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COMMENTARY

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Antiretroviral drug–drug interactions: A comparison of online drug interaction databases

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Abstract

What is known and objective: Antiretrovirals have a high drug interaction potential, which can lead to increased toxicity and/or decreased efficacy. Multiple databases are available to assess drug–drug interactions. The aim of our study was to compare interaction identification for commonly used ARVs and concomitant medications between six different online drug–drug interaction databases.

Comment: This was a cross-sectional review using each of the following six databases: LexiComp®, Clinical Pharmacology®, Micromedex®, Epocrates®, University of Liverpool, and University of Toronto. Sixteen antiretroviral drugs and 100 of the DrugStats Database "Top 200 of 2019" list of medications were included. Each of the six databases identified a different number of actual or potential interactions. The number of interactions ranged from 211 to 283.

What is new and conclusions: A variety of databases exist with inconsistent identification of actual or potential drug–drug interactions amongst them. It may be beneficial to cross-reference multiple databases prior to making decisions regarding patient care.

KEYWORDS
antiretroviral therapy, drug–drug interaction

1 | WHAT IS KNOWN AND OBJECTIVE

People with human immunodeficiency virus (HIV) are living longer as a result of highly active antiretroviral therapy (HAART) and the likelihood of encountering patients with chronic conditions continues to grow.[1–4] Providers are likely to encounter polypharmacy in this patient population.

Antiretrovirals (ARVs) are known for their high drug interaction potential, frequently due to CYP3A4 metabolism, including the risk of interacting with common medications prescribed for many chronic disease states. Drug–drug interactions (DDIs) can lead to increased toxicity and/or decreased efficacy of one or multiple drugs. Adequate concentrations of ARVs are critical to suppressing and maintaining an undetectable HIV viral load and preventing the development of resistance. The identification and appropriate management of DDIs can reduce preventable harm.

Multiple databases are available for providers to check for drug interactions and ensure patient safety when evaluating treatment regimens. It has been demonstrated that drug interaction experts utilize a variety of methods to search for potential DDIs.[5] Databases for assessing DDIs are available through subscription and open-access platforms. Previous studies have evaluated ARVs with concomitant medications and demonstrated discrepancies between online DDI databases with older ARVs.[6–9] Since these studies, newer agents have

TABLE 1 Medications Included

Antiretrovirals	Concomitant medications		
Bictegravir	Acetaminophen	Estradiol	Lovastatin
Dolutegravir	Acetaminophen/hydrocodone bitartrate	Ethinyl estradiol/norethindrone	Meloxicam
Elvitegravir/cobicistat	Albuterol	Ethinyl estradiol/norgestimate	Metformin
Raltegravir	Alendronate sodium	Fenofibrate	Methylphenidate
Darunavir/cobicistat	Allopurinol	Ferrous sulfate	Metoprolol
Darunavir + ritonavir	Alprazolam	Finasteride	Metronidazole
Atazanavir/cobicistat	Amitriptyline	Fluoxetine hydrochloride	Montelukast
Atazanavir + ritonavir	Amlodipine besylate	Fluticasone	Naproxen
Doravirine	Amoxicillin	Fluticasone propionate/salmeterol xinafoate	Omeprazole
Rilpivirine	Aspirin	Folic acid	Ondansetron
Efavirenz	Atenolol	Furosemide	Oxycodone
Tenofovir alafenamide	Atorvastatin	Gabapentin	Pantoprazole
Tenofovir disaproxil fumarate	Azithromycin	Glimepiride	Paroxetine
Abacavir	Bacitracin/neomycin/polymyxin B	Glipizide	Potassium
Lamivudine	Budesonide/formoterol	Hydrochlorothiazide	Pravastatin sodium
Emtricitabine	Bupropion	Hydrochlorothiazide/lisinopril	Prednisone
	Buspirone hydrochloride	Hydrochlorothiazide/losartan potassium	Pregabalin
	Carvedilol	Hydrochlorothiazide/triamterene	Propranolol hydrochloride
	Cetirizine hydrochloride	Hydroxyzine	Quetiapine fumarate
	Citalopram	Ibuprofen	Ranitidine
	Clonazepam	Insulin aspart	Rosuvastatin calcium
	Clonidine	Insulin glargine	Sertraline hydrochloride
	Clopidogrel bisulfate	Insulin human	Simvastatin
	Cyclobenzaprine	Insulin lispro	Sitagliptin phosphate
	Dextroamphetamine, dextroamphetamine saccharate, amphetamine, amphetamine aspartate	Lamotrigine	Spironolactone
	Diclofenac	Latanoprost	Tamsulosin hydrochloride
	Diltiazem hydrochloride	Levetiracetam	Tiotropium
	Donepezil hydrochloride	Levothyroxine	Topiramate
	Duloxetine	Lisdexamfetamine dimesylate	Tramadol hydrochloride
	Enalapril maleate	Lisinopril	Trazodone hydrochloride
	Ergocalciferol	Loratadine	Valsartan
	Escitalopram oxalate	Lorazepam	Venlafaxine hydrochloride
	Esomeprazole	Losartan potassium	Warfarin
			Zolpidem tartrate

been approved for the treatment of HIV. The aim of our study was to compare interaction identification and severity classification for commonly used ARVs and concomitant medications between six different online DDI databases.

2 | COMMENT

2.1 | Methods

This study was a cross-sectional review designed to identity differences in how online drug interaction databases identify and classify ARV DDIs. Sixteen ARVs were selected by HIV-trained clinical pharmacists to represent the most commonly used ARVs in each class in the United States. From the DrugStats Database "Top 200 of 2019" list of medications,[10] the top 100 most frequently prescribed medications were utilized for our study. All medications included in the analysis are listed in Table 1.

Each unique drug pair was evaluated for DDIs in each of the following six databases: LexiComp®, Clinical Pharmacology®, Micromedex®, Epocrates®, University of Liverpool, and University of Toronto. A description of the characteristics of the DDI databases are described in Table 2. These were specifically selected to represent a variety of databases available including subscription and open-access. The University of Liverpool and University of Toronto databases were both HIV-specific, whereas the other databases included are general DDI databases. Most databases included grouped DDI severity in four categories. Lexicomp® included five categories and the University of Toronto database included 3. Additionally, Lexicomp® and Epocrates® databases both provide a clinical recommendation of how to address the DDI as their severity category.

TABLE 2 Drug interaction database characteristics

Database	Access	Content	Severity scale
Clinical Pharmacology®	Subscription	General	Severe
			Major
			Moderate
			Minor
Micromedex®	Subscription	General	Contraindicated
			Major
			Moderate
			Minor
LexiComp®	Subscription	General	Avoid
			Modify
			Monitor
			No action
			No known interaction
Epocrates®	Open Access	General	Contraindicated
			Avoid/use alternative
			Monitor/modify
			Caution advised
University of Liverpool	Open Access	HIV	Do not coadminister
			Potential interaction
			Potential interaction or weak intensity
			No interaction expected
University of Toronto	Open Access	HIV	Red
			Yellow
			Green

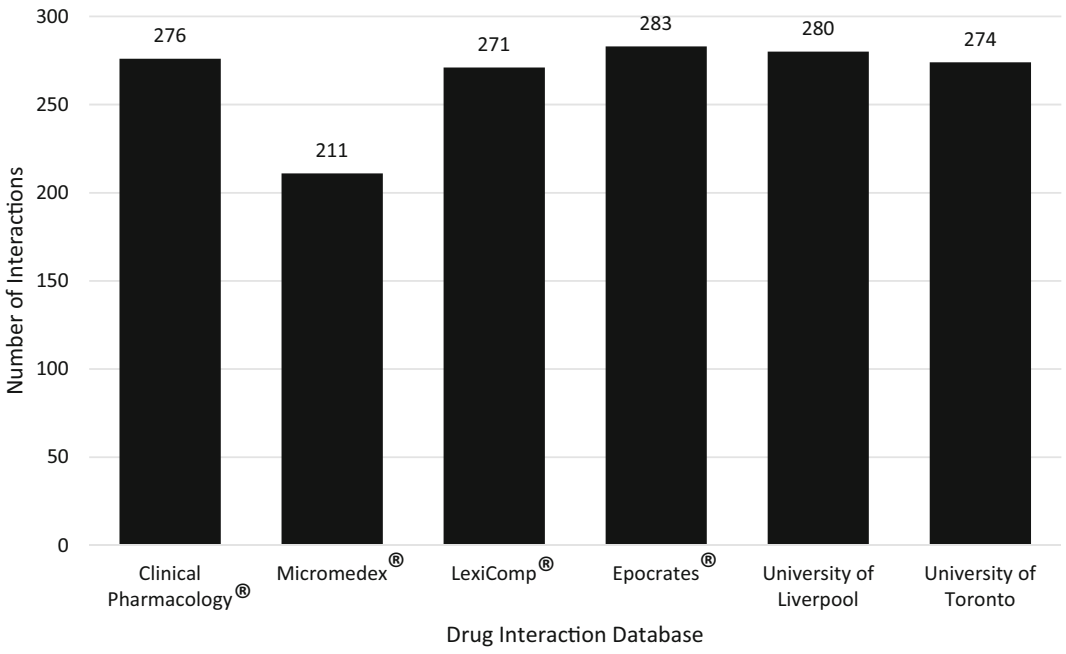

FIGURE 1 Actual or potential drug–drug interactions identified

We reviewed characteristics of each DDI database including their severity ranking. We also assessed whether an actual or potential DDI was identified for each ARV-concomitant medication drug pair, in each of the six databases. The percent of pairs which resulted in a DDI was also evaluated. Data were analysed using descriptive statistics.

2.2 | Results

There were 1520 drug pairs evaluated for interaction, after removing duplicates. Each of the six databases identified a different number of actual or potential DDIs of any severity. The number of DDIs ranged from 211 to 283. These are described in Figure 1. The most DDIs were identified by Epocrates® and the least number of DDIs were identified by Micromedex®. The percent of pairs in which a drug interaction was identified ranged from 13.9% to 18.6%.

3 | DISCUSSION

Each of the six DDI databases identified a different number of actual or potential DDIs between the ARVs and concomitant medications. This variability has been demonstrated in multiple studies with other drug classes, outside of ARVs and with a variety of online DDI databases.[11–18] Databases were selected to represent resources at varying levels of access, including subscription and open access. Additionally, of the selected databases, some were general resources while others were HIV-specific. Each database has its own severity ranking system and categories. There was no consistency between types of databases and number of actual or potential DDIs identified.

Micromedex® identified 211 drug interaction pairs, 60 pairs fewer than the next most identified pairs by Lexicomp®. The remaining five databases identified a similar number of actual or potential DDIs, demonstrated by a range of 12 DDIs between the database identifying the most interactions and the least interactions. The clinical impact of each recommendation was not assessed, thus we are unable to make conclusions on the relevance of the identified DDIs.

A similar study was performed by Pehlivanli et al. comparing potential DDIs of immunosuppressants in kidney transplant recipients in four different online data bases.[11] Potential DDIs identified were compared to a gold standard reference to determine sensitivity and specificity of each database. Such a gold standard does not exist for ARVs, making it difficult to determine a single, most-reliable online database.

Our study is the only study to date specifically evaluating the number of identified actual or potential DDIs between ARVs and concomitant medications for six different DDI databases, but it is not without limitations. Our study only included 16 ARVs and 100 concomitant medications, assessing for only 1520 DDI pairs. Additionally, the type of recommendation, severity, and clinical impact of each DDI was not evaluated. Heterogeneity of DDIs identified amongst databases was also not assessed. Finally, the Department of Health and Human Services has frequently referenced guidelines with drug interaction recommendations, but this was not included in our review as it was not a searchable database.

Online DDI databases do not consistently identify potential ARV DDIs and such discrepancies could impact patient care. Cross-referencing databases may be beneficial when evaluating ARV DDIs. Further evaluation of ARV DDIs is necessary. Future studies that include more medications that are commonly taken, as well as over-the-counter medications and herbal supplements, are necessary.

4 | WHAT IS NEW AND CONCLUSIONS

Online DDI databases are a tool for clinicians to identify potential DDIs between ARVs and concomitant medications, and to find guidance regarding management. A variety of databases exist with inconsistent identification of actual or potential DDIs amongst them. Results should be interpreted with caution, and it may be beneficial to cross-reference multiple databases prior to making decisions regarding patient care.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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