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POSSIBLE METABOLIC INTERACTIONS BETWEEN ANTIRETROVIRAL DRUGS AND ANTIDIABETIC DRUGS: AN OVERVIEW

SK. Mastan[1, 3*], G. Chaitanya[2], K. Raghunandan Reddy[2, 3] and K. Eswar Kumar[4]

[1]Department of Pharmacology, Vignan Institute of Pharmaceutical Technology, Duvvada, Gajuwaka, Visakhapatnam-530046, Andhra Pradesh, India

[2] Vikas College of Pharmacy, Jangaon–506 167, Warangal, Andhra Pradesh, India

[3]Department of Pharmacology, Roland Institute of Pharmaceutical Sciences, Ambapua, Berhampur (GM) - 760 010, Orissa, India

[4]Pharmacology Division, University College of Pharmaceutical Sciences, Andhra University, Visakhapatnam – 530 003, Andhra Pradesh, India

Email : shkmastan@gmail.com

ABSTRACT : The availability of potent combination antiretroviral regimens has resulted in a dramatic reduction in HIV-1 associated morbidity and mortality in the developed world. However, HIV infection and treatment has been associated with the development of insulin resistance, glucose intolerance and diabetes. Besides, there can be co-morbid situations of HIV infection and diabetes. Safe pharmacological treatment of these complications requires an understanding of the drug-drug interactions between antiretroviral drugs and the drugs used in the treatment of diabetes. Since formal studies of most of these interactions have not been performed, predictions must be based on our understanding of the metabolism of these agents. All HIV protease inhibitors and non-nucleoside reverse transcriptase inhibitors that have been approved by the Food and Drug Administration (FDA) are metabolized by the cytochrome P-450 enzyme system, primarily by the CYP3A4 isoform and each of these drugs may alter the metabolism of other antiretroviral and concomitantly administered drugs. In addition, protease inhibitors and non-nucleoside reverse transcriptase inhibitors are substrates, inducers and inhibitors of the cytochrome P-450 enzyme system. Sulphonylureas are metabolized by CYP2C9. Gliclazide, nateglinide, pioglitazone, troglitazone involves CYP3A4 metabolism also. Some drugs from each category are having mixed properties on cytochrome P-450 enzyme system. The concomitant administration of these drugs causes potentially significant drug interactions from induction or inhibition. Overall, well-designed drug-drug interaction studies at steady state are needed to determine whether antiretroviral drugs may be safely co-administered with the drugs used in the treatment of the diabetic complications of HIV infection.

Key words: Pharmacokinetics, Antiretroviral agents, Diabetes, Metabolism, Substrate

INTRODUCTION:

One of the most challenging issues facing providers treating with human immunodecificiency virus-1 (HIV) infection is the complex problem of drug interactions associated with highly active antiretroviral therapy (HAART). HAART is a combination of at least three antiretroviral agents, two nucleoside reverse transcriptase inhibitors (NRTIs) plus a third agent, a protease inhibitor (PI), a non-nucleoside reverse transcriptase inhibitor (NNRTI) or possible a third NRTI[1]. Each of individual antiretroviral drugs is associated with significant drug interactions. Further increasing the risk of drug interactions

is the concurrent treatment of co-morbid disease states and therapies for prevention and/or treatment of opportunistic infections. HIV-infected patients often require multiple drug therapy and are thus considered at high risk for drug-drug interactions, which in turn pose challenges to clinicians treating HIV-infected individuals[2].

It is well known that antiretroviral therapy/HAART is associated with an increase in prevalence of insulin resistance, glucose intolerance and diabetes[3-10]. The emergence of these glucose disturbances and diabetic conditions presents a pharmacological challenge because of the possible pharmacokinetic interactions associated with antidiabetic drugs and antiretroviral drugs. There are limited published studies on metabolic interactions between antididabetic medications and antiretroviral agents[11]. This review will focuses on the primary mechanisms of drugs interactions, effect of antiretroviral drugs and antidiabetic drugs on CYP-450 system and discuss about the possible metabolic interactions between antiretroviral drugs and antidiabetic drugs.

Drug interactions can be broadly classified into pharmacokinetic and pharmacodynamic interactions[12]. Pharmacokinetic interactions alter the absorption (A), transport, distribution (D), metabolism (M), or excretion (E) of a drug[13]. Pharmacodynamic interactions alter the pharmacologic response to a drug. The response can be additive, synergistic, or antagonistic. Pharmacodynamic interactions do not always modify a drug's concentration in tissue fluids. The clinical importance of any drug interaction depends on factors that are drug-, patient- and administration-related[14]. Less pronounced pharmacokinetic interactions may still be clinically important for drugs with a steep concentration response relationship or narrow therapeutic index, such as warfarin or digoxin. Antihyperglycaemic agents acting through the release of insulin (sulphonylureas, meglitinide derivatives) are considered to have a narrow therapeutic index because they have a higher risk of hypoglycaemia[15].

The vast majority of drug interactions encountered in HIV medicine are pharmacokinetic in nature and occur as a result of change in ADME of either the HIV drug itself or the concurrently administered medication[2]. They may involve alterations in drug metabolism mediated by the CYP-450 system, modulation of p-glycoprotein (a cellular transport protein), changes in renal elimination, changes in gastric pH and drug absorption, and fluctuations in intracellular drug concentrations. These processes may take place at various sites in the body[2].

CYTOCHROME P450 (CYP450) ENZYMES

CYP450 enzymes play a central role in the biotransformation of a great number of drugs. Among the several CYP enzyme families, the first three, CYP1, CYP2 and CYP3 are involved in human drug metabolism[16]. Drugs can be classified as cytochrome P-450 substrates, inhibitors, or inducers. However, some drugs may have properties of all the three. Substrates are drugs metabolized through this enzyme system, and the plasma concentrations of such drugs may be increased or decreased by other drugs.

Drugs that inhibit CYP450 enzymes generally lead to decreased metabolism of other drugs metabolized by the same enzyme. The decreased metabolism can result in higher drug levels and increased potential for toxicity. The mechanisms of CYP inhibition can be roughly divided in to 2 groups: reversible inhibition and irreversible inhibition, with the former being probably the more common mechanism[17].

Reversible inhibition can be divided, on a kinetic basis, in to competitive, noncompetitive and uncompetitive inhibition. Reversible inhibition can be divided, on a kinetic basis, into competitive, noncompetitive, and uncompetitive inhibition. In competitive inhibition, the inhibitor competes with the substrate for the same binding site within a CYP enzyme. In noncompetitive inhibition, the inhibitor binds to the same enzyme as does the substrate, but the binding site differs. In uncompetitive inhibition, the inhibitor binds only to an enzyme that forms a complex with the substrate[18].

Induction of the CYP450 system results in the increased clearance of concomitant medications metabolized by the same enzyme. The induction of CYP enzymes can be caused by at least 5 different mechanisms. 1) Stabilizing the enzyme protein[19] 2) mediated by aryl hydrocarbon receptor **(**AhR) 3) mediated by constitutive androstane receptor (CAR) 4) mediated by pregnane X receptor (PXR) 5) mediated by the peroxisome proliferator-activated receptor (PPAR) [19].

All HIV protease inhibitors and non-nucleoside reverse transcriptase inhibitors that have been approved by the Food and Drug Administration (FDA) are metabolized by the cytochrome P-450 enzyme system, primarily by the CYP3A4 isoform and each of these drugs may alter the metabolism of other antiretroviral and concomitantly administered drugs[20].

EFFECT OF ANTIRETROVIRAL DRUGS ON DRUG-METABOLIZING ENZYMES

Both PIs and NNRTIs are liphophilic drugs with affinity for the haem-containing mono-oxygenases known as CYP-450[21-23]. These lipophilic drugs are either metabolized by these isoforms to make them more water soluble for eventual elimination, or simply inhibit or induce these enzymes without being a substrate for metabolism. Of all the CYPs involved in drug metabolism, CYP3A4 is the most prominent[24].

Nucleoside reverse transcriptase inhibitors (NRTIS)

NRTIs are prodrugs that require intracellular metabolism for activity. Because NRTIs are primarily eliminated by the kidneys, they do not interact with other drugs through the cytochrome P-450 system[2, 11].

Non-nucleoside reverse transcriptase inhibitors (NNRTIS)

Delavirdine undergoes extensive N-dealkylation via oxidative metabolism; with the primary circulate metabolite being N-desisopropyl-delavirdine[25]. Delavirdine is a substrate for CYP3A4 and a potent inhibitor of CYP3A4, CYP2C9 and CYP2C19[26]. The ability of delavirdine to inhibit CYP3A4 has been shown to be mechanism based[27]. Because of its effect on CYP3A4, concurrent administration of drugs metabolized by the same isoenzyme is likely to cause increased drug levels and potential drug toxicity.

The primary routes of nevirapine biotransformation and elimination include CYP metabolism, glucuronide conjugation and urinary excretion of the glucuronide metabolite. Studies using human liver microsomes have shown that nevirapine is primarily metabolized by the CYP3A4 and CYP2B6 isozymes and a substrate[22]. Nevirapine induces both CYP3A4 and CYP2B6 metabolism, and does not appear to be an inhibitor of the CYP system[28]. Drugs that are metabolized through these isozymes result in potentially significant drug interactions from induction. Since nevirapine is metabolized by and is an inducer of the CYP3A4 isozyme, auto-induction of its own metabolism has been demonstrated. Therefore, nevirapine is usually initiated at a dosage of 200 mg once daily, and increased to 200 mg twice daily after 2 weeks of treatment.

Efavirenz is converted to inactive metabolites by the CYP system, primarily by CYP3A4 and CYP2B6. The oxidative metabolites are then excreted in bile and urine, with <1% appearing as unchanged drug in the urine. It has a long half life, ranging from 52-76 h following single oral doses, and 40-55 h following long term administration as a result of autoinduction of efavirenz metabolism[23]. The long plasma half life allows for once daily administration with long term administration of a single 600 mg daily dose. Efavirenz is an inhibitor of CYP3A4, CYP2C9 and CYP2C19 *in vitro*. The effect on CYP3A4 appears to be mixed, however, as efavirenz has also shown to be an inducer of this isozyme[29]. Efavirenz is a substrate for CYP3A4 and CYP2B6[29]. In addition, efavirenz inhibits CYP2C19[29, 30].

In vitro experiments with human liver microsomes (HLMs) indicate that etravirine primarily undergoes metabolism by CYP3A4, CYP2C9, and CYP2C19 enzymes. Etravirine is a substrate of CYP3A4, CYP2C9, and CYP2C19. Etravirine is an inducer of CYP3A4 and inhibitor of CYP2C9 and CYP2C19. Therefore, co-administration of drugs that are substrates of CYP3A4, CYP2C9 and CYP2C19 with Etravirine may alter the therapeutic effect or adverse reaction profile of the co-administered drugs[31].

Protease inhibitors (PIs)

Evidence suggests that PIs are metabolized by the CYP-450 enzymes present in the liver and the gut wall[32]. The degree to which gut wall metabolism influences the oral bioavailability of PIs is difficult to quantify. In humans the liver: intestinal CYP ratio has been reported as approximately twenty[33]. This suggests that the contribution of gut wall metabolism may not be of great importance for PIs.

Drug interactions are important considerations with the use of PIs. *In vitro* evidence suggests that the most influential isozyme involved in the metabolism of the PIs is CYP3A, with the isoforms CYP2C9 and CYP2D6 also contributing[34]. PIs are substrates for the CYP-450 system (primarily CYP3A4) and are themselves, to varying degrees, inhibitors of this system. Some PIs, such as lopinavir and tipranavir are also inducers of CYP3A4[35]. This leads to a significant number of interactions with drugs that are inducers, inhibitors or substrates of this system.

The HIV PIs are organic bases with high affinity for CYP3A4. All the clinically used PIs inhibit CYP3A4 to varying degree[36]. Ritonavir is by far the most potent inhibitor of this CYP isoform, followed by indinavir, nelfinavir, amprenavir and saquinavir in decreasing order of potency[36, 37].

In addition to inhibiting CYP3A4, ritonavir and nelfinavir also induce CYP3A4 to induce their own metabolism, but because they are attracted to this enzyme with such high affinity the overriding effect in terms of other drugs is inhibition. Both ritonavir and nelfinavir induce other CYP450 isoforms (CYP2C9, 2C19, 1A2 and 2E1) as well as conjugative enzymes, UDP-glucuronosyltransferases, for which they have very low affinity[38, 39]. Thus ritonavir and nelfinavir have the ability to induce the metabolism of drugs that are metabolized by these enzymes. The pan-inductive effect of ritonavir is much more firmly established than that of nelfinavir[40]. CYP2D6 plays a minor role in the metabolism of ritonavir[41]. Atazanavir is metabolized by cytochrome P450 pathway. It is an inhibitor and a substrate of the enzyme, therefore major drug-drug interactions are expected.

Tipranavir induces CYP3A4 and P-glycoprotein. Tipranavir also inhibits CYP1A2, 2C9, 2C19 and 2D6[42]. Lopinavir, tipranavir and darunavir require co-administration with ritonavir to achieve effective serum concentrations. All currently licensed PIs are commonly prescribed as boosted agents with the exception of nelfinavir, which is not well and reliably augmented by ritonavir[43].

The combination of lopinavir and ritonavir is likely to have interactions that are similar to those of full-dose ritonavir alone, but the magnitude of the interactions may be smaller[44].

EFFECT OF ANTIDIABETIC DRUGS ON DRUG-METABOLIZING ENZYMES

Sulphonylureas

Drug-drug interactions were initially and commonly assumed to be due to the displacement of the sulphonylurea from plasma proteins by the co-administered drug[45, 46]. However, based on pharmacokinetic models of tolbutamide interactions, displacement from plasma proteins should have a small and only transient effect, if any, on insulin release from the pancreas. With further analysis and clinical studies, many of the drug interactions originally ascribed to changes in plasma protein binding are considered to result from inhibition of the enzymes responsible for metabolic clearance of the sulphonylurea compound. Indeed, most sulphonylurea drugs are extensively metabolized, increasing the potential for metabolism-based, drug-drug interactions.

The effects of the CYP2C9 amino acid polymorphisms may be important for drug treatment with tolbutamide[47]. In a study performed in healthy volunteers, tolbutamide was confirmed as a substrate of the genetically polymorphic enzyme CYP2C9[48]. Glimepiride is a substrate of CYP2C9, and the importance of this metabolic pathway has been confirmed *in vivo* by comparing glimepiride pharmacokinetics in subjects with different CYP2C9 genotypes. Other sulphonylurea drugs also mainly utilize CYP2C9 for metabolism[49]. CYP2C9 may be induced by HIV protease inhibitors, such as ritonavir and nelfinavir, with a resulting decrease in the antihyperglycaemic efficacy of the sulphonyurea[11]. There are limited studies that have examined the interaction between antiretroviral drugs and sulfonylurea compounds. Most of the first-generation and second-generation sulfonylurea compounds are hepatically metabolized by CYP2C9[50].

Gliclazide is extensively metabolized, mainly by hydroxylation in the liver, and has no circulating active metabolite[51]. Among all the sulphonylureas, gliclazide metabolism is special and complex to predict the drug-drug interactions as it is metabolized by CYP2C9 and CYP3A4[52]. Physicians should consider this potential interaction in the management of HIV-infected patients in whom highly active antiretroviral therapy frequently triggers diabetes[11].

Biguanides

Three drugs (metformin, phenformin and buformin) were initially marketed, but only metformin is still available since the withdrawal of phenformin and buformin because of an exaggerated risk of lactic acidosis, especially in diabetic patients with renal impairment. Metformin is not metabolized in humans after oral or intravenous administration. No oxidative or conjugated metabolites of metformin have been observed in the plasma, urine or faeces. The drug is eliminated by renal excretion by way of active tubular secretion. Although many medications have been reported to interact with metformin, there are relatively few clinically important interactions[53]. This is largely because metformin is not protein bound and is not metabolized in the liver, making drug interactions with antiretroviral drugs through pharmacokinetic mechanisms rare.

Meglitinides

Repaglinide, a meglitinide class of antidiabetic agent with similar mechanism of action as sulfonylureas, is metabolized differently from the sulfonylureas[54, 55]. This drug uses CYP3A4 for oxidative metabolism, and therefore all the HIV PIs can potentially inhibit the metabolism of this drug, resulting in excessive response. Repaglinide is extensively metabolized by direct oxidation and glucuronidation. The metabolites are not pharmacologically active. An important role for both CYP3A4 and CYP2C8 in the transformation of repaglinide has been reported in studies of human liver microsomes[56]. The contribution of CYP2C8 to the metabolism of repaglinide was further demonstrated by *in vivo* by showing that polymorphism that in CYP2C8 was associated with reduced plasma concentrations of repaglinide[57]. This dual CYP biotransformation may have consequences for the clinical pharmacokinetics and drug-drug interactions of repaglinide.

According to *in vitro* data obtained using human liver microsomes, CYP enzymes CYP2C9, CYP2D6 and CYP3A4 appear to mediate nateglinide biotransformation reactions and CYP2C9 appears to be the predominant enzyme (responsible for about 70% of nateglinide intrinsic clearance)[58, 59]. The effect of CYP2C9 polymorphisms on nateglinide kinetics may cause a slightly increased risk of hypoglycaemia in diabetic patients. Consequently, drug interactions with substrates of CYP3A4 and CYP2C9 might be anticipated for nateglinide.

Thiazolidinediones

Thiazolidinediones have been associated with significant metabolic interactions with antiretroviral drugs. Troglitazone has been associated with significant clinical drug interactions due to liver enzyme induction, particularly when used with compounds that are substrates for CYP3A4[60]. An *in vitro* study showed that all three thiazolidinediones (troglitazone, pioglitazone and rosiglitazone) have the potential to induce CYP3A4[61]. The *in vitro* inhibition data indicate that, in general, troglitazone is the most potent CYP inhibitor of the three compounds. As already mentioned, there are no reports on the clinical

induction of CYP enzymes by rosiglitazone or pioglitazone to date. It is the last of these scenarios that requires additional research in order to better use *in vitro* inhibition data to predict potential drug-drug interactions of these and future thiazolidinediones[61].

Pioglitazone undergoes extensive hepatic metabolism, predominantly via the CYP2C8 system. Secondary pathways include CYP3A4, CYP2C9 and CYP1A1/2[62]. Although pioglitazone is partially metabolized via CYP3A4[62], no evidence exists *in vivo* that pioglitazone induces hepatic CYP3A4 activity[63].

CYP2C8 is primarily responsible for the hydroxylation and N-demethylation of rosiglitazone in human liver, with minor contributions from CYP2C9[64]. Therefore, rosiglitazone pharmacokinetics may be affected by CYP2C9 inducers. Rosiglitazone does not markedly alter CYP3A4 mediated drug metabolism[65]. Rosiglitazone is primarily metabolized by CYP2C8 and has shown no clinically significant interactions with CYP3A4 metabolized substrates[66, 67].

CONCLUSIONS

With the increasing recognition of metabolic complications associated with HIV infection and/or antiretroviral therapy, understanding drug-drug interactions between antiretroviral drugs and drugs used in the treatment of diabetes becomes critical. So far only a few drug-drug interaction studies have been performed to guide concomitant therapy. Sulphonylureas and repaglinide require pharmacokinetic studies with PIs and NNRTIs before these drugs can be used concomitantly with confidence. Among the sulphonylureas, gliclazide metabolic pathway is associated with complex drug-drug interactions with PIs and NNRTIs, which needs to be explored to guide concomitant therapy. In addition, drug-drug interaction studies with pioglitazone and PIs are necessary to assure the safety and efficacy of these drug combinations.

Since concomitant use of antiretroviral drugs and drugs used in the treatment of the diabetes is increasing, only well-performed drug-drug interaction studies under steady state conditions for all drugs involved will give us definitive answers in terms of safety and efficacy of concomitant therapy.

Clinicians should be diligent in educating themselves about pharmacokinetics, especially metabolism of antiretroviral drugs and antidiabetic drugs to help to recognize potential medications that may be problematic. As therapy for HIV changes very rapidly, clinicians may utilize internet resources to help screen for potential drug interactions and to identify new treatment options and issues surrounding HIV infection. With such interventions, toxicity or adverse events associated with drug interactions may be prevented.

Table 1. Examples of substrates, inhibitors and inducers of CYP enzymes and P-glycoprotein

Substrates			
CYP3A4	**CYP2C9**	**CYP2C19**	**P-glycoprotein**
Protease inhibitors, non-nucleoside reverse transcriptase inhibitors, repaglinide and maraviroc	Etravirine, glibenclamide, glimepiride, glipizide and tolbutamide	Etravirine and nelfinavir	Glibenclamide, indinavir, nelfinavir saquinavir and maraviroc
Inhibitors			
CYP3A4	**CYP2C9**	**CYP2C19**	**P-glycoprotein**
Protease inhibitors (except tipranavir and lopinavir), efavirenz (minor) and delavirdine	Delavirdine, efavirenz (*in vitro*), etravirine, atazanavir and tipranavir	Efavirenz, delavirdine, etravirine, ritonavir and tipranavir	Glibenclamide and ritonavir
Inducers			
CYP3A4	**CYP2C9**	**CYP2C19**	**P-glycoprotein**
Nevirapine, efavirenz, etravirine, lopinavir, tipranavir, ritonavir (minor), nelfinavir (minor), troglitazone, pioglitazone (*in vitro*) and rosiglitazone (*in vitro*)	Ritonavir and nelfinavir	Ritonavir and nelfinavir	Tipranavir

Table 2. Routes of elimination/metabolism of antiretroviral drugs

Antiretroviral drug(s)	**Elimination/Metabolism**
Zidovudine	Hepatic metabolism with renal excretion
Didanosine	Renal excretion, 50%
Zalcitabine	Renal excretion, 70%
Stavudine	Renal excretion, 50%
Lamivudine	Renal excretion, 70%
Abacavir sulfate	Hepatic, insignificant effect on CYP 450 system
Tenofovir disoproxil fumarate	Renal excretion, 70-80%
Emtricitabine	Renal excretion, 86%
Nevirapine	Hepatic via CYP3A4, 2B6
Delavirdine	Hepatic via CYP3A4, 2D6, 2C9 and 2C19
Efavirenz	Hepatic via CYP3A4, 2B6
Etravirine	Hepatic via CYP3A4, CYP2C9 and CYP2C19
Saquinavir mesylate, indinavir, amprenavir, fosamprenavir, tipranavir and darunavir	Hepatic via CYP3A4
Ritonavir	Hepatic via CYP3A4 and 2D6
Nelfinavir mesylate	Hepatic via CYP2C19 and CYP3A4
Lopinavir and ritonavir	Hepatic via CYP3A4
Atazanavir sulfate	Hepatic via multiple path ways of CYP3A4

Table 3. Metabolic characteristics of oral antidiabetic drugs

Drug	**Metabolism**	**Metabolic enzyme(s)**
Tolbutamide	Hepatic hydroxylation and caboxylation	CYP2C9
Chlorpropamide	Hepatic hydroxylation or side chain change	CYP2C9
Tolazamide	Hepatic carboxylation and hydroxylation	CYP2C9
Acetohexamide	Hepatic hydroxylation	CYP2C9
Gliclazide	Hepatic hydroxylation	Mainly CYP2C9, partially CYP3A4
Glibenclamide	Hepatic hydroxylation	CYP2C9
Glipizide	Hepatic hydroxylation	CYP2C9
Nateglinide	Hydroxylation followed by glucuronide conjugation	Mainly CYP2C9, Partially CYP3A4
Repaglinide	Oxidative biotransformation and direct conjugation with glucuronic acid	CYP3A4
Pioglitazone	Hydroxylation and oxidation	Mainly CYP2C8, Partially CYP3A4
Rosiglitazone	N-demethylation and hydroxylation, followed by conjugation with sulfate and glucuronic acid	Mainly CYP2C8, Partially CYP2C9
Troglitazone	Conjugation with sulfate and glucuronic acid	CYP3A4

Table 4. Potential effects of antiretroviral drugs on the metabolism of sulfonylureas [11]

Antidiabetic drug	Ritonavir	Nelfinavir	Other PIs	Nevirapine	Efavirenz	Delavirdine
Tolbutamide	Possible induction	Possible induction	No effect	No effect	No effect	Probable inhibition of metabolism
Glibenclamide	Possible induction	Possible induction	No effect	No effect	No effect	Probable inhibition of metabolism
Glipizide	Possible induction	Possible induction	No effect	No effect	No effect	Probable inhibition of metabolism
Glimepiride	Possible induction	Possible induction	No effect	No effect	No effect	Probable inhibition of metabolism

PIs: Protease inhibitors

Table 5. Potential effects of antiretroviral drugs on the metabolism of meglitinides and thiazolidinediones [11]

Antidiabetic drug	Ritonavir	Nelfinavir	Other PIs	Nevirapine	Efavirenz	Delavirdine
Repaglinide	Probable inhibition of metabolism	Probable inhibition of metabolism	Probable inhibition of metabolism	Probable induction of metabolism	Possible induction of metabolism	Probable inhibition of metabolism
Troglitazone*	Probable induction Of Protease Inhibitor metabolism	Probable induction of Protease Inhibitor metabolism	Probable induction of Protease Inhibitor metabolism	Cannot determine	Cannot determine	Probable induction of delavirdine metabolism
Pioglitazone*	Possible inhibition Possible induction of protease inhibitor metabolism	Possible inhibition Possible induction of protease inhibitor metabolism	Possible inhibition Possible induction of protease inhibitor metabolism	Cannot determine	Cannot determine	Possible of inhibition Possible induction of delavirdine metabolism

*The comments are related to the effect of antiretrovirals on antidiabetic drugs. If there a potential for an effect of antidiabetic drugs on antiretrovirals, those will be specifically indicated. PIs: Protease inhibitors

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