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Original Research

Antiretrovirals and frequently prescribed medications in people living with HIV: Potential drug-drug interactions detected by three online-databases

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Abstract

Background: Since the advent of antiretroviral therapy, HIV infection, which was once considered a life-threatening condition, can now be managed as a chronic disease. People infected with HIV have high prevalence rates of comorbid illnesses, including cardiovascular diseases, cancers, diabetes, dyslipidemia, chronic renal disease, and chronic liver disease. Comedication of antiretrovirals and frequently prescribed medications for comorbid illness could cause serious drug-drug interactions (DDIs). Objective: To evaluate the level of agreement among the drug interaction tools of three databases (Micromedex, Drugs.com, and Liverpool HIV Drug Interactions Checker) for potential DDIs detection. Methods: Drugs were selected from National List of Essential Medicines of Thailand (2021) and the Ramadhibodi Chakri Naruebodindra Hospital drug list. Potential DDIs were identified by the three databases. The agreement was determined by Fleiss' kappa. Results: Seventeen antiretrovirals and 77 frequently prescribed medications from the National List of Essential Medicines of Thailand (2021) and the Ramadhibodi Chakri Naruebodindra Hospital drug list were included in this study. Overall, 383 pairs of potential DDIs were detected by the three databases. Drugs.com reported the highest number of DDIs (302 pairs), followed by the Liverpool (222 pairs) and Micromedex (160 pairs) databases. Among these DDIs, 113 pairs (29.5%) were reported as contraindicated or major severity in all three databases. The major DDI mechanisms were pharmacokinetic-based cytochrome P450 inhibition (33.4%) and induction (20.1%). Fleiss' kappa agreements were slightly concordant among the three databases (0.0476). Conclusions: Healthcare provider vigilance is important to manage the potentially varying DDI information in different databases that could impact the safety and efficacy of HIV treatment.

Keywords: drug interactions; antiretrovirals; metabolic syndrome; micromedex; drugs.com, liverpool HIV drug interactions checker

INTRODUCTION

HIV infection is no longer a life-threatening condition, but rather a chronic disease that is manageable with antiretrovirals (ARVs). As a result, the Joint United Nations Programme on AIDS/HIV reports that AIDS-related deaths have decreased by 50% since 2010.[1] However, HIV patients are required to take multiple long-term medications to control the viral load. Thailand's national guidelines suggest a triple therapy regimen of 2 nucleoside reverse transcriptase inhibitors (NRTIs) and 1 integrase strand transfer inhibitor (INSTI) or non-nucleoside reverse transcriptase inhibitor (NNRTI). The most common combinations are tenofovir alafenamide (TAF) or tenofovir disoproxil fumarate (TDF), with emtricitabine or lamivudine and dolutegravir.[2] These combinations allow for good viral load suppression with limited adverse effects, enabling long-term medication.

Despite the positive results, many potential consequences of long-term use of certain antiretrovirals, such as alterations of lipid and glucose metabolism, and increased cardiovascular risk, even without host-related risk factors, exist. First, HIV infection may cause altered gene expression in adipose tissue, resulting in lipodystrophy, and may be associated with increased apolipoprotein levels, increased synthesis of very-low-density lipoprotein cholesterol by the liver, and decreased triglyceride clearance. Additionally, *in vitro* studies showed that the use of combinations of ARVs, protease inhibitors (PIs), and NRTIs increased proinflammatory cytokines and led to alterations of adipose functions and dyslipidemia.[3] Furthermore, evidence shows that PIs can increase serum triglyceride, serum cholesterol, and circulating free fatty acid, resulting in hyperlipidemia, increased fat deposition, lipodystrophy,

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and atherosclerosis.[4] Among the PIs, ritonavir has the most severe hyperlipidemic effect in mice.[5] In addition to abnormal lipid metabolism, ongoing inflammation in HIV patients leads to an imbalance in lipid levels and atherosclerosis.[6,7] Second, HIV-infected people have a higher risk of insulin resistance due to the use of ARVs, with the combination of PIs and NRTI altering both lipid and glucose metabolism. Alterations of adipose functions and decreased adiponectin, a hormone released from adipose tissue, lead to insulin insensitivity and diabetes mellitus (DM).[3,8] Furthermore, PIs can promote hepatic gluconeogenesis, debilitate insulin secretion from the pancreas, and reduce glucose uptake in muscle and adipose tissue, which also lead to DM.[9] These findings indicate that people living with HIV, with or without ARVs, have increased risks of metabolic syndrome and cardiovascular disease.[9]

Despite the increased risks, the benefits of ARVs still outweigh their adverse effects.[10] Consequently, ARVs are still being used with add-on cardiovascular medications. Additionally, a study showed that HIV patients receiving NRTI ARVs had a higher risk of peripheral neuropathy, which could only be treated symptomatically.[11] However, it is not only HIV infection itself that can cause peripheral neuropathy; complications from the use of ARVs, such as dyslipidemia and prediabetes, are additional risks of coprescribing peripheral neuropathy medications with ARVs.[12] The relatively longer life expectancy of individuals infected with HIV has also increased the incidence of many age-related comorbidities, such as osteoporosis and insomnia. People with HIV have higher bone fragility, higher risk of bone fracture in 10 years, and higher risk of other coinfections compared with the general population, according to a recent meta-analysis.[13] Bone loss results from increased osteoclast activity due to inflammation during HIV viral replication and ARV initiation, in which there is a reconstitution of the immune system. Therefore, prescription of anti-osteoporotic drugs might be a good option during ARV initiation. Conversely, some NRTIs, such as TDF, also affect bone mineral density and should be avoided in patients with osteoporosis.[14] Insomnia, an age-related disease in people living with HIV, has an immense impact on quality of life due to difficulties in sleep initiation and efficiency, which need to be treated with benzodiazepines or non-benzodiazepines.[15-17] Furthermore, people infected with HIV have an increased risk of hepatitis B virus (HBV) and/or hepatitis C virus (HCV) coinfections, which are also transmitted sexually, vertically, or through blood. Such individuals should be treated simultaneously for these coinfections.[18] In summary, the long-term use of ARVs, together with medications for metabolic syndrome and other chronic diseases, leads to a potential increase in the incidence of drug-drug interactions (DDIs), which could lead to adverse drug reactions and ultimately failure to control the disease.[19]

Currently, many tools are used to detect potential DDIs. The most used online database among healthcare providers in 2022 is Micromedex, a copyright-protected database of IBM Corporation (USA). Drugs.com is the most popular free-access online database among patients and nonsubscribers to paid databases. However, the drug interaction tools of these two databases have differences in sensitivity in detecting DDIs.[20] A third potentially useful database for identification of potential DDIs is the Liverpool HIV Drug Interactions Checker, a free-access online database that specializes in HIV drug interactions and is provided by the University of Liverpool in collaboration with Clubzap Ltd. This study aimed to determine the level of agreement in DDI detection among these three online databases and to find the most appropriate information to support healthcare providers and HIV-infected patients. The results of this study may improve drug prescribing in clinical settings by reducing the risk of DDIs for people living with HIV and providing DDI awareness among databases.

METHODS

Drug selection

This study included lists of selected ARVs and frequently prescribed medications from the Thailand National List of Essential Medicines (NLEM) 2021 and the Ramadhibodi Chakri Naruebodindra Hospital drug list (data accessed on 10 September 2022).[21] Seventeen ARVs and 92 medications frequently prescribed in people with HIV were included in the determination of potential DDIs (Supporting information, Table S1). Fifteen items which were not recognized by one or more databases were exclude: Micromedex (gemigliptin and alfacalcidol); Drugs.com (gemigliptin, vildagliptin, gliclazide, menatetrenone, and alfacalcidol); and the Liverpool database (nicotinic acid, chloral hydrate, melatonin, gemigliptin, bromocriptine, calcitonin, menatetrenone, pamidronate, teriparatide, alfacalcidol, ergocalciferol, cilostazol, and eptifibatide). A flow chart of this study is shown in Figure 1.

Databases and documentation of DDIs

The three major databases used in this study were Micromedex, Drugs.com, and the Liverpool HIV Drug Interactions Checker (from 10 September 2022 to 5 December 2022), as previously reported by Vivithanaporn et al.[19] The severity of potential DDIs classification at all three databases was described.[19] The Micromedex and Liverpool databases also classified the level of DDI documentation, whereas Drugs.com did not. Micromedex classified the levels of documentation as excellent, good, fair, and unknown, while the Liverpool database used high, moderate, low, and very low.

Data analysis

Data analysis was conducted using Stata 17.0 (StataCorp LLC, USA). Assessment of agreement among the three databases in the detection of potential DDIs was performed using Fleiss' kappa. The kappa value ranges from 1 to -1. In this study, values ranging from 0.81-1.00 indicate "almost perfect" agreement, 0.61-0.80 indicate "substantial" agreement, 0.41-0.60 indicated "moderate" agreement, 0.21-0.40 indicate "fair" agreement and 0.00-0.20 indicate "slight" agreement. Finally, values less than 0.00 indicate "poor" agreement.[22]

RESULTS

From the 94 agents that were analyzed, 383 pairs of potential

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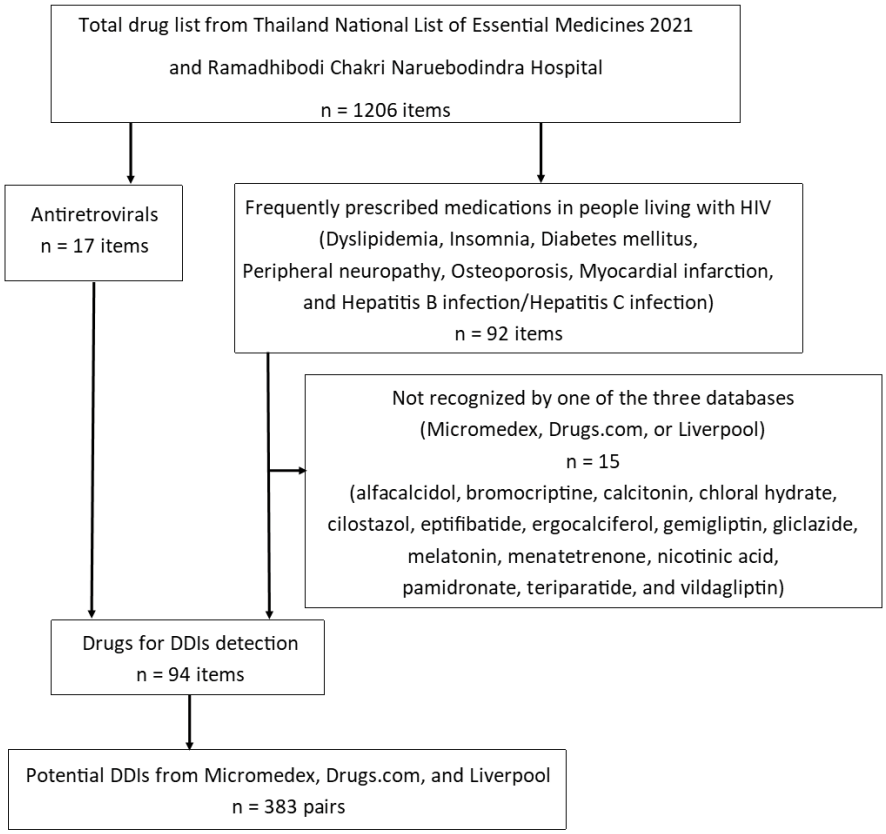

Figure 1. Study flow chart. DDIs = drug-drug interactions

DDIs were detected by the three databases: 160 pairs by Micromedex, 302 by Drugs.com, and 222 by the Liverpool database. The majority of pairs were classified as moderate in severity at Drugs.com (221, 73.2%) and the Liverpool database (138, 62.2%), whereas Micromedex reported major severity for nearly half of the pairs (74, 46.3%) (Figure 2). Micromedex classified the level of documentation of most (60%–70%) reports of severe DDIs as fair, which included the following severity classifications: contraindicated (65.2%), major (70.3%), and moderate (64.5%) (Table 1). The majority of documentation-level classifications by the Liverpool database showed similar tendencies to Micromedex: the largest proportion was classified as very low (45%–96%), comprising severity classifications of do not coadminister (45%), potential interaction (85.6%), and potential weak interaction (96.9%).

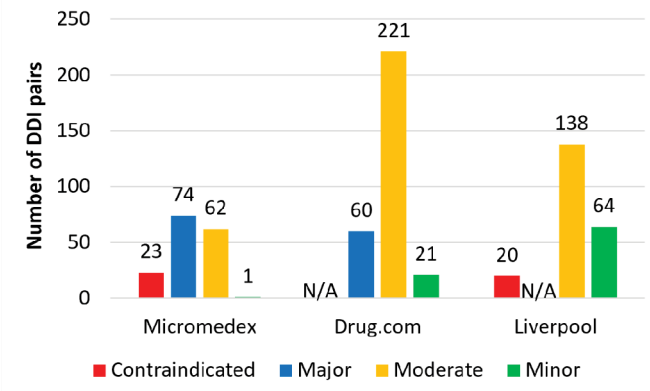

Figure 2. Severity levels of potential drug-drug interactions reported by the Micromedex, Drugs.com, and Liverpool HIV Drug Interactions Checker databases. N/A = not applicable.

Table 1. Documentation level of potential drug-drug interactions categorized by the Micromedex (A) and Liverpool HIV Drug Interactions Checker (B) databases.

(A) Micromedex

Documentation Severity	**Excellent** n (%)	**Good** n (%)	**Fair** n (%)
Contraindicated	6 (26.1%)	2 (8.7%)	15 (65.2%)
Major	17 (23.0%)	5 (6.8%)	52 (70.3%)
Moderate	9 (14.5%)	13 (21.0%)	40 (64.5%)
Minor	0	1 (100%)	0
Total	32 (20.0%)	21 (13.1%)	107 (66.9%)

(B) Liverpool

Documentation Severity	**High** n (%)	**Moderate** n (%)	**Low** n (%)	**Very low** n (%)
Do not coadminister	1 (5.0%)	6 (30.0%)	4 (20.0%)	9 (45.0%)
Potential interaction	5 (3.6%)	7 (5.0%)	8 (5.8%)	119 (85.6%)
Potential weak interaction	0	0	2 (3.1%)	62 (96.9%)
Total	6 (2.7%)	13 (5.8%)	14 (6.3%)	190 (85.2%)

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The major DDI mechanisms were cytochrome P450 (CYP) inhibition (128 pairs, 33.4%), followed by CYP induction (77 pairs, 20.1%), and QT interval prolongation (13 pairs, 5.7%) (Figure 3). However, a quarter of DDIs involved other mechanisms, including additive effect (7 pairs, 1.8%), hyperlactatemia and lactic acidosis (6 pairs, 1.6%), and multidrug resistance protein 2 inhibition (5 pairs, 1.3%).

Surprisingly, 113 (29.5%) of the total 383 DDI pairs were classified as contraindicated or major severity in all three databases. A list of the DDI pairs and mechanisms of serious DDIs among ARVs and frequently prescribed medications in people with HIV are reported in Table 2.

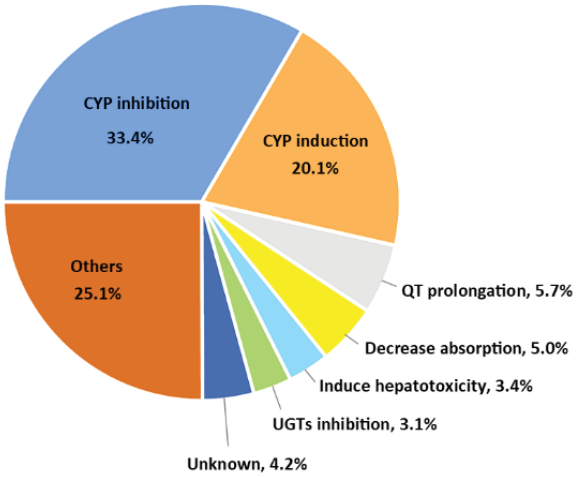

Figure 3. Potential drug-drug interaction mechanisms. CYP = cytochrome P450; UGT = uridine diphosphate glucuronosyltransferase.

Table 2. List of drug-drug interaction (DDI) pairs and mechanisms of serious DDIs among antiretrovirals and frequently prescribed medications in people with HIV.

	DDI Pair	DDI Mechanism(s)
1	Abacavir-Ribavirin	PD: Increase the risk of symptomatic hyperlactatemia and lactic acidosis
2	Atazanavir-Alprazolam	PK: CYP3A4 inhibition by atazanavir
3	Atazanavir-Amitriptyline	PK: CYP3A4 inhibition by atazanavir
4	Atazanavir-Atenolol	PK: CYP3A4 inhibition by atazanavir
5	Atazanavir-Atorvastatin	PK: CYP3A4 inhibition by atazanavir
6	Atazanavir-Bisoprolol	PK: CYP3A4 inhibition by atazanavir
7	Atazanavir-Carbamazepine	PK: CYP3A4 induction and P-glycoprotein induction by carbamazepine
8	Atazanavir-Carvedilol	PK: CYP3A4 inhibition by atazanavir
9	Atazanavir-Clopidogrel	PK: CYP3A4 inhibition by atazanavir and clopidogrel-prodrug and conversion to its active metabolite via CYP3A4
10	Atazanavir-Diltiazem	PK: CYP3A4 inhibition by atazanavir
11	Atazanavir-Fluvastatin	PK: CYP3A4 inhibition by atazanavir
12	Atazanavir-Hydroxyzine	PD: Addition of QT-interval prolongation
13	Atazanavir-Imipramine	PD: Addition of QT-interval prolongation
14	Atazanavir-Metoprolol	PK: CYP3A4 inhibition by atazanavir
15	Atazanavir-Phenytoin	PK: CYP2B6, CYP3A4, CYP3A5-7, and UGT1A1 induction by phenytoin
16	Atazanavir-Pravastatin	PK: CYP3A4 inhibition by atazanavir
17	Atazanavir-Propranolol	PK: CYP3A4 inhibition by atazanavir
18	Atazanavir-Repaglinide	PK: CYP3A4 inhibition by atazanavir
19	Atazanavir-Rosuvastatin	PK: OATP1B1-mediated hepatic uptake and/or BCRP-mediated intestinal and hepatobiliary efflux inhibition by atazanavir
20	Atazanavir-Simvastatin	PK: CYP3A4 inhibition by atazanavir
21	Atazanavir-TDF	Unknown
22	Atazanavir-Ticagrelor	PK: CYP3A4 inhibition by atazanavir
23	Atazanavir-Tramadol	PK: CYP3A4 inhibition by atazanavir
24	Atazanavir-Venlafaxine	PK: CYP3A4 inhibition by atazanavir
25	Atazanavir-Verapamil	PK: CYP3A4 inhibition by atazanavir
26	Cobicistat-Alprazolam	PK: CYP3A4 inhibition by cobicistat
27	Cobicistat-Carbamazepine	PK: CYP3A4 induction and P-glycoprotein induction by carbamazepine
28	Cobicistat-Clopidogrel	PK: CYP3A4 inhibition by cobicistat
29	Cobicistat-Diazepam	PK: CYP3A4 inhibition by cobicistat
30	Cobicistat-Phenytoin	PK: CYP2B6, CYP3A4, CYP3A5-7, and UGT1A1 induction by phenytoin; CYP3A4 inhibition by cobicistat
31	Cobicistat-Rosuvastatin	PK: OATP1B1-mediated hepatic uptake inhibition by cobicistat
32	Cobicistat-Simvastatin	PK: CYP3A4 inhibition by cobicistat
33	Cobicistat-Ticagrelor	PK: CYP3A4 inhibition by cobicistat
34	Cobicistat-Tramadol	PK: CYP3A4 inhibition by cobicistat
35	Cobicistat-Zolpidem	PK: CYP3A4 inhibition by cobicistat
36	Darunavir-Alprazolam	PK: CYP3A4 inhibition by darunavir
37	Darunavir-Amitriptyline	Unknown
38	Darunavir-Atorvastatin	PK: CYP3A4 inhibition by darunavir
39	Darunavir-Carbamazepine	PK: CYP3A4 induction and P-glycoprotein induction by carbamazepine
40	Darunavir-Duloxetine	PK: CYP2D6 inhibition by darunavir
41	Darunavir-Fluvastatin	PK: CYP3A4 inhibition by darunavir
42	Darunavir-Imipramine	Unknown
43	Darunavir-Nortriptyline	Unknown
44	Darunavir-Phenytoin	PK: CYP2B6, CYP3A4, CYP3A5-7, and UGT1A1 induction by phenytoin
45	Darunavir-Pitavastatin	PK: CYP3A4 inhibition by darunavir
46	Darunavir-Pravastatin	PK: CYP3A4 inhibition by darunavir
47	Darunavir-Propranolol	PK: CYP2D6 inhibition by darunavir
48	Darunavir-Rosuvastatin	PK: OATP1B1-mediated hepatic uptake and/or BCRP-mediated intestinal and hepatobiliary efflux by darunavir
49	Darunavir-Simvastatin	PK: CYP3A4 inhibition by darunavir

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50	Darunavir-Tramadol	PK: CYP3A4 inhibition by darunavir
51	Darunavir-Venlafaxine	PK: CYP3A4 inhibition by darunavir
52	Dolutegravir-Calcium carbonate	PD: Polyvalent cations decrease dolutegravir exposure
53	Dolutegravir-Carbamazepine	PK: CYP3A4 induction and P-glycoprotein induction by carbamazepine
54	Dolutegravir-Metformin	PK: Dolutegravir-mediated inhibition of renal OCT2, of which metformin is a substrate
55	Dolutegravir-Phenytoin	PK: CYP2B6, CYP3A4, CYP3A5-7, and UGT1A1 induction by phenytoin
56	Efavirenz-Amitriptyline	PD: Addition of QT-interval prolongation
57	Efavirenz-Carbamazepine	PK: CYP3A4 induction and P-glycoprotein induction by carbamazepine
58	Efavirenz-Hydroxyzine	PD: Addition of QT-interval prolongation
59	Efavirenz-Imipramine	PD: Addition of QT-interval prolongation
60	Efavirenz-Linagliptin	PK: CYP3A4 induction by efavirenz
61	Efavirenz-Nortriptyline	PD: Addition of QT-interval prolongation
62	Efavirenz-Sofosbuvir+Velpatasvir	PK: CYP3A4 induction by efavirenz
63	Efavirenz-Tizanidine	PD: Addition of QT-interval prolongation
64	Efavirenz-Tramadol	PD: Addition of QT-interval prolongation
65	Efavirenz-Venlafaxine	PD: Addition of QT-interval prolongation
66	Elvitegravir-Calcium carbonate	PD: Polyvalent cations decrease plasma concentrations of elvitegravir
67	Elvitegravir-Carbamazepine	PK: CYP3A4 induction and P-glycoprotein induction by carbamazepine
68	Elvitegravir-Phenytoin	PK: CYP2B6, CYP3A4, CYP3A5-7, and UGT1A1 induction by phenytoin
69	Emtricitabine-Lamivudine	PD: Intracellular phosphorylation inhibition of one another to their respective active derivative
70	Lopinavir/Ritonavir-Atorvastatin	PK: CYP3A4 inhibition by lopinavir/ritonavir
71	Lopinavir/Ritonavir-Alprazolam	PK: CYP3A4 inhibition by lopinavir/ritonavir
72	Lopinavir/Ritonavir-Amitriptyline	PD: Addition of QT-interval prolongation
73	Lopinavir/Ritonavir-Carbamazepine	PK: CYP3A4 induction and P-glycoprotein induction by carbamazepine
74	Lopinavir/Ritonavir -Clopidogrel	PK: CYP3A4 inhibition by lopinavir/ritonavir
75	Lopinavir/Ritonavir-Hydroxyzine	PD: Addition of QT-interval prolongation
76	Lopinavir/Ritonavir-Nortriptyline	PD: Addition of QT-interval prolongation
77	Lopinavir/Ritonavir-Phenytoin	PK: CYP2B6, CYP3A4, CYP3A5-7, and UGT1A1 induction by phenytoin
78	Lopinavir/Ritonavir-Pitavastatin	PK: CYP3A4 inhibition by lopinavir/ritonavir
79	Lopinavir/Ritonavir-Pravastatin	PK: CYP3A4 inhibition by lopinavir/ritonavir
80	Lopinavir/Ritonavir-Rosuvastatin	PK: OATP1B1-mediated hepatic uptake and/or BCRP-mediated intestinal and hepatobiliary efflux by lopinavir
81	Lopinavir/Ritonavir-Simvastatin	PK: CYP3A4 inhibition by lopinavir/ritonavir
82	Lopinavir/Ritonavir-Ticagrelor	PK: CYP3A4 inhibition by lopinavir/ritonavir
83	Lopinavir/Ritonavir-Tramadol	PK: CYP3A4 inhibition by lopinavir/ritonavir
84	Lopinavir/Ritonavir-Venlafaxine	PK: CYP3A4 inhibition by lopinavir/ritonavir
85	Lopinavir/Ritonavir-Zolpidem	PK: CYP3A4 inhibition by lopinavir/ritonavir
86	Nevirapine-Sofosbuvir/Velpatasvir	PK: CYP2B6 and CYP3A4 induction by nevirapine
87	Nevirapine-Tramadol	PK: CYP2B6 and CYP3A4 induction by nevirapine
88	Raltegravir-Calcium carbonate	PD: Polyvalent cations decrease raltegravir exposure
89	Rilpivirine-Calcium carbonate	PD: pH-dependent reduction in dissolution and absorption of rilpivirine
90	Rilpivirine-Carbamazepine	PK: CYP3A4 induction and P-glycoprotein induction by carbamazepine
91	Rilpivirine-Phenytoin	PK: CYP2B6, CYP3A4, CYP3A5-7, and UGT1A1 induction by phenytoin
92	Ritonavir-Alprazolam	PK: CYP2A6, CYP2E1, CYP2C19, CYP2D6, CYP2C9, and CYP3A4 inhibition by ritonavir
93	Ritonavir-Atorvastatin	PK: CYP2A6, CYP2E1, CYP2C19, CYP2D6, CYP2C9, and CYP3A4 inhibition by ritonavir
94	Ritonavir-Carbamazepine	PK: CYP3A4 induction and P-glycoprotein induction by carbamazepine
95	Ritonavir-Clopidogrel	PK: CYP2A6, CYP2E1, CYP2C19, CYP2D6, CYP2C9, and CYP3A4 inhibition by ritonavir
96	Ritonavir-Hydroxyzine	PD: Addition of QT-interval prolongation
97	Ritonavir-Phenytoin	PK: CYP2B6, CYP3A4, CYP3A5-7, and UGT1A1 induction by phenytoin
98	Ritonavir-Pravastatin	PK: Glucuronosyl transferase induction by ritonavir
99	Ritonavir-Rosuvastatin	PK: OATP1B1-mediated hepatic uptake and/or BCRP-mediated intestinal and hepatobiliary efflux inhibition by ritonavir
100	Ritonavir-Simvastatin	PK: CYP2A6, CYP2E1, CYP2C19, CYP2D6, CYP2C9, and CYP3A4 inhibition by ritonavir

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101	Ritonavir-Ticagrelor	PK: CYP2A6, CYP2E1, CYP2C19, CYP2D6, CYP2C9, and CYP3A4 inhibition by ritonavir
102	Ritonavir-Tramadol	PK: CYP2A6, CYP2E1, CYP2C19, CYP2D6, CYP2C9, and CYP3A4 inhibition by ritonavir
103	Ritonavir-Venlafaxine	PK: CYP2A6, CYP2E1, CYP2C19, CYP2D6, CYP2C9, and CYP3A4 inhibition by ritonavir
104	Ritonavir-Zolpidem	PK: CYP2A6, CYP2E1, CYP2C19, CYP2D6, CYP2C9, and CYP3A4 inhibition by ritonavir
105	TAF-Carbamazepine	PK: CYP3A4 induction and P-glycoprotein induction by carbamazepine
106	TAF-Phenytoin	PK: CYP2B6, CYP3A4, CYP3A5-7, and UGT1A1 induction by phenytoin
107	TAF-Zoledronic acid	PD: Additive effect (increased risk of renal failure)
108	TDF-Aspirin	PD: Additive effect (increased risk of renal failure)
109	TDF-Carbamazepine	PK: CYP3A4 induction and P-glycoprotein induction by carbamazepine
110	TDF-Phenytoin	PK: CYP2B6, CYP3A4, CYP3A5-7, and UGT1A1 induction by phenytoin
111	TDF-TAF	PD: Same drugs
112	TDF-Zoledronic acid	PD: Additive effect
113	Zidovudine-Ribavirin	PD: Antagonist

Thirty-seven (9.7%) of the potential DDI pairs, however, showed disagreement in the severity ranking among the three databases (Table 3). The agreement determination by Fleiss' kappa value was 0.0476, which indicated slight agreement of severity classification from the three databases. Subgroup analysis of each ARV group with frequently prescribed medications revealed poor agreement (kappa value < 0.00) of the three databases (Table S2).

DISCUSSION

Dyslipidemia is very common in HIV patients due to viral infection and ARV therapy, particularly with PIs.[23] First-line therapy for dyslipidemia in HIV patients is HMG-CoA reductase inhibitors or statin drugs.[24] Some statins and PIs are metabolized by CYP3A4, and DDIs between these groups have been reported.[25] PIs increase the serum levels of statins through CYP3A4 inhibition. For this reason, simvastatin is contraindicated in HIV patients being treated with any PI.[26] Many studies evaluating statin therapy in HIV-infected patients have been published and reviewed by Chastain et al.[27] For example, atorvastatin and pravastatin are safe for HIV patients being treated with PIs or NNRTIs, while rosuvastatin is generally safe if started at a low dose and administered at a maximum of 20 mg per day.[27] Regarding the coadministration of lopinavir/ritonavir and pitavastatin, the DDIs detected at Drugs.com were reported as "major", whereas those at the Micromedex and Liverpool databases were classified as "none found" and "no interaction expected", respectively. Pitavastatin is mainly absorbed into

Table 3. Drug-drug interaction pairs showing disagreement in the severity ranking among the three databases

		Micromedex	Drug.com	Liverpool
	NRTIs			
1	Abacavir-Ribavirin	●●●	●●	-
2	TAF-Zoledronic acid	-	●●●	-
3	TDF-Aspirin	●●●	-	-
4	TDF-Carbamazepine	-	●●●	-
5	TDF-Phenytoin	-	●●●	-
6	TDF-TAF	-	-	●●●
7	TDF- Zoledronic acid	-	●●●	●●
	NNRTIs			
8	Efavirenz-Nortriptyline	-	●●●	-
9	Efavirenz-Tizanidine	-	●●●	-
10	Nevirapine-Tramadol	●●●	●●	●
	PIs			
11	Atazanavir-Amitriptyline	●●●	●●	-
12	Atazanavir-Atenolol	-	●●●	●●
13	Atazanavir-Bisoprolol	-	●●●	●●
14	Atazanavir-Carvedilol	-	●●●	●●
15	Atazanavir-Clopidogrel	-	-	●●●
16	Atazanavir-Fluvastatin	●●●	-	●

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17	Atazanavir-Hydroxyzine	●●●	-	●●
18	Atazanavir-Pravastatin	●●●	-	●●
19	Atazanavir-Tramadol	●●●	●●	●
20	Darunavir-Duloxetine	●●●	-	●
21	Darunavir-Fluvastatin	●●●	-	●
22	Darunavir-Imipramine	●●●	-	●●
23	Darunavir-Nortriptyline	●●●	-	●
24	Darunavir-Pitavastatin	●●●	-	●
25	Darunavir-Propranolol	●●●	-	●
26	Darunavir-Tramadol	●●●	●●	●
27	Darunavir-Venlafaxine	●●●	●●	●
28	Lopinavir/Ritonavir-Pitavastatin	-	●●●	-
29	Lopinavir/Ritonavir-Pravastatin	●●●	●●	-
30	Lopinavir/Ritonavir-Tramadol	●●●	●●	●
31	Lopinavir/Ritonavir-Zolpidem	●●●	●	●●
32	Ritonavir-Hydroxyzine	●●●	-	●●
33	Ritonavir-Pravastatin	●●●	●●	-
34	Ritonavir-Tramadol	●●●	●●	●
35	Ritonavir-Venlafaxine	●●●	●●	●
36	Ritonavir-Zolpidem	●●●	●	●●
	PK enhancer			
37	Cobicistat-Tramadol	●●●	●●	●

Major/Do not coadminister = ●●●, Moderate/ Potential interaction = ●●, Minor/Potential weak interaction/ = ●, None found/No interaction expected = -
NRTI = nucleoside reverse transcriptase inhibitor; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; NNRTI = non-nucleoside reverse transcriptase inhibitor; PIs = protease inhibitors; PK = pharmacokinetics

human hepatocytes through organic anion transporting polypeptide (OATP) 1B1. Interaction of pitavastatin with other drugs may involve mechanisms other than interaction with CYP enzymes.[28] Use of statins for hyperlipidemia is possible, but with caution and the appropriate ARVs.

People living with HIV have relatively high rates of type 2 DM, with one study reporting a prevalence of 15.1% with a relative risk of 2.4 compared with the general population.[29, 30] Metformin is the first-line medication for DM and has established safety and efficacy profiles.[31] Because metformin is a substrate of renal organic cation transporter 2 (OCT2),[32] using this drug with dolutegravir, an OCT2 inhibitor, might increase metformin concentration.[33] Coadministration of metformin (500 mg twice a day) and dolutegravir (50 mg once or twice a day) in healthy volunteers revealed dose-dependent increases in metformin area under the curve (AUC) and Cmax from 79% to 145% and from 66% to 111%, respectively.[34] Even though it is suggested to adjust the dosage of metformin to regulate blood sugar levels when starting or discontinuing dolutegravir in combination with metformin, the clinical significance of this DDI is unclear, with only a few case reports available.[35, 36] Concomitant use of glibenclamide with ARVs leads to moderate DDIs because glibenclamide is metabolized mainly by CYP3A4, and PIs may increase glibenclamide concentrations. Dipeptidyl peptidase 4 (DPP-4) inhibitors (sitagliptin and linagliptin) do not interfere with CYP, and almost no DDIs or only minor DDIs have been reported between DPP-4 inhibitors and HIV drugs.[37]

HIV-infected patients have a higher risk of cardiovascular disease, with increased rates of acute myocardial infarction or coronary heart disease compared with control patients (~1.5 to 2-fold increase in relative risk).[38] Clopidogrel is the preferred antiplatelet drug used to reduce the risk of heart disease in patients with HIV,[39] and a prodrug with the ability to be transformed into an active form via the CYPs 2C19, 1A2, 2B6, and 3A4. Atazanavir, lopinavir/ritonavir, ritonavir, and cobicistat, CYP3A4 inhibitors, might decrease active metabolites of clopidogrel and reduce clopidogrel response. In the presence of ritonavir or cobicistat as a pharmacokinetics-boosting regimen, prasugrel is preferred unless the patient has a contraindication for its use, in which case an alternative antiplatelet agent should be considered.[40] The atazanavir-clopidogrel DDI differed among the three databases. It was classified as “do not coadminister (contraindicated)” in the Liverpool database, but was classified as “not found” in both the Micromedex and Drugs.com databases. In any case, concomitant use of atazanavir and clopidogrel must be avoided. Calcium channel blockers (diltiazem and verapamil) are potent CYP3A4 inhibitors, thus concomitant use of these drugs with PIs or NNRTIs might cause DDIs.[41] Other antihypertensive drugs, including beta-blockers (e.g. atenolol, bisoprolol, and

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metoprolol), angiotensin II receptor blockers (e.g. azilsartan, irbesartan, and losartan) and angiotensin-converting-enzyme inhibitors (e.g. captopril and enalapril), were involved in mild-to-moderate DDIs in almost all three databases.

Owing to the increased lifespan of people infected with HIV, neurologic disorders such as peripheral neuropathy are common.[42] The prevalence of peripheral neuropathy in people infected with HIV was 31.3%, or even higher in older patients and smokers.[43] Tramadol is an opioid drug used to treat peripheral neuropathy in HIV-infected patients. The major metabolic pathways of tramadol are CYP3A4, CYP2D6, and conjugation of parent drugs and metabolites.[44] Tramadol has the potential for DDIs with PIs (e.g. atazanavir, darunavir, and ritonavir) and NNRTIs (efavirenz and nevirapine), which are CYP3A4 inhibitors and inducers, respectively. Coadministration of CYP3A4 inhibitors was shown to increase tramadol concentration and lead to prolonged opioid effects, such as respiratory depression.[45] Conversely, the use of tramadol with CYP3A4 inducers reduced the tramadol plasma level, leading to therapeutic failure and signs of opioid withdrawal syndrome.[45] There was a low concordance of potential DDIs between tramadol and ARVs from the three databases, classified as "major" by Micromedex, "moderate" by Drugs.com, and "potential weak interaction (minor)" by the Liverpool database. Consequently, healthcare professionals should be aware and vigilant when these drugs are coadministered in their patients. Antidepressants, anticonvulsants, and nonspecific analgesics are also used for peripheral neuropathy.[46] Tricyclic antidepressants (TCA) such as imipramine, amitriptyline, and nortriptyline are metabolized by CYP450 enzymes. ARVs that inhibit CYP can increase serum TCA concentrations.[47] Older-generation anticonvulsant drugs such as phenytoin and carbamazepine are potent CYP450 inducers that may reduce plasma levels of ARVs metabolized by CYP450, which include PIs and NNRTIs. The gabapentinoids (gabapentin and pregabalin), a newer generation of anticonvulsant drugs, are metabolized less than 1% and excreted as unchanged parent drug in urine.[48] No DDIs between gabapentinoids and ARVs were reported by any of the three databases.

HIV infection and some ARVs may increase the risk of osteoporosis in people with HIV, who are at higher risk of fragility (35%–68%) compared with the general population. Individuals who have both HIV and HCV or HBV infections are more likely to experience fractures than those who have HIV infection alone.[13] Calcium carbonate and vitamin D are the main supplements used for osteoporosis. The chelation function of calcium carbonate may lead to treatment failure when used with INSTIs (dolutegravir, elvitegravir, and raltegravir). Administration of raltegravir and elvitegravir should be separated from antacid or calcium supplements by at least 2 and 4 hours, respectively.[49, 50] Dolutegravir can be coadministered with calcium or iron supplements if taken with a meal, and should be taken 2 hours before a meal (under fasting conditions) or 6 hours after the calcium supplement.[51] Alendronate or zoledronic acid are bisphosphonate drugs that are recommended for HIV-infected patients with osteoporosis.[52] Alendronate is eliminated via renal excretion and not metabolized by the liver.[53] Although DDIs between alendronate and ARVs were not found by any of the three databases, the Drugs.com database classified DDIs between zoledronic acid and TDF or TAF as "major" based on the increased risk of nephrotoxicity. However, using alendronate or zoledronate seems to be the preferred drug in HIV population from its efficacy and good tolerance and the lack of significant DDIs with ARVs.[54] There were no reported DDIs between vitamin D3 (colecalciferol) and ARVs in the three databases. Vitamin D supplementation appears to be safe and beneficial for bone loss prevention in ARV initiation, and in combination with bisphosphonates for management of low bone mineral density in HIV patients.[55] The prevalence of insomnia has been reported at 21% in HIV-infected people compared with 5% in HIV-negative controls.[56] Some benzodiazepines (alprazolam and diazepam) and non-benzodiazepines (zolpidem) are commonly used to treat insomnia and are metabolized via CYP3A4. Coadministration of CYP3A4-mediated hypnotic drugs and PIs or cobicistat can increase hypnotic drug concentration. Alternatives to benzodiazepines (e.g. lorazepam) are primarily metabolized via glucuronidation, which may be useful for insomnia treatment in people living with HIV.[16]

Liver disease associated with HBV or HCV is a leading cause of non-AIDS-related mortality in HIV patients.[57] Both HIV and HBV infection treatment require a combination of TDF or TAF plus emtricitabine or lamivudine as the NRTI backbone of an ARV regimen.[58, 59] Most of the DDIs reported in HIV-HBV coinfection were classified as "moderate" interactions. For HIV-HCV coinfection, the standard treatment is direct-acting antivirals (DAAs), such as sofosbuvir-velpatasvir. The effectiveness and safety of DAAs in individuals with both HIV-HCV coinfection and those with only HCV are comparable.[60] The combination of pegylated interferon alpha 2a and ribavirin is retained for HCV treatment in resource-limited patients with end-stage renal disease and those who cannot access DAAs or are DAA-ineligible.[61] Reporting of the DDI between abacavir and ribavirin differed among the three databases, classified as "major" by Micromedex, "moderate" by Drugs.com, and "no interaction expected" by the Liverpool database. Many clinical studies concluded that the effect of abacavir on ribavirin concentration was not significant.[62-64]

Effective handling of DDIs is essential in the management of HIV and conditions related to HIV. Although agreement among the three databases was low, efforts to assess potential DDIs are crucial to ensure that HIV patients receive safe and effective therapy.[65] Identification of suspected DDIs to prevent unwanted side effects and treatment failure is the healthcare practitioner's responsibility in HIV patient care. Because some DDIs only occur in a subset of susceptible individuals, DDI studies that evaluate small numbers of healthy volunteers may not be optimal.[66] Alternatively, *in vitro* studies can be helpful for predicting the magnitude of any interaction and understanding its mechanism, especially for CYP450-mediated interactions.[67]

The present study has a number of limitations. Only drugs from the Thailand NLEM 2021 and the Ramadhibodi Chakri Naruebodindra Hospital drug list, which do not cover all of the drugs in each class, were included. Furthermore, because

the DDIs reported by the three databases are constantly being updated, the information on potential DDIs may change over time. Finally, and most importantly, the absence of reported DDIs does not necessarily mean that no DDIs have occurred. Therefore, to maximize treatment effectiveness while minimizing unwanted adverse effects, healthcare providers should be advised to consult more than one database when assessing potential DDIs.

CONCLUSION

A considerable number of DDIs among ARVs and medications frequently prescribed in people living with HIV were detected by the drug interaction tools from three databases. There was only slight agreement among the three databases. The highest number of potential DDI pairs was reported by the Drugs.com database. CYP inhibition and induction were major potential DDI mechanisms. To identify possible DDIs, it is recommended to utilize all three databases, and final drug selection by healthcare providers should be conducted with patient communication and agreement.

LIST OF ABBREVIATIONS

ARV: Antiretroviral

AUC: Area under the curve

BCRP: Breast cancer resistance protein

CD4: Cluster of differentiation 4 of T helper cells

CYP: Cytochrome P450

DAA: Direct-acting antiviral

DDI: Drug-drug interaction

DM: Diabetes mellitus

HBV: Hepatitis B virus

HCV: Hepatitis C virus

INSTI: Integrase strand transfer inhibitor

NLEM: National List of Essential Medicines

NNRTI: Non-nucleoside reverse transcriptase inhibitor

NRTI: Nucleoside reverse transcriptase inhibitor

OATP: Organic anion transporting polypeptide

OCT2: Organic cation transporter 2

PD: Pharmacodynamics

PI: Protease inhibitor

PK: Pharmacokinetics

TAF: Tenofovir alafenamide

TCA: Tricyclic antidepressant

TDF: Tenofovir disoproxil fumarate

UGT: Uridine diphosphate glucuronosyltransferase

CONSENT FOR PUBLICATION

Not applicable.

CONFLICTS OF INTEREST

The authors declare that they have no competing interests.

AUTHOR CONTRIBUTIONS

Conceptualization: AJ, KT, SS, PK; Data curation: AJ, KT, NS; Data analysis: AS; Writing-Original Draft Preparation: AJ, KT, PK; Writing-Review & Editing: AJ, AS, SS, PK.

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AVAILABILITY OF DATA AND MATERIALS

All data generated or analysed during this study are included in this published article [and its supplementary information files].

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Table S1. List of drugs used for the detection of potential drug-drug interactions by three databases

Antiretrovirals	**Frequently prescribed medications**
A. NRTIs	A. Dyslipidemia
1. Abacavir	1. Atorvastatin
2. Emtricitabine	2. Cholestyramine
3. Lamivudine	3. Ezetimibe
4. TAF	4. Fenofibrate
5. TDF	5. Fluvastatin
6. Zidovudine	6. Gemfibrozil
B. NNRTIs	7. Nicotinic acid*
7. Efavirenz	8. Pitavastatin
8. Nevirapine	9. Pravastatin
9. Rilpivirine	10. Rosuvastatin
C. INSTIs	11. Simvastatin
10. Dolutegravir	B. Diabetes mellitus
11. Elvitegravir	12. Acarbose
12. Raltegravir	13. Bromocriptine*
D. HIV protease inhibitors	14. Canagliflozin
13. Atazanavir	15. Dapagliflozin
14. Darunavir	16. Empagliflozin
15. Lopinavir	17. Gemigliptin*
16. Ritonavir	18. Glibenclamide (Glyburide)
E. Pharmacokinetic enhancer	19. Gliclazide*
17. Cobicistat	20. Glipizide
	21. Insulin
	22. Linagliptin
	23. Liraglutide
	24. Metformin
	25. Pioglitazone
	26. Repaglinide
	27. Sitagliptin
	28. Vildagliptin*
	C. Hypertension and myocardial infarction
	29. Aspirin
	30. Atenolol
	31. Azilsartan
	32. Bisoprolol
	33. Captopril
	34. Carvedilol
	35. Cilostazol*
	36. Clopidogrel
	37. Diltiazem
	38. Enalapril
	39. Eptifibatide*
	40. Furosemide
	41. Hydrochlorothiazide
	42. Irbesartan
	43. Lisinopril
	44. Losartan
	45. Metoprolol
	46. Prasugrel
	47. Propranolol
	48. Spironolactone
	49. Ticagrelor
	50. Valsartan
	51. Verapamil
	D. Peripheral neuropathy
	52. Amitriptyline
	53. Baclofen
	54. Carbamazepine
	55. Duloxetine
	56. Gabapentin
	57. Imipramine
	58. Nortriptyline
	59. Phenytoin
	60. Pregabalin
	61. Tizanidine
	62. Topiramate
	63. Tramadol
	64. Valproic acid
	65. Venlafaxine
	E. Osteoporosis
	66. Alendronate
	67. Alfacalcidol*
	68. Calcitonin*
	69. Calcium carbonate
	70. Colecalciferol (vitamin D3)
	71. Denosumab
	72. Ergocalciferol*
	73. Menatetrenone*
	74. Pamidronate*
	75. Teriparatide*
	76. Zoledronic acid
	F. Insomnia

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	77. Alprazolam
	78. Chloral hydrate*
	79. Chlordiazepoxide
	80. Clonazepam
	81. Clorazepate
	82. Diazepam
	83. Hydroxyzine
	84. Lorazepam
	85. Melatonin*
	86. Zolpidem
	G. Hepatitis B/C infection
	87. Entecavir
	88. Lamivudine
	89. Ribavirin
	90. Sofosbuvir-Velpatasvir
	91. TAF
	92. TDF

*Drugs that were not recognized by one or more databases and thus excluded from the study. NRTIs = nucleoside reverse transcriptase inhibitors; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; NNRTIs = non-nucleoside reverse transcriptase inhibitors; INSTIs = integrase strand transfer inhibitors.

Table S2. Fleiss' kappa assessment of agreement regarding drug-drug interactions (DDIs) among three databases

	Kappa	Micromedex and Drugs.com (95% CI)	Micromedex and Liverpool (95% CI)	Drugs.com and Liverpool (95% CI)
All DDIs	0.0476	0.190 (0.165 – 0.191)	0.109 (0.065 – 0.117)	-0.038 (-0.073 – -0.010)
Major DDIs	-0.1127	-0.118 (-0.141 – -0.055)	-0.020 (-0.040 – 0.002)	0.048 (-0.044 – 0.121)
Moderate DDIs	-0.1072	0.027 (-0.253 – 0.306)	0.108 (-0.074 – 0.290)	-0.159 (-0.189 – -0.087)
Minor DDIs	-0.4073	0.089 (-0.087 – 0.266)	0.026 (-0.026 – 0.079)	-0.734 (-0.838 – -0.513)
Frequently prescribed medications grouped by condition				
Dyslipidemia	0.0327	0.311 (0.159 – 0.404)	0.090	-0.144
Insomnia	0.0027	0.166 (0.122 – 0.254)	0.127 (0.060 – 0.223)	-0.129 (-0.157 – 0.071)
Diabetes mellitus	-0.1826	0.091 (0.074 – 0.150)	0.006 (-0.031 – 0.042)	-0.268 (-0.387 – -0.165)
Peripheral neuropathy	0.0779	0.238	0.093 (0.028 – 0.162)	0.053
Osteoporosis	-0.1875	0.091 (-0.200 – 0.319)	-0.043 (-0.053 – 0.143)	-0.231 (-0.884 – 0.422)
Hypertension and myocardial infarction	0.0960	0.124 (0.051 – 0.126)	0.080 (-0.144 – 0.218)	0.152 (0.149 – 0.222)
Hepatitis B/C infection	0.0751	0.115 (0.029 – 0.212)	0.410 (0.322 – 0.545)	0.081 (0.000 – 0.119)
Antiretroviral drug classes				
NRTIs	-0.1021	0.117 (0.077 – 0.123)	0.091 (-0.016 – 0.283)	-0.268 (-0.363 – -0.203)
NNRTIs	0.0360	0.219 (0.164 – 0.270)	0.126 (0.033 – 0.164)	-0.013
INSTIs	-0.0134	0.306 (0.249 – 0.447)	-0.096 (-0.192 - –0.056)	-0.076 (-0.141 – -0.006)
HIV protease inhibitors	0.0720	0.151 (0.137 – 0.190)	0.113 (0.084 – 0.136)	0.041 (-0.029 – 0.115)
Pharmacokinetic enhancers	-0.1741	0.180 (0.102 – 0.252)	0.000	0.000

CI = confidence interval; NRTIs = nucleoside reverse transcriptase inhibitors; NNRTIs = non-nucleoside reverse transcriptase inhibitors; INSTIs = integrase strand transfer inhibitors.