

# New Antiretroviral Therapies and Potential Drug Interactions in HIV-Infected Drug Abusers

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## Abstract

Substance abuse remains a major obstacle in treating HIV-infected patients. The high prevalence of drug use is responsible for lack of adherence and severe drug interactions to antiretroviral therapy in HIV positive individuals. Over the past decade, newer therapies for HIV have been developed by targeting different stages of HIV life cycle. Of importance, targeting initial binding with receptor and genome integration by CCR5 antagonists and integrase inhibitors, respectively have been effective in reducing viral loads in clinical trials. However, most of these recently approved or investigational antiretroviral drugs are also metabolized by cytochrome P450 (CYP) enzymes. Thus, substance abuse mediated changes in level of CYP enzymes (induction or inhibition) may result in severe drug interactions, failure of therapy, rapid progression to AIDS, and increased mortality in HIV patients who are treated with regimens containing CCR5 antagonists and integrase inhibitors. In this review, we have discussed the pharmacokinetic data, efficacy, lack of adherence to these therapies in drug abusers, and CYP-mediated potential drug interactions for CCR5 antagonists and integrase inhibitors in HIV-infected drug abusers.

## Introduction

The World Health Organization (WHO) surveillance data estimates approximately 35 million HIV-infected people worldwide, 1.3 million of which are in USA [1]. In USA, the rate of new HIV-infected cases is steady at approximately 50,000/year. Importantly, the National Survey on Drug Use and Health (NSDUH) report reveals that ~25% of HIV positive patients are in need of substance abuse treatment [2]. Moreover, a majority (~80%) of the surveyed HIV infected patients report use of illicit drugs, intravenously or non-intravenously, during their lifetime.

Since its introduction in the 1990s, antiretroviral therapy (ART) has been extremely successful in controlling viral loads and improving overall quality of life of HIV positive patients. However, ART also poses several challenges, including drug safety and dosing schedule, especially in populations who use illicit drugs [3,4]. For instance, metabolic problems linked to protease inhibitors (PIs) and skin reactions to non-nucleoside reverse transcriptase inhibitors (NNRTIs) remain longstanding issues with these classes of ART [5]. Therefore, there is an ongoing effort in search of better ART for the past two decades. Over the past decade, new classes of antiretroviral compounds have been discovered by targeting different stages of viral life cycle, which have shown promising results.

HIV entry into host cells involves the binding of viral gp120 protein with host CD4 receptor expressing cells, including lymphocytes and monocytes/macrophages. Subsequent interactions between virus and coreceptors expressed on host cell, CCR5 and/or CXCR4, were identified as a critical step in facilitating fusion and entry of HIV in host cells [6]. Since HIV entry through the interaction with these coreceptors is the first and critical step in HIV replication and disease progression, antagonists for these coreceptors have been developed for HIV treatment [7].

Integration of viral genome into host cell chromatin is an important step for propagation of retroviruses, including HIV. This integration of viral genome is facilitated by viral enzyme integrase. Thus, integrase inhibitors (INIs) have been developed, with the first INI approved in 2007. These INIs inhibit viral replication by binding to the catalytic

domain of integrase enzyme thereby blocking the integration of viral genome.

In this review, we have covered important information from existing literatures related to clinical use, pharmacokinetic profile, and efficacy of these new categories of ART. Since prevalence of drugs abuse is very high in HIV-infected population there are several potential issues, such as lack of adherence to these therapies in drug abusers, drug interactions with substances of abuse, and resistance of these drugs that need to be addressed. Therefore, we have provided our perspectives, especially on non-adherence to medication and potential drug interactions through cytochrome P450 (CYP)-mediated pathways, with HIV-positive patients who consumes alcohol, tobacco, and illicit substances.

## Clinical use of CCR5 Antagonists and Integrase Inhibitors

CCR5 receptor antagonists and INIs are increasingly being used as part of the tool kit of medications for the treatment of HIV. Like all drugs, the individual agents in these classes provide numerous advantages and disadvantages that must be considered when being prescribed.

Several compounds with CCR5 antagonistic properties, including aplaviroc, vicriviroc, maraviroc, cenicriviroc, have been developed and evaluated for their efficacy in HIV-infected patients. While

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further investigations with aplaviroc and vicriviroc were discontinued owing to their severe side effects [8] and below expected activity [9], respectively, CCR5 antagonists maraviroc [10] and cenicriviroc have exhibited promising results in clinical trial.

Currently, CCR5 antagonists are not considered part of the first line of treatment for HIV because only certain subsets of HIV display CCR5 tropism. Therefore, it is essential to test for CCR5 tropism before a regimen with maraviroc can be initiated. In addition, the medication requires twice daily dosing, which is likely to cause an adherence issue [11]. There is, however, considerable evidence that for individuals requiring a switch in medications (due to toxicity with other regimens, poor tolerability with other regimens, or low CD4 counts), maraviroc may be advantageous [12,13]. More recently, there is considerable interest in another CCR5 antagonist, cenicriviroc, which is currently in clinical trials [14,15].

Since introduction, both first generation INIs, raltegravir [16] and elvitegravir [17], and second generation INI, dolutegravir [18], have been clinically identified as potent antiviral therapeutic options for HIV-infected patients. According to the 2014 Health and Human Services (HHS) panel on antiretroviral guidelines for Adults and Adolescents, these three INIs are part of current first line anti-HIV regimens [11]. At present, raltegravir is part of a drug regimen including the NRTIs tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC). Dolutegravir is part of either a regimen with TDF/FTC, as well as part of a regimen including abacavir (ABC) and lamivudine (3TC). Elvitegravir is currently part of a single tablet regimen including TFV/FTC, as well as cobicistat (COBI), a CYP3A inhibitor [11,19]. Currently, COBI is only found in this combination product.

Raltegravir, the first of the INIs, is dosed twice daily. In the STARTMRK trial, raltegravir was compared with efavirenz (EFV). At the earlier time point (48 weeks), treatment with raltegravir was shown to be non-inferior to EFV [20]. However, at 4 years outcomes were better in individuals receiving raltegravir than EFV, due at least in part to a preferable side-effect profile. The SPRING-2 trial compared daily dolutegravir with twice daily raltegravir, with both regimens receiving TFV/FTC or ABC/3TC (depending on physician choice). At 96 weeks, treatment with dolutegravir daily was shown to be non-inferior to raltegravir [21]. Daily, rather than twice daily administration may provide a benefit for a number of patients receiving this regimen. However, this regimen is not available in a co-formulated product. Finally, the GS-US-236-0102 study assessed elvitegravir/COBI/FTC/TDF vs. EFV/FTC/TDF regimen and showed that the elvitegravir product was non-inferior to EFV/FTC/TDF [22]. The decision on which INIs to use for initial therapy is extremely complex and depends on a number of factors. These factors include dosing regimen (raltegravir requires twice daily dosing compared to the other drugs of its class) and CYP-mediated metabolism (discussed in section 5). Furthermore, currently only elvitegravir is part of a single-pill co-formulated regimen, which is advantageous for many individuals.

### CCR5 Antagonists: Efficacy and Pharmacokinetic Data

Maraviroc, FDA-approved in 2007, is an orally active selective CCR5 antagonist developed by Pfizer Inc. [23]. It was first approved for HIV treatment in patients reporting virological failure owing to development of resistance for other antiretroviral medications. Efficacy of maraviroc was confirmed in clinical trials conducted with R5 infected treatment experienced individuals [12]. Maraviroc has an elimination half-life of more than 12 h and is metabolized by CYP3A4.

Resistance to maraviroc, or other CCR5 antagonists can develop

through mutations in HIV attributing to its ability to use CCR5 coreceptor bound to antagonist for entry into host cell or ability to use alternate coreceptors CXCR4 for entry (change in tropism). Mutant viruses, resistant to maraviroc, have been shown to employ inhibitor-bound coreceptor for entry into cell [24]. On the other hand, Van der Ryst et al. have found maraviroc failure in clinical trial to be associated with higher prevalence of change in tropism [25]. Approximately 64% of the patients who did not respond to maraviroc treatment were found to carry R5X4 or X4 strain as opposed to 5% in the placebo group with CXCR4 virus.

Cenicriviroc, the orally active investigational drug, is an antagonist of both CCR5 and CCR2 and is useful in treatment of R5 strain infected patients [26]. Apart from a safe and efficacious drug profile, cenicriviroc has shown promising anti-inflammatory activity in initial studies [14]. In ART experienced HIV positive patients, the mean elimination half-life of daily-once cenicriviroc treatment was found to vary, depending on dose, from 22 to 47 h [15]. Moreover, the potent dose-dependent decrease in viral load persisted over a 40 day follow-up period in treated patients. Cenicriviroc is metabolized by CYP3A4 and CYP2C8. Importantly, PIs were recently reported to boost the bioavailability of cenicriviroc by inhibiting CYP3A4-mediated metabolism of cenicriviroc [27].

### Integrase Inhibitors: Efficacy and Pharmacokinetic Data

A recent review and meta-analysis placed INIs as a preferred drug in treatment-naïve patients and a positive addition to therapy in treatment-experienced individuals [28]. Three distinct advantages have been cited by Blanco et al. for use of INIs in treatment of antiretroviral experienced HIV positive patients—novel mechanism of action, active against HIV strains resistant to other treatments, and viral specific targeting due to lack of integrase enzyme in humans [29].

While raltegravir, FDA approved for both therapy-naïve and experienced patients, is primarily metabolized by uridine glucuronosyl transferase 1A1 (UGT1A1) catalyzed glucuronidation [30], elvitegravir, approved only for therapy-naïve patients, undergoes extensive metabolism by CYP3A4. Based on the reported pharmacological profile of these drugs, potential for drug-drug interactions in HIV-positive patients who are drug abusers exist mainly for elvitegravir and, to a lesser extent, for dolutegravir.

In a controlled study with treatment-experienced patients, single daily elvitegravir dosing was identified as efficacious as twice daily treatment with raltegravir [31]. Although elvitegravir has an elimination half-life of 3 h, co-administration with CYP3A4 inhibitor, such as ritonavir (100 mg), has been demonstrated to increase the elimination half-life to about 9 h [32]. In combination with COBI/FTC/TDF, the elvitegravir containing fixed dose combination tablet, Stribild®, has been reported to be well-tolerated in HIV patients while exhibiting comparable efficacy to other available antiretroviral therapeutic combinations [33,34].

However, a concern with first generation INIs therapy, including ELV, has been the low genetic barrier for resistance and hence therapeutic failure [35]. Two primary mutations, conferring viral resistance to therapy, have been identified in the active site of elvitegravir [36]. Furthermore, these mutations were found to reduce susceptibility towards other INIs suggesting a common mechanism for development of resistance towards first generation INIs. In another study involving limited number of antiretroviral naïve patients from 2007-2013, while

mutations in reverse transcriptase or protease were found in 22% of the cohort, none of the patients were identified carrying major mutations for INIs. This finding suggests limited resistance for INIs compared to other available therapeutic options.

The second generation INIs, dolutegravir, has a favorable pharmacokinetic profile compared to the first generation drugs. Dolutegravir is predominantly metabolized by UGT1A1, while CYP3A4 constitutes the minor metabolic pathway. With an elimination half-life of more than 11h, once-daily treatment with dolutegravir also demonstrated a dose-response efficacy towards attenuation of viral load in HIV patients [37]. Moreover, owing to both the slower dissociation rate from binding pocket of integrase enzyme and its ability to undergo conformational changes in mutated active site of the viral enzyme, dolutegravir has been demonstrated to have a higher threshold for development of viral resistance [38,39].

## New ART: Lack of Response & Potential Drug Interactions in HIV Positive Drug Abusers

### Substance abuse induced non-adherence and lack of response to ART

Several studies have revealed higher prevalence of drug abuse amongst HIV-infected patients compared to general population. An increase in addiction to common drugs of abuse, such as alcohol [40], smoking/tobacco [41], methamphetamine [42], cocaine [43], opioids [44], and marijuana [45], have been reported in HIV-infected patients compared to uninfected population. Importantly, owing to drug dependence, lacks of adherence to ART medication followed by failed virological responses have been reported in these HIV patients. For example, HIV positive alcohol drinkers have been reported to intentionally skip ART medication, and therefore, they are less likely to achieve viral suppression [46]. Similarly, cigarette smoking has been identified as an independent predictor for non-adherence to ART in HIV-infected individuals [47].

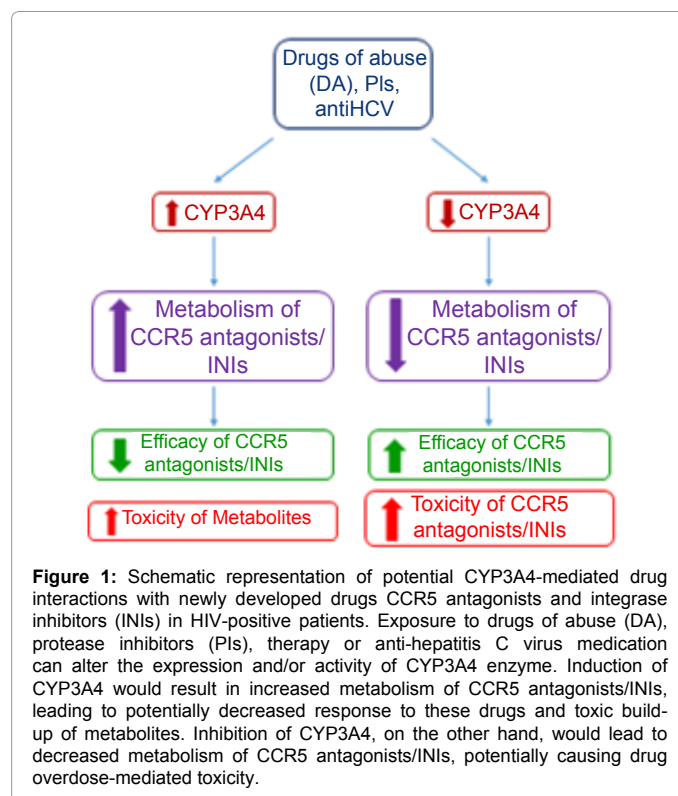
The continued impact of substance abuse on lack of proper adherence to medication in HIV patients is likely to extend to newer classes of ARTs and, therefore, patients are expected to report higher rates of non-adherence to CCR5 antagonists and INIs. Since drug abuse induced non-adherence to medication is linked to higher risks of AIDS and death [48], discontinuation of CCR5 antagonists or INIs in HIV-infected drug abusers may also result in faster progression to AIDS and increased mortality. Importantly, incomplete adherence (adherence rate of 70%-89%) to ART medication is associated with viral rebound and increased chances of clinical drug resistance in HIV patients [49]. Considering the existing propensity of HIV for mutations and development of clinical resistance towards CCR5 antagonists and INIs, there is an additional risk of non-adherence induced development of drug resistance in HIV positive drug abusers. Therefore, clinical interventions for improving adherence are critical for circumventing lack of adherence mediated development of drug resistance and achieving optimal viral responses to CCR5 antagonists and INIs in HIV-positive drug abusers.

### Cytochrome P450 mediated potential drug interactions

Cytochrome P450 (CYP) enzymes are involved in metabolism of various drugs of abuse [50]. In addition, several drugs of abuse have been shown to alter the expression and/or activity of various CYP enzymes by either inducing or inhibiting these enzymes. For example, chronic alcohol exposure has long been known to induce expression

of CYP2E1 and, to some extent, the major drug-metabolic enzyme CYP3A4 [51]. In our previous studies, we have also demonstrated that alcohol induces the expression of CYP2E1 and CYP3A4 in monocytes/macrophages, and this upregulation of CYP2E1 level is associated with increased oxidative stress [52,53]. Furthermore, we have demonstrated alcohol-induced changes in binding of different PIs with CYP3A4 [54,55]. Similarly, we have reported methamphetamine induced changes in the expression of various CYPs in astrocytes [56]. Likewise, literature shows that daily administration of cocaine is associated with induction of hepatic CYP3A4 in rats [57]. In addition to these reports, our group has recently shown significant induction of CYP3A4 in smokers and HIV-infected smokers (unpublished observations). On the other hand, cannabinoids, the major constituent of marijuana, are potent inhibitors of CYP3A4 [58]. Similarly, exposure to  $\beta$ -carbolines, a constituent of cigarette smoke and alcoholic beverages [59], can lead to inhibition of CYP3A4 enzyme [60].

As mentioned in the previous sections, novel antiretroviral drugs including maraviroc, cenicriviroc, elvitegravir, and dolutegravir, also employ metabolic pathways including the CYP3A4 enzyme. Therefore, potential drug-drug interactions and toxicity are likely to exist in HIV-infected drug abusers who are on CCR5 antagonists or INIs therapy (Figure 1 and Table 1). The induction or inhibition of CYP3A4 by drugs of abuse can result in faster or slower metabolism of CCR5 antagonists or INIs therapy. Accelerated metabolism of these medications is likely to result in sub-par efficacy and poor viral responses following treatment. In addition, the excessive accumulation of metabolites of these ART drugs may result in severe toxicity. On the other hand, inhibition of CYP3A4 by the drugs of abuse would result in poor metabolism and enhanced bioavailability of CCR5 antagonists and INIs. Although this may slightly increase efficacy of these drugs, it is expected to cause severe toxicity due to drug overdosing. Overall, decreased response to CCR5 antagonists and INIs and increased



**Figure 1:** Schematic representation of potential CYP3A4-mediated drug interactions with newly developed drugs CCR5 antagonists and integrase inhibitors (INIs) in HIV-positive patients. Exposure to drugs of abuse (DA), protease inhibitors (PIs), therapy or anti-hepatitis C virus medication can alter the expression and/or activity of CYP3A4 enzyme. Induction of CYP3A4 would result in increased metabolism of CCR5 antagonists/INIs, leading to potentially decreased response to these drugs and toxic build-up of metabolites. Inhibition of CYP3A4, on the other hand, would lead to decreased metabolism of CCR5 antagonists/INIs, potentially causing drug overdose-mediated toxicity.



Newer ARTs	CYP involved in metabolism of newer ARTs	Effect of drugs of abuse on CYP expression	Drug-drug interactions
<b>CCR5 antagonists</b>	Maraviroc	<b>Induction of CYP3A4</b> - alcohol, cocaine, tobacco smoking	- Decreased bioavailability of ART - Toxicity from metabolites
	Cenicriviroc		
<b>Integrase Inhibitors</b>	Elvitegravir	<b>Inhibition of CYP3A4</b> -Cannabinoids (marijuana), $\beta$ -carbolines, alcohol	- Increased bioavailability of ART - Toxicity from overdosing
	Dolutegravir		

**Table 1:** Newer ARTs, drugs of abuse, and cytochrome P450-induced potential drug-drug interactions in HIV-infected patients.

toxicity are expected through CYP-mediated drug interactions in HIV positive patients consuming drugs of abuse. Therefore, optimal clinical management of dosage for CCR5 antagonists/INIs and enhanced patient awareness for potential drug interactions and toxicity is needed in HIV-infected drug abusers who are on these newer antiretroviral medications (Table 1).

In addition to single drug (CCR5 antagonists/INIs)-substances of abuse interaction, there is even higher probability of multiple drugs-substance of abuse interactions when CCR5 antagonist/INIs are combined with other antiretroviral drugs. For example, maraviroc is recommended for use with a CYP3A4 inhibitor for enhanced bioavailability and efficacy. Thus combination therapy with various PIs, NNRTIs, and nucleotide/nucleoside reverse transcriptase inhibitors (NRTIs) have been evaluated for effects on pharmacokinetic profile of maraviroc [61]. Based on findings, dose adjustment for maraviroc in the presence of CYP3A4 inducers and/or inhibitors has been suggested in combination therapy. Similarly, cenicriviroc was reported to exhibit elevated levels in the presence of PIs indicating a possible combination therapy in the future [27]. Elvitegravir, relatively newer INIs, is available as a combination of four drugs containing a potent CYP3A4 inhibitor, cobicistat, to enhance the bioavailability of elvitegravir, and is marketed as Stribild®. While combination antiretroviral regimen comprising of CCR5 antagonists and INIs have been effective in controlling viral loads in HIV-infected individuals, the presence of PIs or other CYP3A4 inhibitors as part of combination therapy can complicate drug-drug interactions in HIV positive drug abusers. Therefore, there is a need to optimize drug dose and drug regimens in HIV patients who are on ART combination therapy and also consume drugs of abuse.

The incidence of comorbidity may further complicate treatment with CCR5 antagonists or INIs in HIV positive drug abusers. HIV-infected patients present a weakened immune system and are highly susceptible to co-infections. Co-infection with hepatitis C virus (HCV), for example, is a common occurrence in HIV-infected patients across United States. CDC estimates about one quarter of HIV-infected patients to be co-infected with HCV. As per CDC reports, the rates of HIV and HCV co-infections is as high as 50%-90% in HIV-infected injection drug users. Treatment of HCV with direct-acting antiviral agents (DAAs) like telaprevir and boceprevir, known substrates and inhibitors of CYP3A4, can cause significant interaction with CCR5 antagonists and INIs. The pharmacokinetic profile of the second generation INI, dolutegravir, was significantly affected in the presence of DAAs [62]. Therefore HIV treatments with these new antiretroviral drugs would require dose adjustment when co-administered with DAAs.

## Conclusions

The development of new ART, CCR5 antagonists and INIs, has clearly improved the treatment outcomes of HIV ART-naïve patients as well as patients who have been treated previously using the regimens containing NNRTs/Pis. However, these newer therapy have led to

therapeutic challenges such as development of resistance, reduced adherence to medication, and drug interactions leading to adverse events. Although there is spurious data available on the treatment outcomes with these therapies among drugs of abusers, we speculate potential interactions of these drugs with substances of abuse such as alcohol, tobacco, methamphetamine, cocaine, and marijuana through a common CYP pathway. These interactions would subsequently lead to decreased response to drugs, increased drug toxicity, and decreased adherence to medication in HIV-infected populations who consumes substances of abuse. Further, we speculate potential interactions with other ARTs, as well as drugs that are used for the treatment HCV, common infections among HIV patients. Therefore, there is an urgent need to study the underlying mechanisms of these potential drug interactions to develop a better treatment strategy for HIV patients who consumes substances of abuse.

## Financial & Competing Interest Disclosure

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