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Recognition and Management of Significant Drug Interactions in HIV Patients – Challenges in Using Available Data to Guide Therapy

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Combination antiretroviral therapy (cART) has improved survival of HIV-infected patients, but patients now experience co-morbidities that require pharmacological intervention, increasing the risk of drug-drug interactions. HIV protease inhibitors (PIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), and the CCR5 antagonist maraviroc are primarily metabolized via the cytochrome P450 (CYP) system and are prone to pharmacokinetic interactions.(1,2) This article will address some key challenges prescribers face when using available drug interaction resources in making day-to-day clinical decisions.

Interactions between Antiretroviral Drugs and Other Agents

Drug-drug interactions are considered clinically significant if they result in alteration of the desired outcomes leading to reduced clinical effectiveness or increase in the risk and/or magnitude of toxicities. Drugs are most vulnerable to the consequences of significant pharmacokinetic interactions when they are substrates of major metabolic or drug transport pathways and also have a narrow therapeutic window. Many cART regimens contain an NNRTI, a PI (usually boosted with ritonavir, a strong CYP3A4/5 inhibitor), or both, together with two nucleoside reverse transcriptase inhibitors (NRTIs). As HIV patients live longer, polypharmacy is unavoidable. Many patients may require additional medications to manage antiretroviral-associated adverse effects (such as hyperlipidemia) or other co-morbidities (such as cardiovascular diseases, erectile dysfunction, and depression). There are also patients who enter into care with advanced HIV, requiring treatment for AIDS-defining conditions (such as tuberculosis, invasive fungal infections, or malignancies). Anticipation and recognition of potential pharmacokinetic interactions should start when one intends to add, switch, or discontinue one or more medication(s).

The approval of the PIs in the mid 1990s has dramatically increased the awareness of pharmacokinetic-associated drug-drug interactions and their potential impact on drug therapy. Pharmaceutical companies and HIV experts increased their efforts in raising awareness and educating prescribers on the significance of interactions between PIs, in particular ritonavir, and other drugs metabolized via CYP3A4/5. However, CYP450-mediated interactions are not the sole mechanism by which drug interactions occur. An interaction that received much attention is the effect of acid suppression by proton pump

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inhibitors or histamine-2 (H₂) antagonists on atazanavir absorption. This led to various pharmacokinetic studies that had different study designs and yielded some conflicting results.(3–5) Uridine diphosphate glucuronosyltransferase (UGT)1A1 is an enzyme responsible for the conjugation of many pharmaceutical products, but understanding of the impact of UGT1A1-mediated interactions is still in its infancy.(6) Raltegravir, a UGT1A1 substrate, has an advantage over PIs and NNRTIs because of the lack of CYP-associated interactions. When co-administered with rifampin, a potent UGT1A1 inducer, however, the pre-dose raltegravir concentration is reduced by 60%, necessitating a doubling of the raltegravir dose.(7) Other unexpected drug interactions continue to emerge, recognized only when studies or case reports identify such problems. Noted examples include: 1) reports of some serious and even fatal didanosine-associated toxicities(8,9) when co-administered with tenofovir, as a result of increased didanosine concentrations (10); and 2) ritonavir-boosted PIs causing higher than expected systemic steroid exposure leading to adrenal insufficiency or Cushing's Syndrome after coadministration with inhaled (11) or locally administered corticosteroids (12). There are yet other drugs used in HIV patients, including some herbal and complementary products where the ingredients and metabolic pathways are not well described; interactions with these agents cannot be easily predicted or anticipated.(13)

Data and Tools Used in Providing Guidance

Although most HIV practitioners are aware of potential drug-drug interactions, many find themselves lacking the knowledge and tools needed to recognize and manage such interactions with confidence. To this end, detecting and managing drug interactions should not be the sole responsibility of prescribers. Pharmacists, patients, and other healthcare providers should also be aware of potential drug interactions, and be vigilant when drugs are added or removed from a regimen. Prescribers and pharmacists should be aware of key drugs or drug classes with the highest potential for significant interactions, such as PIs, NNRTIs, rifamycins, macrolides, azoles, anticonvulsants, psychotropic agents, etc., and consult appropriate resources for guidance, but note that there are limitations to all the current available references, as discussed below.

Applying Data from Healthy Volunteer Pharmacokinetic Studies to HIV Patients

As it is generally considered unethical to commit HIV patients to antiretroviral monotherapy even for a short duration, most pharmacokinetic drug interaction studies are conducted in healthy volunteers using stringent dosing schedules, which allow for accurate assessment of the impact of one drug on another. Extrapolation of the data from these studies to generate recommendations for HIV-infected patients does have some limitations. Altered CYP metabolic activities (14) and reduced drug exposure have been reported with some drugs in HIV-infected patients when compared to HIV (–) volunteers (15,16). The small number of participants typically studied in pharmacokinetic trials, wide inter-participant variability, and short study duration are other limitations. Moreover, healthy volunteer data may not be generalizable to populations with altered pharmacokinetics such as pregnant women, children, patients with renal or hepatic impairment, or patients with specific genetic polymorphisms (17).

Information from Product Prescribing Information

Product prescribing information is a readily available source for clinicians to use. Results from pharmacokinetic studies conducted by the manufacturers are presented in table format. Significant interactions requiring prescribers' attention are explicitly outlined. As listed in Table 1, some drugs are listed as “contraindicated” when concomitant use with an antiretroviral agent may result in significant harm; such combinations should be avoided. In less serious cases, a warning may be added to suggest that a drug combination should not be

co-administered, unless no alternative drug is available and the therapeutic benefit outweighs the risk. In recent years, the manufacturers of antiretroviral drugs have been more diligent in conducting healthy volunteer pharmacokinetic studies, particularly with drugs that are frequently prescribed together for HIV-infected patients and where interactions may occur. These efforts have been successful in alerting clinicians to avoid certain drugs (for example, concomitant use of lovastatin or simvastatin and PIs) or to use them with dosage adjustment (for example, sildenafil and PIs). In addition, the results from some studies have led to more sophisticated but sometimes complicated dosage recommendations, particularly for newer agents such as atazanavir, maraviroc, and etravirine. As outlined in Table 2, although thorough, some dosing guidelines can be confusing and may result in both prescribing and administration errors due to misinterpretation of the intended instructions. To illustrate, when atazanavir is used in combination with acid suppressive agents, the atazanavir dose and administration time depends on all of the following factors (1) whether the patient is “treatment-naïve” or “treatment-experienced”; (2) whether or not co-administered with ritonavir, efavirenz, and/or tenofovir; (3) dose of PPI (omeprazole equivalent) or H2-antagonist (famotidine equivalent) used; and (4) timing of the PPI or H2-antagonist.(18) These recommendations are well intended and based on the design of time-limited pharmacokinetic studies; however, it is not practical and almost impossible to counsel patients and expect them to apply this rigid dosing schedule daily for the duration of the combined therapy.

Another challenge arises when the manufacturer of one drug performs a pharmacokinetic study whereby dosage recommendations are made in one drug label but not revised in the label(s) of the interacting drug(s). Recent examples include the interaction between voriconazole with ritonavir and voriconazole with efavirenz. Where the voriconazole label provided warning and recommendations for concomitant use of these combinations, this information did not appear in the antiretroviral drug labels until a couple of years later. The lack of coordination between the manufacturers of these products makes it difficult for clinicians to track interactions and prescribe correct dosages accordingly.

Electronic Drug Interaction Tools

The awareness of the importance of antiretroviral-associated DDI and the wider usage of the internet have led to emergence of various electronic databases for clinicians to assess clinically significant drug interactions (Table 3). Most of these sites provide free access to the public and some can be downloaded into personal digital assistance (PDA) devices. The information and recommendations are based on data compiled from drug product labels, pharmacokinetic studies published or presented at major conferences, and key case reports. These databases are updated periodically when new data become available. Some sites provide interactive tools, where clinicians can enter the drugs in a patient’s medication profile, and a list of interactions will be displayed. They are an excellent starting point when new drugs are prescribed. However, the pharmacokinetic data only represent interactions between two drugs, and the extent of changes in pharmacokinetic parameters in the presence of three or more drugs is complex and almost impossible to predict.

Drug Interaction Programs at Electronic Order Entry and Pharmacy Reconciliation

Medication errors due to prescribing antiretroviral agents with contraindicated drugs or failure to adjust doses as recommended when prescribing interacting drugs are not uncommon.(19,20) Errors may also occur when patients transfer from one healthcare system to another, such as admission to a hospital.(21,22) Many institutions and pharmacies have installed drug interaction detection softwares within the electronic order entry and pharmacy dispensing programs, which provide an alert when drug interactions for the same patient are identified.(2,23,24) Institutions have the option to turn on or off the alarm system based on

the level of severity of the interactions, in order to avoid alarm overload. Such programs serve as a safety net to avoid inadvertent prescribing errors, but studies have shown that prescribers and pharmacists often elect to override the drug interaction warnings without making a true assessment of the interactions due to heavy workload(25) or “alert fatigue” (23).

Challenges of Drug Interactions in Resource-Limited Countries

Expansion of antiretroviral roll-out programs has improved survival for patients in many resource-limited countries. However, drug interactions are becoming a tremendous challenge in those countries with a high burden of tuberculosis where rifampin remains a key component of treatment.(26) Even though efavirenz, given at usual or slightly increased doses in the presence of rifampin appears to result in reasonable virologic responses,(27) the high proportion of women of childbearing age and the increasing reports of NNRTI-failure and resistance necessitate the use of PI-based regimens which have greater potential for clinically significant interactions. The restricted use of fixed-dose combination therapy for both tuberculosis and HIV infections also restrict the ability to individualize therapy when interacting drugs are prescribed. Aside from tuberculosis, many patients in these regions continue to consume traditional herbal medicines, most of which have not been studied, making evaluation of potential drug interactions impossible.(28) HIV clinicians in resource-limited countries see high volume of patients, have little reference resources, no computer system, and less monitoring tools, making it very difficult to avoid, detect, and manage drug interactions.

Summary

While most HIV-infected patients in care have benefitted from effective cART and are living longer, many receive additional medications to manage or prevent comorbidities. Drug interactions are common; some can be anticipated and prevented, some cannot be avoided and others cannot be easily recognized or managed appropriately.(2) A recent survey noted that only 36% of clinically significant drug interaction were identified by physicians in an HIV clinic.(29) The first step to avoiding unwanted interaction is prescriber-initiated assessment of drug interaction potential. Prescribers and pharmacists should always review patients' medication profiles when starting or changing regimens to determine the best therapy with the least interactions and/or toxicities. Patients should be encouraged to disclose all medications they use (including over-the-counter and herbal preparations), especially if they receive care from multiple providers. If possible, providers, especially consultants, should communicate with the primary care team before prescribing new medication(s) for a patient. Although there are some limitations to all available resources, drug interaction tools, including product labels, should be consulted and order entry alert systems should be utilized to identify interacting drugs. Unfortunately, not all drug combinations with similar metabolic pathway and have potential for clinically significant interactions have been formally evaluated, in those case, the clinicians have to use their best judgment and prescribe these drugs with caution. Prescribing of contraindicated drugs should be avoided. When more than two interacting drugs need to be used concurrently, clinicians should be aware of the limitations when using available resources in predicting the true extent of the interactions in these situations. If available, a clinical pharmacologist/pharmacist should be consulted. In selected cases, therapeutic drug monitoring maybe helpful in assessing the adequacy of drug concentrations and the need for dosage adjustment. After prescribing interacting medications, close follow-up is needed to assess therapeutic efficacy and potential toxicities. When unexplained symptoms or responses are seen after initiating or switching therapy, and a drug interaction is the suspected cause, one should consider reporting this to the manufacturer and to the medical

community. In doing so, one adds to the drug interaction knowledge base and assists clinicians in safely prescribing antiretroviral drug combinations.

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Table 1

Drugs Listed as Contraindicated or Use with Caution According to FDA Product Labeling

Antiretroviral Drug	“Contraindicated Antiretroviral Drugs”	“Contraindicated” – Other Drugs	“Do not coadminister” or “Avoid combination” or “Coadministration not recommended” Antiretroviral Drugs	“Do not coadminister” or “Avoid combination” or “Coadministration not recommended” – Other Drugs
NRTI				
abacavir	none	none	none	none
didanosine	none	allopurinol, ribavirin	stavudine + hydroxyurea	none
emtricitabine	none	none	lamivudine	none
lamivudine	none	none	emtricitabine, (zalcitabine)	none
tenofovir	none	none	atazanavir without ritonavir	none
stavudine	none	none	hydroxyurea +/- didanosine, zidovudine	hydroxyurea
zidovudine	none	none	stavudine	doxorubicin, ribavirin,
NNRTI				
efavirenz	none	cisapride, ergot derivatives, midazolam, pimozide, St. John’s wort, triazolam	atazanavir in treatment-experienced patients	none
etravirine	none	none	atazanavir/ritonavir, delavirdine, efavirenz, fosamprenavir/ritonavir, nevirapine, tipranavir/ritonavir, PI without ritonavir,	carbamazepine, phenobarbital, phenytoin; rifabutin when combined with darunavir/ritonavir, lopinavir/ritonavir, or saquinavir/ritonavir; rifampin, rifapentine, St. John’s wort
nevirapine	none	none	atazanavir ± ritonavir, efavirenz, fosamprenavir without ritonavir,	itraconazole, ketoconazole, rifampin, St. John’s wort
PI				
atazanavir ± ritonavir	indinavir	alfuzosin, cisapride, ergot derivatives, irinotecan, lovastatin, midazolam (oral), pimozide, rifampin, sildenafil when used to treat pulmonary hypertension, simvastatin, St. John’s wort, triazolam	efavirenz in treatment-experienced patients, nevirapine	bosentan (without ritonavir), fluconazole >200 mg/day, ketoconazole >200 mg/day, salmeterol
darunavir + ritonavir	none	alfuzosin, cisapride, ergot derivatives, lovastatin, midazolam (oral), pimozide, rifampin, sildenafil when used to treat pulmonary hypertension, simvastatin, St. John’s wort, triazolam	lopinavir/ritonavir, saquinavir	fluconazole >200 mg/day, ketoconazole >200 mg/day, salmeterol

Antiretroviral Drug	“Contraindicated Antiretroviral Drugs”	“Contraindicated” – Other Drugs	“Do not coadminister” or “Avoid combination” or “Coadministration not recommended” Antiretroviral Drugs	“Do not coadminister” or “Avoid combination” or “Coadministration not recommended” – Other Drugs
fosamprenavir ± ritonavir	none	alfuzosin, cisapride, delavirdine, ergot derivatives, flecainide, lovastatin, midazolam (oral), pimozide, propafenone, quinidine, rifampin, sildenafil when used to treat pulmonary hypertension, simvastatin, St. John’s wort, triazolam	none	salmeterol
indinavir	none	alfuzosin, amiodarone, alprazolam, cisapride, ergot derivatives, midazolam (oral), pimozide, sildenafil when used to treat pulmonary hypertension, triazolam	atazanavir	lovastatin, rifampin, rosuvastatin, salmeterol, simvastatin, St. John’s wort
lopinavir/ritonavir	none	alfuzosin, cisapride, ergot derivatives, lovastatin, midazolam (oral), pimozide, rifampin, sildenafil when used to treat pulmonary hypertension, simvastatin, St. John’s wort, triazolam	tipranavir/ritonavir	fluconazole >200 mg/day, ketoconazole >200 mg/day, salmeterol
nelfinavir	none	alfuzosin, amiodarone, ergot derivatives, midazolam, pimozide, quinidine, sildenafil when used to treat pulmonary hypertension, triazolam	none	lovastatin, proton pump inhibitors, rifampin, salmeterol, simvastatin, St. John’s wort
saquinavir + ritonavir	none	alfuzosin, amiodarone, cisapride, ergot derivatives, flecainide, lovastatin, midazolam (oral), pimozide, propafenone, quinidine, rifampin, sildenafil when used to treat pulmonary hypertension, simvastatin, triazolam	tipranavir/ritonavir	garlic capsules, ketoconazole >200 mg/day, salmeterol, St. John’s wort
tipranavir + ritonavir	none	alfuzosin, amiodarone, cisapride, ergot	other PI	fluconazole >200 mg/day, ketoconazole

Antiretroviral Drug	“Contraindicated Antiretroviral Drugs”	“Contraindicated” – Other Drugs	“Do not coadminister” or “Avoid combination” or “Coadministration not recommended” Antiretroviral Drugs	“Do not coadminister” or “Avoid combination” or “Coadministration not recommended” – Other Drugs
		derivatives, flecainide, lovastatin, midazolam (oral), pimozide, propafenone, quinidine, rifampin, sildenafil when used to treat pulmonary hypertension, simvastatin, St. John's wort, triazolam		>200 mg/day, salmeterol, If oral solution is used, do not use supplemental vitamin E > dose in multivitamin
INSTI				
raltegravir	none	none	none	none
CCR5 antagonist				
maraviroc	none	none	none	St. John's wort
Fusion inhibitor				
enfuvirtide	none	none	none	none

Table 2

FDA Product Labels' Dosing Recommendations and Modifications for Selected Antiretroviral Drugs Based on Pharmacokinetic Drug-Drug Interactions and Treatment Experience Status

Antiretroviral Drug	FDA Recommended Dose <i>Treatment-naïve patients</i>	FDA Recommended Dose <i>Treatment-experienced patients</i>
Atazanavir ± ritonavir	Atazanavir 400mg once daily, or (Atazanavir 300mg + ritonavir 100 mg) once daily <u>When coadministered with H2-receptor antagonists</u> (Atazanavir 300mg + ritonavir 100mg) once daily; H2-receptor antagonist not to exceed a dose comparable to famotidine 40mg twice daily; Administer atazanavir/ritonavir simultaneously with and/or at least 10 hours after H2-receptor antagonist. Atazanavir 400mg once daily (unboosted); H2-receptor antagonist not to exceed a dose comparable to famotidine 20mg twice daily and no single dose to exceed a dose comparable to famotidine 20mg; Administer atazanavir at least 2 hours before and at least 10 hours after H2-receptor antagonist. <u>When coadministered with proton pump inhibitors (PPI)</u> (Atazanavir 300mg + ritonavir 100mg) once daily; PPI not to exceed a dose comparable to omeprazole 20mg once daily; Administer PPI approximately 12 hours prior to atazanavir/ritonavir. <u>Coadministered with efavirenz</u> (Atazanavir 400mg + ritonavir 100mg)once daily;	(Atazanavir 300mg + ritonavir 100mg) once daily <u>When coadministered with H2-receptor antagonists</u> Atazanavir 300mg + ritonavir 100mg (without tenofovir); Atazanavir 400mg + ritonavir 100mg (with tenofovir); H2-receptor antagonist not to exceed a dose comparable to famotidine 20mg twice daily; Administer atazanavir/ritonavir simultaneously with and/or at least 10 hours after H2-receptor antagonist. Atazanavir/ritonavir and PPIs should not be coadministered in treatment-experienced patients. Atazanavir/ritonavir and efavirenz should not be coadministered in treatment experienced patients.
Efavirenz	<u>Recommended Dose: Efavirenz 600mg once daily</u> Coadministered with Voriconazole: Efavirenz 300mg once daily (one 200mg + two 50 mg capsules); Voriconazole dose should be increased to 400mg every 12 hour	
Fosamprenavir ± ritonavir	(Fosamprenavir 700mg + ritonavir 100mg) twice daily (Fosamprenavir 1,400mg + ritonavir 100–200mg) once daily Fosamprenavir 1,400mg twice daily <u>Coadministered with efavirenz</u> (Fosamprenavir 1,400mg + ritonavir 300mg) once daily (Fosamprenavir 700mg + ritonavir 100mg) twice daily	(Fosamprenavir 700mg + ritonavir 100mg)twice daily <u>Coadministered with efavirenz</u> (Fosamprenavir 700mg + ritonavir 100mg) twice daily
Lopinavir/ritonavir	Lopinavir/ritonavir 800mg/200mg once daily or 400mg/100mg twice daily <u>Coadministered with efavirenz, nevirapine, fosamprenavir, or nelfinavir</u> Once daily lopinavir/ritonavir is not recommended. Lopinavir/ritonavir (tablet formulation) 500mg/125mg twice daily (use two 200mg/50mg tablets + one 100mg/25mg tablet) or Lopinavir/ritonavir (oral solution) 533mg/133mg twice daily	
Etravirine	Etravirine is not approved for use in treatment-naïve patients	Etravirine should <u>not</u> be coadministered with <ul style="list-style-type: none"> • atazanavir/ritonavir, • fosamprenavir/ritonavir, • tipranavir/ritonavir, • unboosted protease inhibitors, • or other NNRTIs.
Maraviroc	<u>Coadministered with potent CYP3A inhibitors (with or without a CYP3A inducer) including protease inhibitors (except tipranavir/ritonavir), delavirdine, ketoconazole, itraconazole, clarithromycin, telithromycin, nefazodone, etc.</u> Maraviroc 150mg twice daily	

Antiretroviral Drug	FDA Recommended Dose <i>Treatment-naïve patients</i>	FDA Recommended Dose <i>Treatment-experienced patients</i>
	<u>Coadministered with other concomitant medications, including tipranavir/ritonavir, nevirapine, raltegravir, all NRTIs, and enfuvirtide</u> Maraviroc 300mg twice daily <u>Coadministered with potent CYP3A inducers (without a potent CYP3A inhibitor) including efavirenz, etravirine, rifampin, carbamazepine, phenobarbital, and phenytoin</u> Maraviroc 600mg twice daily	
Raltegravir	<u>Recommended Dose:</u> Raltegravir 400mg twice daily <u>Administered with Rifampin:</u> Raltegravir 800mg twice daily	
Didanosine	<u>Recommended Dose for Patients > 60 kg:</u> Didanosine 400mg once daily <u>Co-Administered with Tenofovir:</u> Didanosine 250mg once daily	

Table 3**Drug Interaction Information Resources**

Source	Website	Description
Clinical Care Options ¹	www.clinicalcareoptions.com/HIV/Treatment%20Updates/ARV%20Interactions/Interactive%20Tool/drug-drug%20tool.aspx	Specific for antiretroviral drug interactions. Interactive tool to identify individual antiretroviral drugs for common interactions or a concomitant drug for interactions. Includes severity, pharmacokinetic data, and dosing recommendations. Disadvantage: no interactive tool for drug interactions included.
DHHS HIV Adult and Adolescent Guidelines	www.aidsinfo.nih.gov/Guidelines/	Specific for antiretroviral drug interactions. Drug Interaction section includes text with considerations and with specific, common interactions, including general pharmacokinetic information and recommendations. Disadvantages: no interactive tool, as of the latest guideline release date.
Epocrates Online Premium	https://online.epocrates.com/	Interactive tool to identify individual antiretroviral drugs for common interactions or a concomitant drug for interactions. Includes severity, general pharmacokinetic data, and dosing recommendations. Disadvantages: no pharmacokinetic data.
Facts & Comparisons	http://online.factsandcomparisons.com/	Interactive tool to identify individual antiretroviral drugs for common interactions or a concomitant drug for interactions. Includes severity, mechanism of interactions, and pharmacokinetic data. Disadvantages: no dosing recommendations.
FDA package inserts	www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm	Drug Interaction section of Clinical Pharmacology sections contain information of drug interaction and pharmacokinetic data. Disadvantages: no dosing recommendations. Interactive tool, included data from pharmaceutical companies only current as of package insert release date.
Johns Hopkins POC-IT Center ¹	www.hopkins-hivguide.org/management/antiretroviral_therapy/drug_interactions.html?contentInstanceId=11813	Specific for antiretroviral drug interactions.

Source	Website	Description
Lexi-Comp Lexi-Interact ²	www.lexi-comp.com	Text with general considerations and specific, clinically significant drug interactions. Includes general pharmacokinetic and dosing recommendations. Disadvantages: not an interactive tool.
Micromedex ²	www.micromedex.com	Interactive tool to search for individual antiretroviral drug interactions or a concomitant drug for interactions. Includes risk, prevalence, ratings, mechanism of interactions, pharmacokinetic dosing recommendations. Disadvantage: pay subscription required.
Medscape ¹	www.medscape.com/druginfo/druginterchecker	Interactive tool to search for individual antiretroviral drug interactions or a concomitant drug for interactions. Includes severity rating, mechanism of drug interaction, pharmacokinetic dosing recommendations.
NIH, CDC, and HIVMA/ IDSA Opportunistic Infections in HIV-Infected Adults and Adolescents Guidelines	www.aidsinfo.nih.gov/Guidelines/	Tables include specific drug interactions for antiretroviral drugs used for treatment of opportunistic infections. Includes general pharmacokinetic and dosing recommendations. Disadvantages: not an interactive tool, as of the latest guideline release date, limited interactions between antiretroviral drugs used to treat opportunistic infections.
University of California, San Francisco	http://hivinsite.ucsf.edu/insite?page=ar-00-02	Specific for antiretroviral drug interactions. Search for interactions between individual antiretroviral drug, interacting drug. Includes mechanism.

Source	Website	Description
The University of Liverpool	www.hiv-druginteractions.org/	interaction, pharmacokinetic data, and dosing recommendation Specific for antiretroviral drug interactions Search for interactions between individual antiretroviral drug, interacting drug, interacting drug Includes risk ratio pharmacokinetic information, and recommendation provides links to interaction data presented at conference Educational based on interaction slide available.
UpToDate ² (linked to Lexi-Comp Lexi-Interact)	www.uptodate.com	See Lexi-Comp

¹Free registration required

²Paid subscription required

DHHS = Department of Health and Human Service

FDA = Food and Drug Administration

NIH = National Institutes of Health

CDC = Centers for Disease Control and Prevention

HIVMA/IDSA = HIV Medicine Association of the Infectious Diseases Society of America