-1 infection has not yet been determined, but genotype D has been shown to be involved in liver fibrosis especially in immunocompromised individuals [94].

Liver disease in chronic HBV patients has not only been associated with the presence of specific genotypes, as indicated above, but also with mutations within the precore and core regions of the HBV genome [95, 96] that appear to arise during the course of chronic infection. These mutations have been found in HBV monoinfected patients who had progressive liver disease, who were on immunosuppressive drug therapy [96], and who were associated with enhanced virulence and, in some cases, enhanced replication of the virus [97]. It is possible that certain precore/core region HBV mutants are more prevalent in individuals coinfected with HIV-1/HBV than in monoinfected individuals. In this regard, HBV core deletion mutants are known to be associated with aggressive liver disease, so the presence of this core region mutant could be responsible, in part, for accelerated liver disease in individuals coinfected with HIV-1/HBV [98]. Thus, HIV could be responsible for placing selective genetic pressure on HBV that results in the enrichment of specific HBV mutants that may be involved in causing more severe HBV infection (Fig. 3). The changes in cytokine profiles during the course of coinfection may also be involved in the etiology of more severe liver disease.

HIV-1 infection also affects the HCV life cycle, resulting in a more progressive form of liver disease [19]. This situation is likely attributable to the increased HCV viral load found in the population coinfected with HIV-1/HCV compared to the population monoinfected with either HCV or HIV-1 [99-101]. During acute HCV infection, it is imperative that T cells clear the infection to prevent the development of a chronic state of HCV infection [102]. As previously demonstrated with HBV-infected individuals, immune suppression in HIV-1-infected individuals allows acute HCV infection to develop into a chronic state of infection (Fig. 3) because $CD4^+$ and $CD8^+$ T-cell responses are significantly reduced in these individuals [103]. HCV has six genotypes and multiple subtypes, each associated with specific clinical implications, as reviewed previously [103]. A small study analyzed the HCV genetic diversity using multiple HCV clones at two different time points from individuals coinfected with HIV-1/HCV using only HCV genotype 1a-positive patients. The clones examined represented two different regions of the HCV genome, the hypervariable region 1 (HVR-1) and the nonstructural protein 3, which have been shown to encode for epitopes that are targets for neutralizing antibodies and cellular immune responses, respectively. Decreased HCV genetic diversity was observed in the clones obtained from the coinfected patients compared to the clones from HCV monoinfected patients. The authors suggested that the decline in genetic diversity could be attributable to the changes found in the immune responses, particularly the low CD4 counts brought about by infection with HIV-1 [104]. Although there have been conflicting studies in the past that have shown increased genetic diversity in the HVR-1 region of HCV in clones obtained from patients coinfected with HIV-1/HCV, not all of the patients were infected with the same genotype of HCV, which may also account, at least in part, for the results obtained in these studies [105].

HBV/HCV coinfection with HIV-1 has also been associated with increased morbidity and mortality compared to monoinfection with either HBV or HCV [19, 84]. In addition to immune suppression, HIV can also alter HBV or HCV pathogenesis as a result of an intrahepatic interaction between the viruses. Viral proteins such as gp120 can interact with hepatitis gene products and can affect hepatocytes via interactions with the chemokine

receptors CXCR4 and CCR5, leading to an increase in viral replication. Some pathogenic mechanisms have been identified that result from the interaction of HIV-1 with HCV. It is possible that HIV-1 can infect hepatic stellate cells, activating them and leading to increased fibrosis [19]. HIV-1 affects the natural course of hepatitis infection and of treatment regimens for chronic hepatitis infection. However, the exact molecular mechanisms by which it does so remain unclear, warranting additional studies in this area.

The above-mentioned studies provide ample evidence that HIV-1 affects and accelerates hepatitis disease progression with increased viral loads and establishment of liver diseases such as fibrosis and cirrhosis. Both of these conditions are important pathological intermediates leading to the development of HCC. Although HIV-1 is not routinely considered to be an oncogenic virus, its detrimental effect on the immune system has led to increased risk of infection with pathogens that do cause cancer, for example, cervical cancer due to human papilloma virus infection, non-Hodgkins lymphoma due to Epstein-Barr virus, and Kaposi's sarcoma due to human herpes virus type 8 [106]. Similarly, HIV-1 does not allow for clearance of acute hepatitis infection, causing an increased frequency of chronic hepatitis infections. The acute hepatitis infection will ultimately lead to cirrhosis, which will increase the probability of developing HCC. Thus, there is an indirect, but definite, correlation between coinfection with HIV-1/HBV or HCV and increased risk for HCC. A number of cohort studies investigated the incidence rates of HCC in individuals coinfected with HIV-1/hepatitis. One such report was a retrospective cohort study of 16,439 HIV-1-infected US veterans, of which 4,761 were coinfected with HIV-1 and HCV. When they divided their cohort into pre-HAART versus those who received HAART, they found that HCV coinfection with HIV-1 increased the risk of cirrhosis 10-fold in the pre-HAART era whereas in the HAART era it increased the risk approximately 20-fold; the risk for HCC increased 5-fold [107]. Another retrospective study of 14,018 HIV-1-infected US veterans demonstrated that these individuals had a higher prevalence of HCC compared to HIV-1-negative individuals. The increased prevalence of HCC could be associated with HCV coinfection and/or alcohol abuse [108]. A smaller study involving 2,383 individuals infected with HIV-1 also identified a higher incidence rate of HCC compared to that of the general population. Of six cases of HCC, four were in individuals coinfected with HCV and two were in individuals with a history of alcohol abuse [109]. With HAART treatment, there is an improvement in the survival of coinfected individuals, and the increased life expectancy can lead to an increase in the emergence of cases of HCC and end-stage liver disease due to coinfection with HCV and HIV-1. Other chronic conditions that develop as comorbidities in HIV-1-infected patients such as type II diabetes mellitus, metabolic syndrome, and obesity, are also emerging as HCC risk factors in the general population [110-112]. With HAART therapy extending the lifespan of HIV-1-infected individuals, these conditions are expected to become much more prevalent, and there remains the potential that viral hepatitis may exacerbate this effect. Other studies have also reported a trend toward increased numbers of HCC cases over time [113]. In these studies, this effect was adjusted for age suggesting that the overall increase in the incidence over time was even greater, with the reported risk in older adults aged 50 and greater 10 times higher than those between 30-39 years of age. An increase in the number of HCC cases in the future, within the context of the aging HIV-infected population, has the potential to greatly increase the total number of HCC cases reported overall [113]. This again demonstrates another indirect effect of HAART treatment on the development of HCC, however in the context of increased lifespan. Although these observations suggests interplay between HIV-1 and HCV, it is necessary also to determine the effect of HAART treatment in the coinfected patients. HAART, which is known to be hepatotoxic [114], could increase liver injury and this toxicity could potentially contribute to HCC, as documented in a study in which HIV-HCV coinfected individuals on HAART were frequently diagnosed as having coexistent cholestatic and cytolytic hepatotoxicity [114]. An interesting question that remains unanswered is the mechanism via which HAART affects

the liver of an HIV/HCV coinfected individual. To address this question, a cohort of 39 HIV/HCV coinfected individuals were examined for their immune status and its association with severity of liver disease [115]. Patients with low or undetectable viral load and a $CD4^+$ cell count of >200 cells were more at risk for cirrhosis as compared to the individuals with lower $CD4^+$ cell counts or higher viral load [115]. An explanation for this phenomenon could be attributed to HAART facilitating the restoration of CD4+ T cell counts by rescuing viral load and restoring immune system responses, which could adversely impact the severity of HCV disease [115]. While HAART is being regarded as one of the leading causes of liver-related mortality in HIV-infected individuals [116], it obviously needs to be utilized for keeping HIV-1 infection under control. Given this, several studies have begun to try and understand whether the potential hepatotoxic effects of HAART can be minimized in HIV-1 and HBV/HCV coinfected individuals. These studies have shown in coinfected individuals that treatment of viral hepatitis can be targeted with hepatitis-specific antivirals, leading to a significant reduction or regression [117, 118] in liver fibrosis progression, while suppressing HBV and HCV (reviewed in [119]). Antiretroviral drugs such as nevirapine, that are now being included in the HAART regimen, show a favorable liver safety bioprofile [120]. These drugs provide HIV control, increased $CD4^+$ cell count, which can lead to a positive benefit to the liver of a HIV/HCV coinfected individual [121]. Several retrospective studies of HIV/HCV coinfected individuals, have examined liver biopsies and have found that slower progression of liver fibrosis is associated with the use of HAART, suppression of HIV and higher $CD4^+$ cell counts [120,122][123]. The current consensus is that initiation of HAART including the antiretrovirals with a favorable biosafety profile, at an early stage is favorable as it may preserve the immune system, while working at controlling HIV infection and thus, protecting the health of the liver [121, 124].

Impact of Substance Abuse on HIV Disease within the BM

A large population of HIV-1-infected individuals is known to abuse a variety of drugs, with almost one-third of the individuals with AIDS frequently abusing opioids [125]. Considerable evidence exists that opioids modulate the function of the immune system [126, 127]. In addition to being expressed within the CNS, opioid receptors are also expressed by primary human $CD34^+$ HPCs. Specifically, within $CD34^+$ cells, the μ-opioid receptor (MOR-1) was identified on the immature $CD38^{dim}$ (low to negative expression of CD38) and $CD38^{bright}$ (high expression of CD38) cell subpopulations, whereas the fully differentiated blood cells lacked MOR-1. This observation suggests that MOR-1 plays a role in the differentiation process of early $CD34^+$ stem and progenitor cells [128]. In addition, the expression of MOR-1 has been demonstrated on PB and cord blood $CD34^+$ cells with increased levels of the receptor detected on immature cord blood $CD34^+$ cells. Activation of MOR-1 by the endogenous opioid enkephalin or the exogenous opioid morphine (Fig. 4) induces the MAPK pathway, which has been shown to induce processes associated with cellular proliferation and differentiation [129]. Morphine has been shown to result in a significant decrease in the number and proportion of $CD4^+/CD8^+$ double-positive cells and in an increase in the populations of $CD4^+/CD8^-$, $CD4^-/CD8^+$, and $CD4^-/CD8^-$ double-negative cells leading to morphine-induced thymic hypoplasia in mice [130]. In vitro chronic morphine exposure has also been implicated in $CD4^+$ T-cell Th2 differentiation [131, 132]. This finding was confirmed in vivo when mice were implanted with morphine pellets, exposing them to morphine for 72 h, resulting in a cytokine profile that was consistent with $CD4^+$ T-cell Th2 differentiation [132]. Thus, MOR-1 agonists, both endogenous (enkephalins) and exogenous (morphine), may be imperative factors to consider for hematopoietic stem cell differentiation and proliferation (Fig. 4). Cocaine is another powerful addictive CNS stimulant, abused by a significant number of HIV-1-infected individuals, and is responsible for eliciting various alterations in the functions of multiple organs [133]. No studies have reported any effect of cocaine on HIV disease within the BM

or during BM-mediated erythropoiesis [134]. However, a large number of studies have shown the significance of cocaine in modulating the functions of the immune system [135, 136]. Such studies have demonstrated in an HIV-1-infected humanized PB leukocyte (huPBL)-severe combined immunodeficient (SCID) mouse model, wherein systemic cocaine administration led to accelerated HIV-1 infection of huPBLs, a decrease in $CD4^+$ T cells [137] and a dramatic rise in viral load that eventually led to an accelerated form of HIV disease [138].

Effects of Substance Abuse on HIV-1 Pathogenesis and Hepatitis Coinfection

Substances of abuse add another complex dimension to the already complicated effects associated with HIV-1 and hepatitis coinfection. Morphine, the most active metabolite of heroin, has been shown to induce many biological effects including cell survival or proliferation (Fig. 4). However, the exact molecular mechanisms involved in these processes have yet to be established [139]. Evidence from many studies has suggested that opioids play an important role in HIV-1 pathogenesis. Opioids interact with the cell surface receptor MOR-1 (Fig. 4), and this interaction can stimulate cells. After the interaction of the drug and receptor, MOR-1 can then trigger a signaling cascade leading to an alteration in viral gene expression, thus affecting HIV-1 infection and replication [140]. Morphine-treated SIV-infected lymphocytes have been known to survive for longer periods of time, indicating that opioids exert a protective effect on cells from apoptosis induced by SIV, thus allowing continued viral proliferation [141, 142]. Studies have shown that PBMCs treated with morphine exhibited an increase in the level of HIV-1 replication [143] (Fig. 4). Morphine was also responsible for amplifying HIV-1 gene expression in chronically HIV-1-infected promonocytes cocultured with lipopolysaccharide-stimulated human brain cells [144]. In addition to altering the immune system, opioids can also affect the CNS directly, causing neurological dysfunction. HIV-1 Tat and morphine act cooperatively, leading to activation of microglial cells, which, when activated, can secrete proinflammatory cytokines that are detrimental to neurons and cause the upregulation of the chemokine receptor CCR5, thus exacerbating HIV-1 pathogenesis [145] (Fig. 4). Infection of rhesus macaques with the HIV/SIV chimeric strains $SHIV_{KU\text{-}1B}$, $SHIV_{89.6P}$, and $SHIV_{17E\text{-}Fr}$ resulted in the establishment of a higher viral set point and increased viral replication in the CNS when the monkeys were exposed to chronic doses of morphine [146]. However, there is a paucity of information concerning the effects of opioids on HBV/HCV infection within the BM and on the process of hematopoiesis. This gap in knowledge needs to be addressed.

Cocaine can modulate the immune system by depressing it [147], which can result in progression to AIDS; it can also increase the risk for developing secondary opportunistic infections [137]. The $sigma_1$ receptor is responsible for mediating many of the acute and chronic effects of cocaine abuse [148]. Previous studies using the SCID mouse model have shown the effects of cocaine on HIV-1 replication. The SCID mice were implanted with huPBLs, infected with HIV-1, and given cocaine. The huPBLs from cocaine-treated animals were more susceptible to HIV-1 infection than were animals exposed to cocaine (Fig. 4). Exposure to cocaine was associated with an increase in viral load and a lower CD4:CD8 ratio. This in vivo study also confirmed the negative relationship between cocaine use and HIV-1 pathogenesis and disease progression [137]. Perivascular macrophages and microglial cells are major target cell populations in the brain for HIV-1 infection [60]; however, the virus does not infect neurons, though indirectly the virus and/or viral proteins (gp120, Tat, and Vpr) may lead to neuronal loss and HIVD [149-152]. Not only does cocaine impact the immune system, but chronic cocaine exposure can also lead to a decrease in the proliferation of neural progenitor cells, thus targeting the CNS through yet another pathological pathway as previously reviewed [153] (Fig. 4). Therefore, HIV-1 and cocaine can both have a detrimental effect on the CNS. Cocaine can also have an important effect on

latent HIV-1 infection in that it can activate viral replication. Buch et al. have shown increased HIV-1 replication in cocaine-treated human monocyte-derived macrophages. Cocaine treatment could also activate latent infection within a promonocytic cell line (Fig. 4), suggesting that HIV-1 patients abusing cocaine could have an increased severity of HIV-1 infection and accelerated progression toward HIVD [30].

Cohort studies are complex due to the various biological interactions that occur within humans while having to control for variables such as cohort demographics, adherence to HAART, attrition etc., and hence, a multi-pronged approach along with in vitro studies and in vivo mouse model studies are warranted to understand the effects of specific drugs of abuse on HIV-1 pathogenesis. However, a number of cohort studies have clearly demonstrated an association of cocaine abuse and acceleration of HIV disease [154-156]. A 30-month longitudinal study of 222 HIV-1-seropositive active substance-abusers, showed a significant elevation in the viral loads of individuals who were crack-cocaine users independent of HAART [154]. A lower proportion of the crack-cocaine users showed a higher but controlled viral load but these individuals were also on HAART, thus, implicating the lack of adherence to therapy as a risk factor for HIV disease progression, among substance-abusers [154]. Additionally, it was also demonstrated that the active drug-using cohort had a significant association with accelerated decline in $CD4^+$ cell counts, thus accounting for accelerated disease progression [154]. Another study, which was a six-center national cohort of 1686 HIV-1-infected women who were non-drug users and 483 crack-cocaine-abusing HIV-1-infected women, examined patterns of crack-cocaine use and its association with several parameters of HIV disease, including $CD4^+$ T lymphocytes and viral RNA. This prospective study of crack-cocaine users showed greater $CD4^+$ cell loss and higher viral RNA levels in the using population [155]. While, both of these studies compared the effect of cocaine on HIV-1-infected individuals, another study comparing 80 HIV-1 seropositive and 42 seronegative crack-cocaine smoking African-American women, demonstrated that $CD4^+$ cell counts were lower for a given viral load as cocaine-doses increased, and it was concluded that this was due to the effects of cocaine on viral load and $CD4^+$ cells [156].

A number of studies and reviews have reported and discussed the prevalence of HIV-1 and hepatitis coinfection in a substance-abusing population [157-160]; however, few of these studies considered the molecular effects of substance abuse on the two infections [161, 162]. A recent study evaluated liver fibrosis among 497 patients, including HCV-monoinfected and HIV/HCV-coinfected substance abusers for whom opiates and cocaine were the dominant drugs of choice. Advanced liver fibrosis was three- to five-fold more prevalent in coinfected patients than in patients with HCV monoinfection [161]. Although the investigators did not comment on the molecular mechanisms driving advanced liver fibrosis, it is possible that HIV and substance abuse are partially involved in the etiology of the advanced stage of fibrosis. Another study explored the possible effects of IVDU on immune responses in HCV-monoinfected and HIV/HCV-coinfected individuals who were segregated into substance abusing and nonusing groups. The group with coinfection and concurrent substance abuse had significantly higher interferon-γ and interleukin-10 HCV-specific responses than the coinfected nonuser group [162]. The same investigators had previously shown that higher interferon-γ responses in coinfected individuals correlated with lower liver inflammation and fibrosis scores [163], thus contradicting results from other studies. With respect to HIV/HBV coinfection however, there is a general lack of investigations that examine the impact of substance abuse on the immune responses in HIV/HBV coinfection, further suggesting that detailed, systematic research is needed to rigorously define the impact of substance abuse on HIV-1 and HBV/HCV mono- and coinfection. Despite the lack of knowledge concerning the molecular mechanisms that drive these results, it is clear

that substance abuse emerges as a key player in modifying immune responses during the course of viral disease.

DISCUSSION

The BM plays a vital role in the pathogenesis of HIV-1 because it serves as one of the reservoirs for latent HIV-1 infection, which when activated can spread from the BM to distant sites including the brain and other end organs. HIV-1 in turn adversely affects the process of hematopoiesis and the cytokine environment within the BM. Infection of the cells of the BM can further affect and seed infection to other end organs, but its effects are particularly well-defined in the CNS. Various studies have shown the similarities between viral sequences found within the BM and the CNS, providing evidence for the migration of HIV-1-infected BM cells across the BBB, thereby spreading infection into the brain. HIV-1 is not the only virus to impact the BM environment; coinfection with members of the hepatitis virus family is also known to have a depressive effect on the differentiation and proliferation of cells within the BM compartment. Although there is ample information concerning the detrimental effects of HBV and HCV on BM function, there is a dearth of knowledge relative to the effects of other hepatitis viruses such as hepatitis A virus. The effects of hepatitis are not localized only to the BM but also extend to the PB compartment and the peripheral immune system, significantly impacting PBMCs and the T-cell populations.

Coinfections with HIV and hepatitis have harmful effects on the body. Interestingly, HIV-1 seems to have a considerable impact on the pathogenesis of hepatitis but hepatitis does not seem to have a significant impact on HIV-1 pathogenesis. Coinfected individuals usually develop a more hostile and accelerated form of liver disease, such as fibrosis and cirrhosis, eventually leading to the development of HCC. It is still debated whether HIV-1 monoinfection can be considered a risk factor for development of HCC. However, there are enough studies to prove that it definitely remains a strong risk factor when present during coinfection with hepatitis.

Although HIV-1 alters cell function in a number of cellular and tissue compartments and may alter the natural history of a number of coinfecting pathogens, including members of the hepatitis virus family, factors such as substance abuse and coinfections may alter the course of HIV-1 pathogenesis and disease. Studies concerning chronic opioid exposure and cocaine abuse during the course of HIV-1 infection have shown higher viral loads, increased viral replication, and alterations of cytokine levels within the infected cell populations. However, little is known about the effect of substance abuse on the biological makeup of BM or on HIV-1 infection within the BM. Studies targeting this gap in knowledge will help define the mechanistic basis for chronic substance abuse-mediated alterations in HIV-1-infected cell physiology and trafficking of cells from the BM compartment into the peripheral circulation. Results from these investigations will be important for understanding the impact that substance abuse has on HIV-1 pathogenesis and may facilitate the design of more effective therapeutic strategies for HIV/AIDS.

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LIST OF ABBREVIATIONS

AIDS	acquired immune deficiency syndrome
BBB	blood-brain barrier
BM	bone marrow
CNS	central nervous system
HAART	highly active antiretroviral therapy
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HIV-1	human immunodeficiency virus type 1
HIVD	HIV-1-associated dementia
HPCs	hematopoietic progenitor cells
huPBL	humanized PB leukocyte
IVDU	intravenous drug use
MOR-1	μ-opioid receptor
PB	peripheral blood
PBMCs	peripheral blood mononuclear cells
SCID	severe combined immunodeficient
SIV	simian immunodeficiency virus

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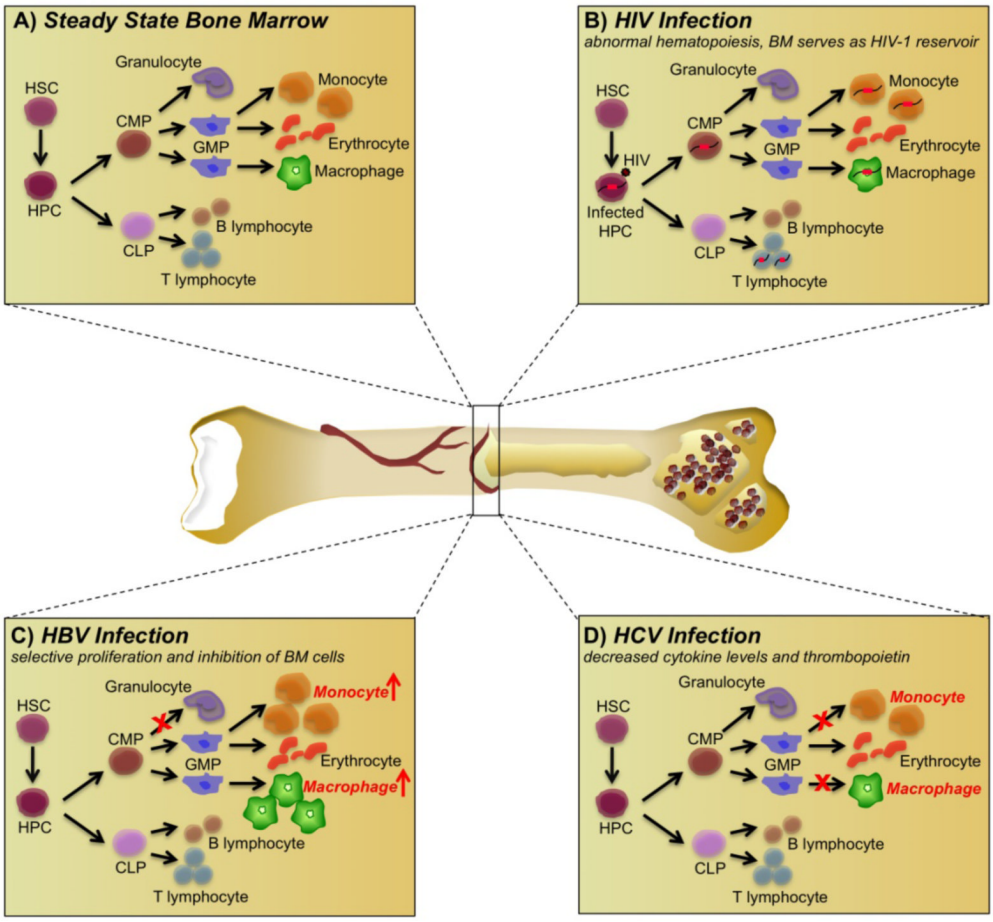

Fig. (1).

Effects of human immunodeficiency virus (HIV), hepatitis B virus (HBV), and hepatitis C virus (HCV) on bone marrow (BM) biology. (A) The steady state within the BM compartment consists of hematopoietic stem cells (HSC), which can differentiate into hematopoietic progenitor cells (HPC). The HPCs can further differentiate into various committed progenitor populations such as committed lymphoid progenitors (CLP) and committed myeloid progenitors (CMP). CMPs can further differentiate into granuloctye-macrophage progenitors (GMPs), which develop into monocytes and erythrocytes. The CLPs can develop into B and T lymphocytes. In addition, dendritic cells, fibroblasts, and mesenchymal stem cells form the BM microenvironment. (B) HIV exerts a global effect on the BM, infecting HPCs, myeloid cells, and stromal cells, leading to an alteration in cytokine profiles within the BM, abnormal hematopoiesis, and growth patterns, and forming a latent reservoir in the HPCs. (C) HBV exerts a selective effect on BM hematopoiesis, wherein progenitor cells committed to the monocyte-macrophage lineage are induced into differentiation; the resultant monocytes and macrophages are induced into proliferating, while progenitors committed to differentiating into granulocytes are inhibited from proliferating. (D) HCV exerts an inhibitory effect on the monocyte-macrophage progenitors, thus hampering the proliferation of monocytes, macrophages, and erythrocytes, resulting in anemia in patients with chronic HCV, accompanied by a decrease in thrombopoietin and cytokine levels, responsible for platelet production.

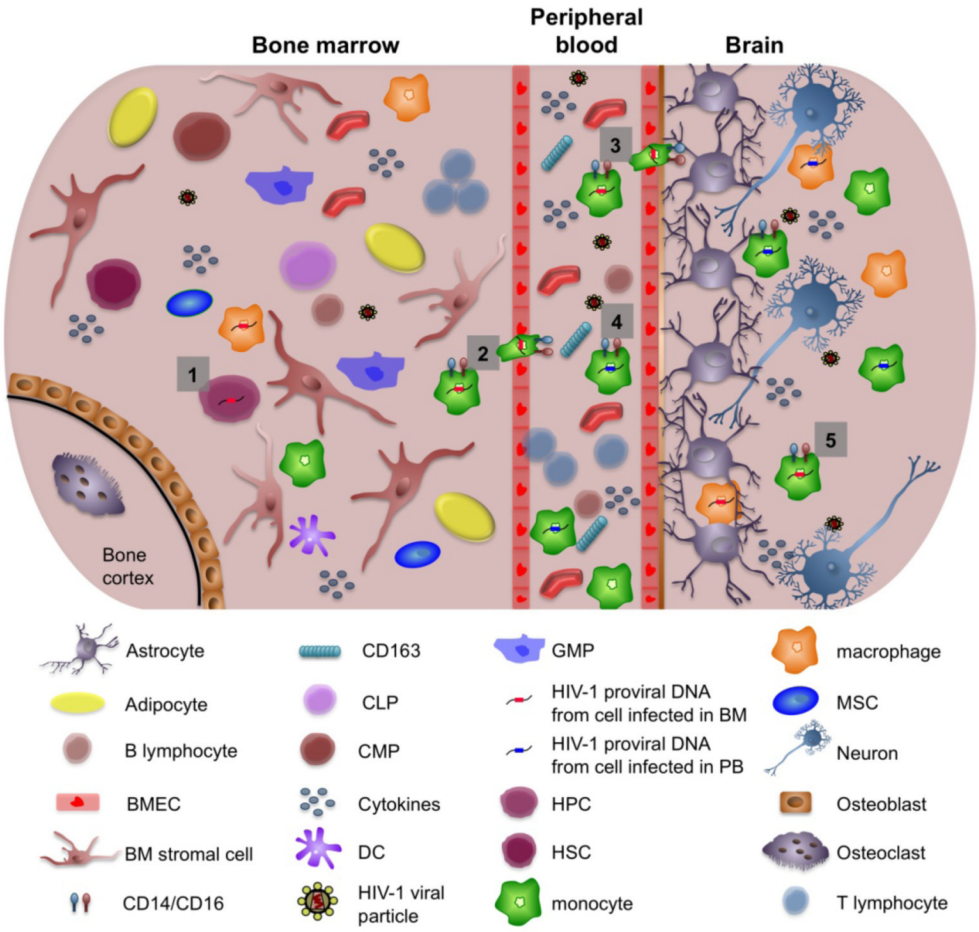

Fig (2).

Migration of human immunodeficiency virus 1 (HIV-1)-infected cells from the bone marrow (BM) to the central nervous system (CNS). (1) Hematopoietic progenitor cells (HPCs) expressing CD4 and CXCR4/CCR5 can be infected in the BM of HIV-1-infected patients. (2) HIV-1-infected monocytes and macrophages from the bone marrow reseed the peripheral blood (PB). (3) HIV-1-infected cells from the BM that have reseeded the peripheral blood traverse the blood-brain barrier as well as (4) monocytic cells infected within the peripheral blood compartment. These cells have been shown to be more $CD14^{+}/16^{+}$ and associated with increased neurological disease. (5) Both monocytic cells that were infected in the BM and cells infected in the peripheral blood contribute to carrying HIV into the CNS, thereby spreading infection to cells found within the CNS such as perivascular macrophages, microglial cells, and astrocytes. Changes in cytokine profiles brought about by HIV-1 infection can also affect the migration of HIV-1-infected cells, thus helping to enhance the progression of HIV-1 infection. In addition, soluble CD163 found within the peripheral blood has been associated with HIV-1-associated neurological disease. BMEC, bone marrow microvascular endothelial cell; CLP, committed lymphoid progenitors; CMP, committed myeloid progenitors; DC, dendritic cells; GMP, granuloctye-macrophage progenitors; HSC, hematopoietic stem cells; MSC, mesenchymal stem cells.

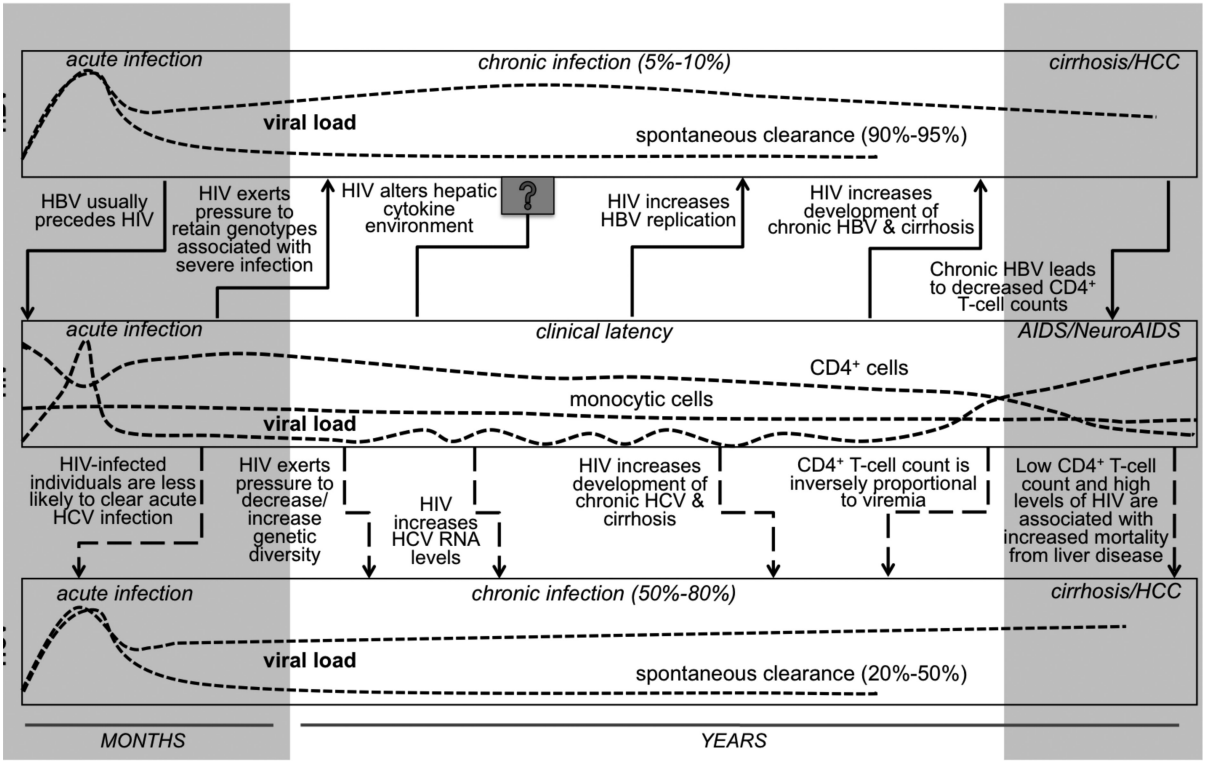

Fig. (3). Effect of human immunodeficiency virus (HIV) on hepatitis pathogenesis

HIV can affect the natural history of hepatitis B virus (HBV) and hepatitis C virus (HCV) pathogenesis. HIV has been identified as a risk factor for increased probability of developing hepatocellular carcinoma (HCC). It leads to accelerated fibrosis and cirrhosis and also to increasing viral load (HBV) and RNA levels (HCV). It is still unclear whether HBV and HCV exert effects on HIV-1 pathogenesis. AIDS, acquired immunodeficiency syndrome.

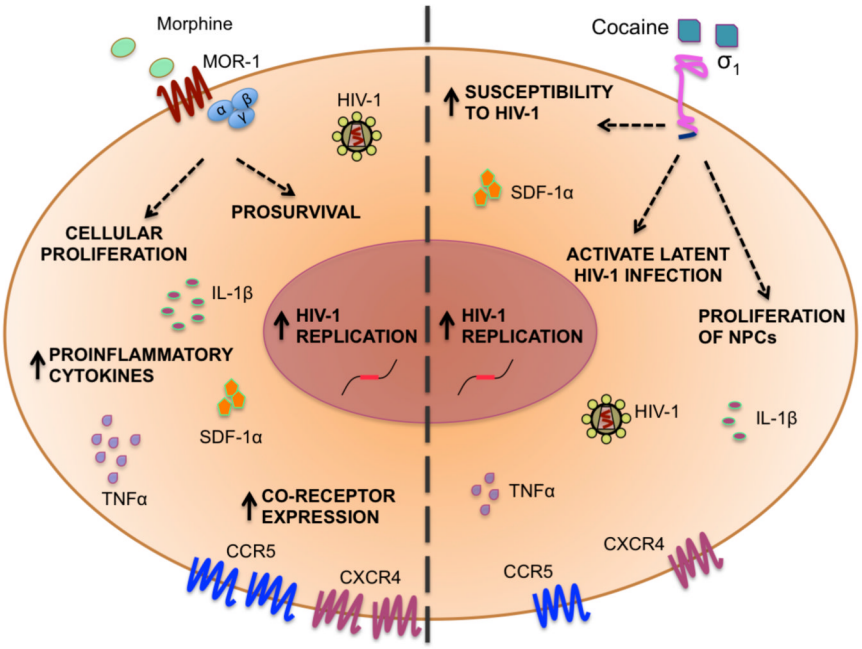

Fig. (4). Impact of opioids and cocaine on human immunodeficiency virus (HIV) disease

Opioids such as morphine, an agonist for the μ-opioid receptor (MOR-1), have a variety of effects on HIV to exacerbate disease progression including increased replication of HIV-1 and altered cytokine profiles, which can prove to be detrimental to the central nervous system. Morphine can upregulate coreceptor expression levels, have a prosurvival effect on cells, and can act as an inducer of cell proliferation. Cocaine, a $sigma_1$ receptor agonist, can increase susceptibility of peripheral blood leukocytes to HIV-1, decrease proliferation of neural progenitor cells (NPCs), activate latent HIV-1 infection, and increase cytokine profiles. IL, interleukin; SDF, stromal cell-derived factor; TNF, tumor necrosis factor.