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Review

Development of NanoART for HIV Treatment: Minding the Cytochrome P450 (CYP) Enzymes

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Abstract

Sustained suppression of HIV viral load is the primary objective for HIV treatment, which successfully achieved by the use of a wide array of antiretroviral therapies (ART). Despite this enormous success low level of virus persists in the anatomical and cellular reservoirs of the body causing a multitude of immunological and neurocognitive deficits. Towards this, nano-formulations are gaining attention to solve these problems by delivering ART to the targeted locations such as brain, lymphoid tissues, and monocytes/macrophages. As cytochrome P450 (CYP) enzymes play a critical role in the metabolism of drugs and other xenobiotics, it is expected that the interaction of nanoparticles with CYP enzymes may result in adverse drug reactions, cellular toxicity, and alterations in CYP-mediated metabolism of other drug molecules. Considering these potential adverse outcomes it is imperative to design the nano-carriers that will have minimal impact on CYP enzymes. Therefore, developing a long-acting nanoART regimen with minimal side effects is an essential step to improve patient's adherence to the treatment paradigm, effective treatment strategy, and to combat the HIV infection & AIDS.

Keywords: Cytochrome P450 (CYP); HIV; Nanomedicine; Pharmacogenomics; Antiretroviral therapy

Introduction

The recommended highly active antiretroviral therapy (HAART), which are usually comprised of more than two drugs, effectively suppresses the viral load by disrupting the HIV life cycle at different stages [1]. There are 26 FDA approved drugs that belong to six different categories for the antiretroviral therapy (ART) of HIV infection. These active pharmaceutical ingredients have averted scores of HIV related deaths and have greatly increased the life expectancy of HIV positive individuals [2]. However, these patients will need to be on the ART for the rest of their lives due to persistence of virus in the HIV reservoirs [3]. Relapses in the treatment or discontinuation causes viral rebound and progression to AIDS. The prolonged ART therapies also present other obstacles such as rise of drug-resistant virus and cumulative drug-induced toxicity in the system [4,5]. To overcome these challenges, HIV researchers have explored several strategies to expel the virus from infected cells [6]. For example, induction of infected latent cells by using interleukin-2, a chemokine that activates immune cells, or by inhibiting histone deacetylases in a 'shock-and-kill' therapeutic approach [7-9] suggests the possibility of activation of latent virus and reducing the spread of infection. In addition, other approaches like stem-cell transplantation, chemotherapy, and gene-editing were tested to eliminate the virus from the body [10-12]. As these methodologies are still at discovery stage and considering potential problems in implementation of these strategies to larger populations, attaining sustained remission of virus would be the primary goal of HIV treatment.

For persistent reduction of the virus, nanomedicine offers a unique advantage to increase the benefits of HAART to the patient. Nanotechnology, using structures that ranges from 1-100 nm in size, has been vastly studied for its applications in preventive, diagnostic, and treatment approaches especially in the cancer research [13]. The inherent versatile properties of nanosystems such as high surface area, control of drug release, increased circulation time, and low cost to produce in mass scale favor their use in HIV/AIDS treatment [14]. The use of nanotechnology for infectious diseases especially for HIV prevention and treatment is gaining pace in recent years. For instance, ARTs that are incorporated into nanoformulations as topical microbicides are being tested in clinical trials for the prevention of sexual transmission of HIV [15]. In addition, feasibility of various nanocarriers to increase the pharmacokinetic profile of antiretroviral agents, and the use of nanosystems to increase the immunogenicity of potential HIV vaccines are being extensively studied [16].

Cytochrome P450 (CYP) isoforms are responsible for the phase 1 drug metabolism of various pharmaceutical drugs, xenobiotics, and other endogenous substances [17]. CYPs are primary source of variability for the drug response among

individuals. Moreover, several drugs and other exogenous compounds can interact with CYPs that may increase or decrease their expression and/or activity [18]. These drug interactions for some drug molecules can lead to clinically relevant adverse drug reactions or decrease their efficacy [19]. The critical role of CYP-mediated drug metabolism can be explained by stringent evaluation of potential drug interactions for all the drugs that are being approved by the FDA. As several chemical agents are being used to make nanoparticles, it is expected that nano-based systems may alter the functions of CYP enzymes. Direct or indirect interaction of the nanoparticles with CYPs is expected to influence the metabolism of ART leading to drug-mediated toxicity and decreased drug efficacy. Therefore, the scope of this article is to discuss the latest developments in field of nanomedicine for the improvement of current therapeutic regimen for HIV infection with special emphasis on the CYP enzymes, and potential applications of pharmacogenomics of CYPs in the HIV treatment (Figure 1).

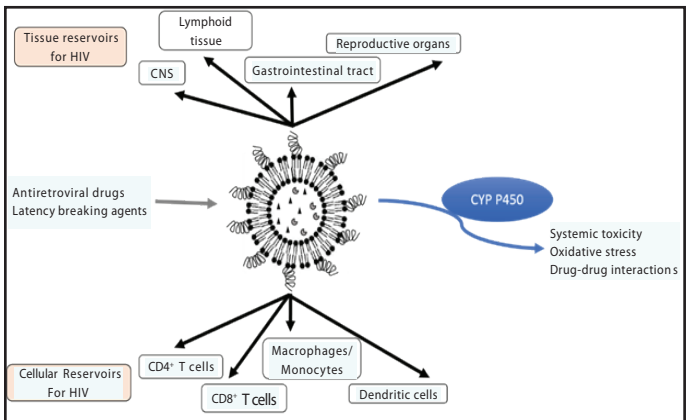

Figure 1. Schematic representation of nanoparticles to deliver antiretroviral drugs to HIV reservoirs and their possible interaction with CYP enzymes. Surface-modified nanoparticles that are loaded with combination drugs can localize to specialized anatomical and cellular structures. As CYPs are the key enzymes for detoxification and clearance of exogenous compounds, nanoparticles may induce or inhibit CYP enzymes. This nano-CYP interaction will result in drug-induced toxicity, oxidative stress as well as DDI due to combinational therapy for HIV treatment.

Nanotechnology for the Treatment of HIV Infection and AIDS

Several nanotechnology-based therapeutics have been investigated towards HIV prevention and control of infection. For instance, nanosuspensions, solid lipid nanoparticles (SLN), liposomes, micelles, dendrimers, polymer and magnetic nanoparticles are some of the approaches that are being tested for this purpose. Several reviews have been compiled in detail to discuss the nanosystems with emphasis on specific aspects of HIV infection. Some of these papers focused on prevention [20,21], drug delivery [14,22], immunotherapy [23], diagnosis [24], nanoformulations [25], target based [26,27], and neuroAIDS [14,28]. Here, we briefly discuss some of the research efforts that exploited nanotechnology to maximize the benefits of ART to curb HIV infection, especially in HIV reservoir compartments and cells.

Brain being the key sanctuary for HIV, several nanocarriers have been studied to improve the penetration of ART into the CNS. Polymer-based nanoparticles, such as poly-butyl cyanoacrylate and polylactide with or without surface modifications, increase ART blood brain barrier (BBB) permeability with limited toxic effects on the brain [29-31]. Further surface modifications of the polymers are encouraged as these carriers are suitable to carry drugs that have ionic properties. In addition, administration of pluronic P85 micelles, amphiphilic molecules that arrange themselves an assembly in aqueous solution, with ART exhibits 30% more reduction in HIV viral load compared to ART treatment alone [32]. Similarly, efavirenz loaded poly(ethylene oxide)-poly(propylene oxide) polymeric micelles administered through intranasal route show four-fold increase in the bioavailability of the drug in the CNS [33]. Liposomes are one of the well investigated drug delivery systems in nanomedicine. As the liposomes are natural targets for mononuclear phagocytic cells and these cells can cross the BBB [34], it is anticipated that liposomes could be a potential system to increase ART delivery to the brain. In support of this rationale, encapsulation of ART into liposomes has shown to increase its availability and half-life in the brain and other organs of rats [35,36]. Recently, solid phase nanoparticles emerged as potential drug delivery system for CNS. In vitro studies using these particles suggested promising results to effectively increase ART concentrations across BBB [37-40]. Although these are very promising nanoART systems for the effective treatment of HIV, further in vitro and in vivo studies are needed to increase the applicability of these systems in HIV treatment. In fact, magnetic nanoparticles are making their way into nanoART realm due to their superior properties over other nanosystems that are being examined for HAART [14,41]. A recent in vitro study using magnetically guided nanocarriers achieved sustained release of anti- HIV drug as well as HIV latency breaking agent, and good trans-migration across the BBB with minimal cytotoxicity [42], suggesting the promising role of these new nano formulations to combat neuroAIDS.

Lymphoid system and associated cells are other well-known viral sanctuaries of the HIV. In fact, these shelters are established during the early course of HIV infection [43,44]. To reduce the viral load in the lymphoid organs, a few studies attempted to increase the transport of ART to these organs using nanoformulations. Liposomal association of antiretroviral agents resulted in a robust increase in the accretion of drug in the lymph nodes compared to free administration of ARTs in rodent as well as primate models [45-47]. Moreover, lipid-associated indinavir dramatically increased the CD4+ cell count with substantial reduction in viral load in HIV-infected macaques [46,48]. In addition, liposomes with modified surfaces for charge and ligands were shown to improve the localization of ART in the lymphatic system [49]. Dendrimers, defined branched nanopolymeric molecules, are also being tested to decrease the viral stores in the lymphoid tissue. Recently, a study successfully designed a dendrimer for targeted drug delivery

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using a dual ligand dendritic system with sialic acid and mannose conjugation to increase the biocompatibility and specificity of tissue distribution of zidovudine [50]. The authors demonstrated that these dendrimers greatly increase zidovudine concentration in lymph nodes with better hemolytic and cytotoxic profiles compared to free drug.

Latently infected cells especially CD4+ T cells, monocytes, and macrophages have the ability to be reactivated upon stimulation, and initiate production of infectious virions [3,51]. Considering the migratory potential of these cells to other anatomical structures such as CNS and their proliferative capability, it is critical to eliminate these cells or at least suppress proviral activation to control the spread of HIV infection. In this respect, nanoparticles are becoming new hopes to attain these objectives. With specific surface modifications, nanoparticles offer a unique advantage for targeted delivery to a particular cell type [52]. Furthermore, the ability to incorporate different agents in a single nano-carrier enhances our chances to fight the disease at different levels. For example, a recent proof of concept study showed that lipid nanoparticles containing latent reactivating agent, bryostatin-2 and a protease inhibitor (PI) nelfinavir, was able to break the latency of CD4+ cells, stimulate HIV replication, and inhibit the spread of infection [53]. Some researchers are also exploiting the intrinsic migratory properties of these immune cells as potential drug delivery vehicles to target specific tissue or cell types [54,55].

Taken together, HIV dissemination from these specialized microenvironments is key for reverberation of the disease even after long-term HAART (Fig. 1). To eradicate or suppress viral burden, it is vital to develop various approaches to maintain therapeutic levels of drugs in these organs. Most of the research that was done in this area is either in vitro or in vivo using small animal models. Nevertheless, it appears that these newly developed nanoART formulations are convenient and effective to achieve high level of ART concentrations with less frequent dosing requirements.

Effect of Nanoparticles on the Cytochrome P450 Enzymes

Currently many nanotechnology based delivery systems and formulations are under investigation to treat HIV infection. Majority of these studies focus on their potential to increase payload, target specificity, and sustained release of the ART. However, limited information is available on how these nanoARTs themselves may inflict risk to the HIV-infected individuals. As CYPs are primary xenobiotic enzymes that metabolize exogenous compounds, understanding the effect of nanoparticles on these enzymes is essential to overcome potential safety issue that may arise during clinical trials.

Existing data on the influence of nanoparticles on CYP induction or inhibition is mainly focused on metallic nanoparticles such as silver and gold. The inhibitory experiments using CYP baculosomes showed that gold nanoparticles are moderate inhibitors of CYP3A4, CYP2C19, CYP2C9, and CYP1A2 isoforms [56,57]. Concurrent with these findings, an in vitro study using cell lines demonstrated that the silver nanoparticles inhibit the metabolism of the drugs/substrates of CYP3A4, CYP2C19, and CYP2C9 enzymes [58]. As CYP3A4, CYP2C19, and CYP2C9 together contribute to the metabolism of more than 60% of available pharmaceutical drugs in the market [17], it is apparent that nanoparticles that interact with these CYPs may cause alterations in ART metabolism and subsequently possible drug-drug interactions (DDI). Among other CYPs tested, the activities of CYP2D6 and CYP2E1 were also moderately affected by the silver nanoparticles [58]. Interestingly, a biodistribution study with a single intravenous injection of gold nanoparticles in rats demonstrated 28-fold upregulation of CYP1A1 and 2-fold increase in the mRNA expression of CYP3, CYP4 and CYP8 family of enzymes after 2 months of the injection [59]. This suggests that even low levels of nanoparticles can cause significant induction of CYP enzymes that may alleviate the cellular toxic effects of these metallic nanoparticles. Moreover, it is worth noting that substantial accumulation of nanoparticles occurred in the liver, and this accumulation significantly altered the signaling pathways of lipid metabolism [59]. This altered lipid metabolism may lead to non-alcoholic fatty liver diseases and inflammation of the liver.

Fish exposed to silver nanoparticles exhibited increased induction and expression of CYP1A enzymes [60,61], suggesting a defense mechanism to counter the toxic or apoptotic effects of nanoparticles. It has been suggested that the induction of CYP1A family of enzymes may be due to free oxygen-radicals generated by nanoparticles in the tissue [60]. In agreement with this data, silver nanoparticles up to 100 µg/ml concentration showed an inhibitory action on CYP1A, CYP2E1, and CYP3A enzymes in rat liver microsomal system [62]. Interestingly, the same study also reported that oral administration of silver nanoparticles to Sprague-Dawley rats for 2 weeks did not show any significant impact on the CYPs at all tested doses. It was suggested that larger size (~180 nm) of the administered nanoparticles and short duration of experimental paradigm could be the potential reasons for no inhibition of CYP enzymes in this study [62].

Inherent characteristics of nanoparticles such as chemical composition, size, shape, and charge, as well as, non-covalent interactions between nanoparticles and biological molecules dictate their effects on the cellular functions [63]. Usually smaller particles provide larger surface area to mass ratio, which is a useful property especially to deliver drugs to specialized anatomical structures like brain [14,64]. However, it is inevitable that these particles will interact with biological components and cause alterations in their functions. In this regard, an in vitro study using microsomes and heterologously-expressed CYP enzymes in baculosomes demonstrated that small carboxyl polystyrene particles inhibits the catalytic activity of CYPs, but not the larger particles (≥ 200 nm) [65]. This inhibitory activity is the strongest for CYP3A4 followed by CYP2C9 and CYP2D6. This effect is consistent with the actions of metallic nanoparticles conferred above. In addition, the authors reported that polystyrene nanoparticles increase the effect of known pharmacological inhibitors of CYPs. Consistent with these findings, a recent in vitro study using different sizes of gold nanoparticles (5 to 100 nm) showed that smaller particles have a greater impact on the activities of CYP enzymes [66]. This study

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also revealed that CYP2C9, CYP2C19, CYP2D6, and CYP3A4 were affected in that order in a dose-dependent manner. Taken together, these studies reveal that even though particle size is a limitation to deliver drugs to certain cellular compartments, smaller particles may induce cellular toxicity by interacting with CYP enzymes.

Several mechanisms were proposed to explain how the nanoparticles interact with CYP enzymes. However, the suggested views are not in accord to clarify the exact mechanism due to lack of extensive characterization of various nanomaterials that are being used in the nanomedicine. These interpretations can broadly be applied to CYPs' structural and functional changes through nanoparticle-CYP interactions. Accordingly, hydrophobic and micelle forming nature of metallic nanoparticles has been proposed to compete with substrate binding site on the CYP enzyme [57]. Yet, based on the above described findings, size of the nanoparticle could be a critical factor to determine whether a nanoparticle reaches the catalytic site of CYP. In addition, nanoparticles can inhibit CYP enzyme activity by binding to CYP enzyme at a site other than catalytic site [58]. CYP enzymes are known to have non-active as well non-substrate recognition sites that influence substrate binding and metabolism [67]. Several rational, semi-rational, and irrational (directed evolution) approaches for CYP engineering have demonstrated numerous non-active site residues that are important for substrate binding and metabolism [68]. Furthermore, X-ray, NMR, and isothermal titration calorimetry (ITC) studies with several CYP enzymes including CYP3A4 have shown that CYP enzymes are very flexible and show ligand-induced conformational changes to adapt a particular substrate in the active site [69]. Thus, it is highly feasible that nanoparticles of relatively smaller sizes interact with CYP non-active sites and change its conformation leading to altered substrate binding and metabolism. Nanoparticle-induced membrane perturbations and interaction with cellular proteins are also believed to be because of the amphiphilic and hydrophobic nature of these particles [65]. A recent study proposed that the impairment of CYP-mediated metabolism may be due to combination effects on enzyme conformation as well as alterations in the co-factor availability [70]. Similarly, Ye et al. thought that gold nanoparticle-induced CYP inhibition may be attributable to adhesion of particles onto enzyme as well as blocking of substrate binding pocket on CYP enzymes [66]. In summary, nanoparticles alter CYPs activities by directly interacting with these isoforms or indirectly by influencing the catalytic processes required for the CYP-mediated metabolic reactions. Nonetheless, it is clear that whether a particular nanoparticle alters CYP activity is greatly dependent on the innate characteristics of nanomaterials.

Implications of CYP Pharmacogenomics in Personalized NanoART

Inter-individual variability in ART response among HIV infected patients, and cellular toxicity as a result of continuous ingestion of antiretroviral agents are significant obstacles in HAART implementation. CYP family predominantly dictates the fate of a drug and associated patient's response to a drug. Single nucleotide polymorphisms (SNPs) in the CYPs especially in CYP1, CYP2 and CYP3 families are the key inherent traits that are responsible for the expression and function of these enzymes in a particular patient [71]. Polymorphism in CYP2B6 was shown to effect efavirenz, a non-nucleoside reverse transcriptase inhibitor (NNRTI), plasma concentration differentially between African-American and Europeans-Americans [72-74]. Furthermore, CYP2B6 genetic variants were also demonstrated to alter the pharmacokinetic parameters and clinical response of other NNRTI, nevirapine [75,76]. It appears that these SNPs did not exhibit significant impact on the efficacy of ART but prolonged drug exposure may have caused adverse drug reactions and generation of drug-resistant virus. Similarly, disposition of protease inhibitors (PIs), such as saquinavir and indinavir, was shown to be influenced by the CYP3A variants [77-79]. These studies indicate that CYP3A allelic differences in HIV infected individuals are associated with the oral clearance of these drugs. However, considering the importance of PIs in the long-term management of HIV-infection and small sample size used for these reports, future studies with large cohorts are necessary to confirm these findings.

As described in previous sections nanomaterials can interact with CYP enzymes and alter their functional attributes. Evidently, most of these alterations may negatively influence the therapeutic efficacy of the drugs. However, these unique biological-nano interactions can be tailored using the knowledge gained from the pharmacogenetics of CYP and extensive characterization of interactions between nanoparticle and biological molecules. Considering the worldwide and chronic use of ART medications in HIV treatment, designing nanoART that are specific for a certain patient population would be advantageous to increase treatment adherence and to reduce drug-induced toxicity. Moreover, the CYP genetic variations can be used to device a specific ART regimen to maintain optimal dose response for different ethnic descendants [80].

Clinical Implications of CYP-nanoparticle Interactions under various Conditions in HIV-infected Populations

The aforementioned literatures clearly suggest an interaction between nanoparticles and several CYP enzymes such as CYP3A4, CYP2E1, CYP2D6, and CYP enzymes from 2C and 1A subfamilies. These enzymes are known to metabolize numerous therapeutic drugs and drugs of abuse [17]. Besides, pharmaceutical drugs and drugs of abuse are known to induce or inhibit these enzymes [18] suggesting a potentially complex DDI between nanoparticles used with ART and other drugs. As presented in figure 2, inhibition of CYPs by these chemical agents decreases CYP enzymatic activity, which results in reduced ART metabolism leading to increased therapeutic efficacy and drug-mediated toxicity. On the other hand, induction of CYP enzymes by these agents is expected to increase CYP activity that would reduce available drug concentration leading to decreased drug efficacy and increased metabolites-induced toxicity in the system.

In addition to interacting with ART drugs such as NNRTIs and PIs, CYP3A4 is highly induced (up to 20-fold) by rifampicin class of drugs, which are commonly used to treat tuberculosis bacillus (TB) infection [81,82]. TB is highly prevalent in HIV-

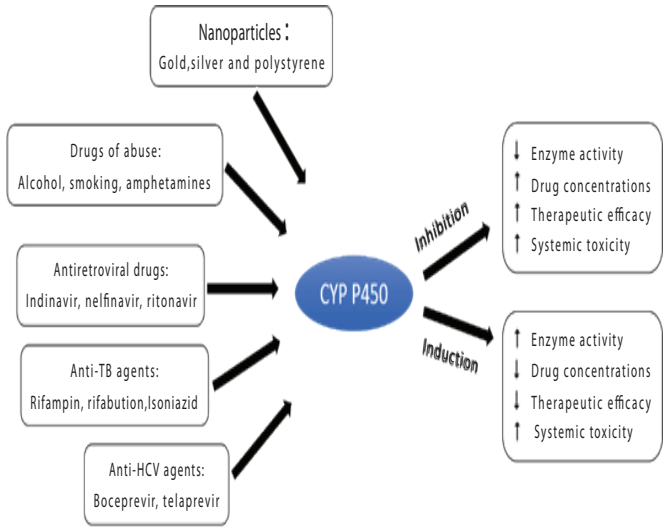

Figure 2. Potential drug-drug interactions (DDI) in HIV positive individuals who has comorbidities like tuberculosis or hepatitis C or use substances of abuse. As most of the drugs that are being used for the treatment of these co-infections and illicit drugs can act as either inhibitors or inducers of CYP isoforms, the use of nanoformulations for ART delivery supplements one more layer of complexity to DDI. Consequently these interactions differentially manipulate the CYP enzymatic activity leading to alterations in therapeutic efficacy and contribute to drug-induced toxicity.

infected populations, especially among children in Sub-Saharan Africa countries [83]. Therefore, it is possible that the induction of CYP3A4 by rifampicin would further alter the interaction between nanoparticles with CYP3A4 leading to potentially complex three-way DDI among nanoparticles, rifampicin, and ART drugs. Similarly, anti-HCV drugs are substrates and inhibitors of CYP3A4 [84], which have a potential to further influence ART bioavailability in the presence of these nanoparticles. Conversely, the bioavailability of these anti-HCV drugs may also be changed in the presence of the nanoparticles used with ART leading to a decrease in anti-HCV drugs and/or an increase in anti-HCV drug-mediated toxicity. It can be noted that the comorbidity of HCV with HIV is very common [85]. CYP3A4 is also involved in the metabolism or activation of various drugs of abuse including constituents of tobacco and marijuana, as well as, cocaine and methamphetamine [86]. Thus, inhibition of CYP3A4 by nanoparticles is expected to decrease the metabolism of tobacco constituents, cocaine, marijuana, and methamphetamine thereby causing increased levels of these substances, which could be associated with increased neurotoxicity. The use of these substances are highly prevalent in HIV-infected populations [87]. For example, smoking is as much as three-times higher in HIV-infected population than the normal population [88].

CYP2E1 is involved in the metabolism of alcohol in chronic and binge drinkers [89]. Alcohol consumption is highly prevalent in HIV-infected population with as much as 3-times higher in these populations than the normal population [90]. Thus, inhibition of CYP2E1 by nanoparticles would decrease the metabolism of alcohol in the HIV-infected alcohol users causing an increase in the plasma alcohol levels. An increase in alcohol plasma levels in HIV-infected individuals may cause toxicity to many organs including the liver and blood cells. Our previous work has demonstrated the presence of CYP2E1 in HIV-infected cells such as monocytes/macrophages and astrocytes [91]. We have further shown that CYP2E1 is involved in alcohol-mediated cytotoxicity in these cells. Thus, nanoparticle-CYP2E1 interaction is expected to increase alcohol-mediated toxicity in these HIV model cells that may ultimately lead to neurotoxicity.

CYP isozymes from the CYP1A family such as CYP1A1 and CYP1A2 are involved in the metabolism or activation of several polyaromatic hydrocarbons (PAHs), which are the major tobacco constituents involved in lung cancer and cellular toxicity. Since nanoparticles have shown to induce CYP1A1 and CYP1A2, it is possible that the induction of these enzymes may further increase activation of these PAHs causing increased carcinogenicity and cellular toxicity. We have earlier shown a relatively high abundance of CYP1A enzymes in monocytes/macrophages [92]. Our unpublished observations have further shown severe toxicity of monocytic cells by a PAH compound benzo(a)pyrene, perhaps through increased CYP-mediated activation of benzo(a)pyrene leading to increased oxidative stress and apoptosis. Thus, further induction of the CYP1A enzymes by nanoparticles used for ART delivery has a potential to cause toxicity in the HIV systems, which may ultimately lead to neurotoxicity.

CYP2D6, which is known to metabolize 15-20% of pharmaceutical drugs, is the most polymorphic CYP enzymes in the humans that vary from 1% to 50% in certain ethnic populations [17]. CYP2D6 alleles in these individuals may either have rapid- or slow-metabolizing CYP2D6 enzymes, which may lead to drug interactions in the presence of metallic or non-metallic nanoparticles. For example, if an individual has a slow-metabolizing CYP2D6 allele and nanoparticles further inhibit these enzymes, the level of CYP2D6 drugs may reach very high and cause drug-mediated toxicity. On the other hand, if an individual has a rapid- or normal-metabolizing CYP2D6 allele and nanoparticles inhibit these enzymes, the level of CYP2D6 drugs may decrease drug metabolism leading a decrease in drug efficacy. Since the drug dose is based on the fact that its level is unaltered by external factors, a change in CYP2D6 level in the presence of the nanoparticles would require a drug-dose adjustments in normal as well as individuals who have CYP2D6 mutant alleles.

Conclusions

In the past few years, the research related to ART drug deliver using a variety of nanoparticles to reduce ART-induced toxicity and to deliver these drugs into various HIV sanctuary sites including the CNS is rapidly increasing. However, several new studies have shown that these nanoparticles may cause toxicity through a variety of mechanisms. One such mechanism could be associated with CYP systems because these enzymes are known to metabolize the majority of marketed drugs including several

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ART drugs, drugs of abuse, and other exogenous compounds. Since nanoparticles used for ART drug delivery have shown to inhibit or induce several CYP isozymes, there is a strong potential for DDI among nanoparticles, ART drugs, and drugs used under various conditions. Considering the comorbidities of TB and HCV among HIV-infected population, nanoparticles-CYP interactions have the potential to alter the bioavailability of the drugs used for TB and HCV treatment. Similarly, high prevalence of drugs of abuse, which are substrates, inhibitors, and/or inducer of CYP enzymes, also have capacity to interact with the ART nanoparticles through CYP pathways. Therefore, understanding the complex interplay between CYPs and nanoparticles, especially in the presence of other drugs, and designing nanoformulations accordingly will certainly improve therapeutic profile and specificity of the HAART and reduce toxicity. Although in its budding stage, CYP pharmacogenomics will be an essential component in the personalized medicine. Combining nanotechnology applications with pharmacogeneitc knowledge will enhance drug safety with reduced side effects and also this interdisciplinary field offers potential to make tailor-made treatments for the populations who have unique genetic predisposition.

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Conflict of Interest

The authors declare no conflict of interest.

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