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Use of antineoplastic agents in cancer patients with HIV/AIDS

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Abstract

In the era of highly active antiretroviral therapy (HAART), patients with human immunodeficiency virus (HIV) have reduced morbidity and mortality of AIDS-related complications. However, there is an increase in the prevalence of AIDS-defining and non-AIDS-defining cancers. This article provides an up-to-date review of management of HAART pharmacotherapy in the context of cytotoxic chemotherapy or targeted antineoplastic agents.

Keywords

antiretroviral; antineoplastic agents; pharmacology

Introduction

Treatment of patients with human immunodeficiency virus (HIV) infection with highly active antiretroviral therapy (HAART) substantially restores immune function, reduces opportunistic infections, lowers plasma viral RNA load, and reduces morbidity and mortality of AIDS-related complications.[1,2] However, cancer remains a significant problem in patients with HIV/AIDS. Kaposi's sarcoma, non-Hodgkin's lymphoma, and invasive cervical cancer are not typical in the immunocompetent adult population but are prevalent in those with HIV/AIDS and have thus been deemed as “AIDS-defining cancers.” Hodgkin's lymphoma, anal, lung, and testicular germ cell cancers lack the same definitive association with HIV/AIDS and are being deemed as “non-AIDS-defining cancers” when the patient also has a co-diagnosis of HIV/AIDS.

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Contributions

M.A.R. performed the literature search and interpretation. M.A.R., C.F., and R.F.A. were involved with the concept and design, manuscript writing, and final approval of manuscript.

Search Strategy: Data for this review were identified by searches of Medline with the search terms “antiretroviral agents,” “cancer,” “HAART,” and individual drug names. Additional references were selected from relevant articles. Abstracts and reports from meetings were included only when they related directly to previously published work. Only papers published in English between January, 1990, and January, 2011, were included.

The number of non-AIDS-defining cancers has increased significantly as patients with HIV/AIDS have increased life expectancies. In the Antiretroviral Therapy Cohort Collaboration that examined 39,272 patients diagnosed with HIV who initiated antiretroviral therapy during the time period of 1996 until 2006, 1597 patients had a documented cause of death.[3] A total of 236 patients (14.8% of 1,597) have died of AIDS-defining cancers from 1996 to 2006 but the proportion has declined from 20.5% (70/341) during 1996-1999 to 12.5% (78/624) during 2003-2006. While 189 patients (11.8% of 1,597) have died of non-AIDS-defining cancers during the same time period, the proportion has increased from 7.3% (25/341) during 1996-1999 to 15.4% (96/624) during 2003-2006. A similar trend was also noted when assessing the 5-year cumulative incidence of cancer in 472,378 individuals with HIV or AIDS who were cancer-free at the time of diagnosis from 1980 to 2006 in 3 distinct timeframes: 83,789 patients from 1980-1989 (prior to antiretroviral use), 213,029 patients from 1990-1995 (monotherapy/dual therapy with antiretroviral drugs), and 175,560 patients from 1996-2006 (HAART).[4] There was a decline in cumulative incidence of AIDS-defining cancers from 18% (15,728/83,789) to 11% (23,603/213,029) to 4.2% (7,570/175,560) over the 3 timeframes and a rise in non-AIDS-defining cancers from 1.1% (1,056/83,789) to 1.5% (4,348/213,029) with no change noted from 1996-2006 (2,911/175,560). While there was no change noted from 1990-1995 to 1996-2006, the incidence for non-AIDS-defining cancers such as anal cancer, Hodgkins lymphoma, and liver cancer did have a continued increase in incidence in all timeframes.

While the type of cancer HIV patients are getting may be changing, the need for treatment with concurrent antineoplastic agents and HAART is increasingly common. The potential of HAART to cause drug interactions is well documented.[5,6] However, little is known about the interaction potential of either cytotoxic or targeted antineoplastic agents with HAART. In addition to pharmacokinetic drug interactions, overlapping toxicities are also possible. This review will highlight what is known about potential pharmacologic interactions between antiretroviral and antineoplastic therapy. We will also consider how to combine antiretroviral and antineoplastic agents in patients with HIV who are on HAART therapy.

Antiretroviral Therapy

Antiretroviral Drug Classes

Current antiretroviral drugs classes include: nucleoside or nucleotide reverse-transcriptase inhibitors (NRTIs), non-nucleoside reverse-transcriptase inhibitor (NNRTIs), HIV-1 protease inhibitors (PI), integrase strand transfer inhibitors (INSTI), fusion inhibitors, and entry inhibitors which include chemokine receptor antagonists.[7] All recommended HAART regimens include a minimum of three active drugs to prevent resistance, with initial regimens including combinations of two NRTIs with an NNRTI, a PI boosted with ritonavir, or an INSTI.[8] Table 1 provides an overview of the potential drug interactions of each antiretroviral drug class with regards to the primary elimination route and alterations in drug metabolizing enzymes with emphasis on potential for interactions with anticancer agents. The potential for overlapping toxicities with anticancer agents and each antiretroviral drug class will be discussed in the toxicity section.

NRTIs inhibit the activity of HIV reverse transcriptase, an enzyme that copies the viral single stranded RNA into a double-stranded DNA. Nucleoside NRTIs or nucleotide NRTIs (NtRTIs) compete for incorporation into DNA with naturally occurring deoxynucleotides. NRTIs have relatively short plasma half-lives but have longer intracellular half-lives thus allowing for once daily administration for most NRTIs or NtRTIs. Certain NRTI/NtRTI-based regimens are associated with anemia, dyslipidemia, gastrointestinal symptoms, insulin resistance, neutropenia, nephrotoxicity, lactic acidosis associated with hepatic steatosis,

noncirrhotic portal hypertension, pancreatitis, peripheral neuropathy, and an increased risk of cardiovascular events.

NNRTIs bind to a pocket distant from the enzyme active site, and inhibit HIV reverse transcriptase by inducing conformational changes. Single point mutations in reverse transcriptase can dramatically alter virus susceptibility to first generation NNRTIs. Etravirine is a second generation NNRTI with the ability to bind to various conformations of the reverse transcriptase enzyme thus maintaining activity with single point mutations that confer resistance to first generation NNRTIs. Various NNRTI-based regimens are associated with rash, central nervous system toxicity, and hepatic transaminase elevations.

PIs block viral replication by preventing the HIV-1 protease from cleaving precursor proteins necessary to form infectious virions. Multiple mutations in the HIV protease enzyme are required to develop high level resistance to most PIs. Various PI-based regimens have been associated with dyslipidemia, fat maldistribution, gastrointestinal symptoms, insulin resistance, hepatic transaminase elevations, hyperbilirubinemia, and an increased risk of cardiovascular events.

Integrase strand transfer inhibitors block the final step in integration of viral genes into the host cell DNA. Single point mutations in integrase have been noted to cause resistance to the integrase strand transfer inhibitor, raltegravir.[66,67] Raltegravir is the first approved integrase inhibitor and has been associated with creatine kinase laboratory abnormalities, headache, insomnia, myopathy, rash, and rhabdomyolysis.

Fusion inhibitors interfere with the entry or fusion of HIV-1 to the host cell by blocking one of several targets including the viral envelope protein or a chemokine co-receptor (i.e., chemokine co-receptor 5 (CCR5)). Enfuvirtide, a synthetic peptide, was the first fusion inhibitor approved is injected twice daily but is currently reserved for heavily treatment-experienced patients only. Side effects associated with enfuvirtide include diarrhea, fatigue, injection site reactions, and nausea. Maraviroc is an entry inhibitor which binds the chemokine receptor CCR5 and is approved for the use in patients who have CCR5-trophic virus. Maraviroc has been associated with dizziness, hepatotoxicity, pyrexia, rash, and upper respiratory tract infections.

Initiating and Stopping Antiretroviral Therapy

Guidelines for developed countries now recommend that treatment is offered to HIV infected patients with: 1) a history of an AIDS-defining illness or 2) a CD4 lymphocyte count of <500 cells/mm^3.[8] Resistance testing is recommended for patients with HIV infection prior to initiating HAART treatment. The ultimate goal of therapy is to preserve or improve immune function while decreasing HIV-associated morbidity and mortality. Initial regimens should be selected to allow for maximal compliance while taking into consideration comorbidities, pretreatment genotypic drug resistance testing, and drug-specific factors such as convenience, drug interaction potential and side effect profiles. All NNRTI-based and PI-based regimens are typically administered once or twice daily.

Due to tolerability and viral sensitivity, the initial HAART regimen can change over time with special considerations being given to starting and stopping any component in the regimen. New regimens should contain at least two, and preferably three, active drugs from multiple antiretroviral drug classes. If treatment failure is suspected, compliance, tolerability, pharmacokinetic related issues, drug resistance, immunologic and virologic failure should be considered.

Caution is warranted when stopping treatment because of the risk of creating a resistant HIV strain.[68] In cases of severe or life-threatening toxicity, all components of the regimen should be stopped simultaneously. If drugs that have differing half-lives are stopped simultaneously, this may result in functional monotherapy if the drug with the longest half-life remains in circulation for a prolonged period after the short half-life drugs are eliminated (i.e., longer half-life NNRTIs with short half-life NRTIs). In this case, the strategy varies from either a staggered stop, or an exchange or replacement of an NNRTI with a PI to decrease the risk of functional monotherapy. The best approach to discontinuing therapy is unproven.

Drug Interactions with Antiretroviral Therapy

The pharmacokinetic drug interaction potential with the various antiretroviral therapies is considerable. Since each drug is metabolized by differing metabolic isozymes, generalizations based on each class are not possible (see Table 1). The drug interaction potential for NRTIs and NtRTIs is minimal but may occur if another drug alters renal clearance and/or intracellular phosphorylation. Tenofovir has been shown to cause unexpected changes in the concentration of other antiretroviral drugs, in some cases reflecting possible effects on drug transporters.[69,70] There is a high potential for pharmacodynamic interactions with some NRTIs, for example those causing hematologic toxicity. For PIs and NNRTIs, which are extensively metabolized by and induce or inhibit the CYP450 system, the drug interaction potential is high. Raltegravir undergoes glucuronidation by UGT1A1 and has lower drug interaction.[60] Maraviroc is a substrate of the CYP3A enzyme and ABCB1 transporter and susceptible to multiple drug interactions.[62,63]

For the majority of antiretroviral drugs that are CYP450 substrates, inducers, or inhibitors, coadministration with other metabolized drugs could result in drug accumulation and possible toxicity, or decreased efficacy of one or both drugs. Drug interaction resources should be consulted when determining interaction potential (see Table 2). For example, with the benzodiazepam class, PIs should not be coadministered with alprazolam, diazepam, oral midazolam, and triazolam but can be coadministered with lorazepam, oxazepam, or temazepam.[8] Intravenous midazolam utilized for conscious sedation should be used at a reduced dose and with caution when combined with ritonavir PI-based therapy.[71]

Antiretroviral Therapy and Anticancer Treatment

As HIV patients continue to live longer and develop AIDS-related malignancies or non-AIDS-defining cancers, more information on how to treat patients with anticancer treatment will be needed. Drug interactions are certainly one aspect, but overlapping toxicities are also a concern. Several antiretrovirals, including didanosine, stavudine, and zidovudine, have significant toxicities described below and are therefore not utilized in first-line HAART regimens in the developed world.

Assessing hepatic function in patients on antiretrovirals

Bilirubin is often used as a guide for dose adjustment for cancer chemotherapy agents such as docetaxel,[72] doxorubicin,[73] etoposide,[74] imatinib,[75] irinotecan,[76] paclitaxel,[77] sorafenib,[78] vincristine,[79] and vorinostat.[80] Several antiretrovirals, most notably atazanavir and indinavir are associated with unconjugated hyperbilirubinemia secondary to UGT1A1 inhibition similar to that which occurs in association with Gilbert's syndrome.[53,81,82] When assessing liver function in HIV patients on these antiretroviral agents, it is useful to also assess transaminases and alkaline phosphatase. Unconjugated hyperbilirubinemia in association with these agents and in the absence of other evidence of hepatic dysfunction

may be ignored in dosing chemotherapeutic agents. On the other hand, didanosine, stavudine, and zidovudine may produce hepatotoxicity associated with lactic acidosis and steatosis.[83] Maraviroc has been noted to rarely produce a hepatotoxicity associated with allergic features.[84] Such hepatotoxicity should not be ignored and didanosine, maraviroc, stavudine, and zidovudine should be stopped or replaced before initiating cytotoxic chemotherapy with agents that have hepatic metabolism at standard doses but use reduced dosing based on the degree of hepatotoxicity. The NRTIs, abacavir, emtricitabine, lamivudine, and tenofovir, and the NNRTI efavirenz are the less likely to be hepatotoxic and may often be substituted.

Toxicity-related Concerns

Zidovudine is associated with severe neutropenia in ~8% of patients with advanced AIDS.[85] Since traditional cytotoxic chemotherapy regimens are also associated with neutropenia, this combination should be avoided and an alternative NRTI should be prescribed. If zidovudine use cannot be avoided, less myelosuppressive chemotherapy should be administered or the patient monitored closely for neutropenia.

Didanosine and stavudine have been frequently associated with peripheral neuropathy which may be irreversible.[86] While the onset is typically weeks to months after initiation of therapy, patients with pre-existing neuropathy may experience this toxicity sooner. Platinums, taxanes, and vinca-alkaloids are the three classes of chemotherapeutics frequently associated with peripheral neuropathy. The first proteasome inhibitor, bortezomib, is associated with a reversible peripheral neuropathy which appears to be a class-effect.[87,88] Chemotherapy-induced neuropathy is generally cumulative or dose related, with management consisting of dose-reduction or lower dose-intensity. If an HIV patient develops a malignancy and is on one of the NRTIs listed above, the following options exist: 1) select an alternative chemotherapy regimen without overlapping toxicity; 2) substitute an alternate NRTI or other appropriate antiretroviral; 3) temporarily discontinue antiretroviral therapy.

Atazanavir,[89] ritonavir boosted lopinavir,[90] and saquinavir[91] are associated with QT prolongation. Multiple anticancer agents also are associated with QT prolongation including cytotoxic agents and the newer molecularly targeted anticancer agents such as anthracyclines,[92] arsenic trioxide,[92] dasatninb,[93] lapatinib,[94] nilotinib,[95] sunitinib,[96] and tamoxifen.[97] Due to the potential for sudden death, combinations of these agents should be avoided.

Anticancer Drug Interaction Potential

Since many anticancer agents are also metabolized by CYP450, the potential for drug interactions with HAART is high. Anthracyclines, antimetabolite agents, antitumor antibiotics, and platinums undergo non-CYP450 routes of elimination and would be unlikely to be altered by HAART.[98,99] Camptothecins undergo non-enzymatic routes of elimination, are substrates but not inhibitors or inducers of CYP450 and UGT isozymes and therefore are likely to be altered by HAART.[100] Proteasome inhibitors are substrates but not inhibitors or inducers of CYP450s at clinically relevant drug concentrations.[101] Bidirectional drug interactions could be anticipated by other classes of anticancer agents including alkylating agents,[102] corticosteroids, epipodophyllotoxins,[102] taxanes,[102,103] tyrosine kinase inhibitors,[104] and vinca alkaloids.[102] Antoniou and Tseng recently reviewed the potential drug interactions between antiretroviral and anticancer therapy.[105] As recently reviewed by Deeken and colleagues, some molecularly targeted agents may have pharmacokinetic-based drug interactions with HAART.[106]There is little information available from prospective drug interaction trials and so the review was largely predicted from metabolic fate of the

combinations. Several case reports, small series, and clinical trials have suggested antiretroviral drug interactions with several anticancer agents including bexarotene,[107] cyclophosphamide,[108] docetaxel,[109] irinotecan,[110] and vinblastine.[111] It is possible that newer classes of antiretrovirals, such as the integrase strand transfer inhibitor raltegravir,[112] will have reduced interaction potential than NNRTIs and PIs.

When trying to address patient specific cancer regimens in patients with HIV/AIDS on HAART, the oncologist should partner with an infectious diseases specialist to review anticipated changes in the HAART regimen. At the current time, there is no guidance on dose adjustments of either HAART or chemotherapy. This is in part the consequence of HIV patients being excluded from early cancer drug development studies.[113] In 2006, the Cancer Therapy Evaluation Program (CTEP) of the National Cancer Institute (NCI) advised that "Individuals known to be HIV-positive should not be arbitrarily excluded from participation in clinical cancer treatment trials," without scientific justification for exclusion.[114] Therefore, it will take several years before guidelines provide scientifically sound recommendations for novel agents still undergoing development.

The dilemma for the clinician becomes how to treat patients who require anticancer drug treatment given the propensity of drug interactions. Since the advent of HAART, HIV has become a chronic disease. There has been no such success with the majority of cancers especially with the deadliest forms such as esophageal, lung, metastatic melanoma, and pancreatic cancers. The maintenance of dose-schedule and dose-intensity are the primary principals which are thought to contribute to cancer cure. In some cases, cancer treatment should take priority over HIV treatment, despite the risk associated with stopping HAART.[115,116] However, the oncologist must also recognize that continuous HAART therapy is recommended in order to prevent resistant HIV strains, opportunistic infections, and eventual death.[116]

When cancer occurs in patients with HIV who are not yet on antiretroviral therapy, many clinicians opt to initiate cancer chemotherapy first, and only to add antiretroviral therapy after side effects (e.g., nausea, vomiting, and mucositis) associated with chemotherapy are adequately managed. This avoids starting and stopping antiretroviral therapy in a way that might engender antiretroviral resistance. For some chemotherapy regimens, notably continuous infusion regimens and high dose/ablative regimens such as are used in the setting of autologous transplant, concerns with possible adverse drug interactions are such that it is routine to stop antiretroviral therapy before initiating such treatment. For example, Little and colleagues were able to successfully treat AIDS–related lymphomas (ARLs) with dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin) with suspension of antiretroviral therapy.[117] The choice to stop antiretroviral therapy was to ensure that the maximum intensity of the dose-adjusted EPOCH regimen could be achieved while minimizing drug interactions and preserving immune function. The majority (74%) of patients achieved a complete remission with viral loads decreased below baseline by 3 months and CD4+ counts recovered by 12 months after HAART was reinstituted. When EPOCH was studied by ECOG, institutional investigators were allowed to determine whether to administer or hold HAART therapy.[118] No clear adverse effects were noted in patients who received combined HAART and EPOCH chemotherapy, and so it would appear that for many patients and many regimens, either approach is allowable. Most clinicians would avoid the combination of zidovudine with any myelosuppressive regimen, many would interrupt HAART for continuous or high dose chemotherapy regimens, and most would search for alternatives to ritonavir-based regimens when combination chemotherapy regimens are being administered since no clear consensus exists.

Future of Antiretroviral Therapy and Targeted Anticancer Treatment

The trend in anticancer drug development is to move from the use of cytotoxic chemotherapy which is indiscriminate to molecularly targeted agents which are more selective at killing cancer cells.[119] Since molecularly targeted agents tend to have less myelosuppression and peripheral neuropathy, there may be fewer concerns about overlapping toxicity with HAART. However, the newer anticancer agents are not without toxicity such as QT prolongation or hypertension.

The AIDS Malignancy Consortium, a National Cancer Institute-supported clinical trials group, is starting to address some of these issues by conducting prospective clinical trials with molecularly targeted agents in patients on HAART. Patients are stratified according to HAART regimens: NNRTI-based HAART therapy, efavirenz- based HAART therapy, non-ritonavir-based PI therapy, and ritonavir-based PI therapy. Patients on NNRTI-based, efavirenz- based, or non-ritonavir-based PI therapy commence treatment at the FDA-approved dose of the anticancer drug, while patients on ritonavir-based PI therapy will start at a reduced dose and escalate according to a standard '3+3' dose escalation. Patients on efavirenz-based therapy may be escalated above the FDA-approved dose while cautiously monitoring both drug concentrations and toxicity. As standard of care in HAART regimen change over time[8], this stratification schema may shift, but in general will include considerations of drug interaction potential. This design was modeled after organ dysfunction studies conducted in cancer patients.[120] A translational approach may be warranted to aid in prioritizing anticancer agents for the next clinical trials based on their propensity to interact with HAART *in vitro* and in animals models.

Conclusion

Detailed guidelines for dose adjustment based on clinical trials data are generally not available for anticancer and antiretroviral drugs used concurrently. We look forward to a time when the results of prospective clinical trial data will be available to guide clinical decision making. For the time being, clinicians and clinical investigators must be cognizant of the potential for interactions that may be inferred from knowledge of drug metabolism and make judicious treatment decisions. The importance of oncologists and infectious disease specialists partnering in the management of these patients and discussing the particulars of strategies that involve combinations of drugs cannot be overstressed. As patients with HIV live longer, and more develop malignancies whether HIV related or not, a better understanding of cancer chemotherapy and antiretroviral drug interactions will grow in importance.

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Table 1

Drug Interaction Potential of HAART

Drug	Route of Elimination (Substrate)	Effect on CYP450/Transporters	Potential for Clinically Significant Pharmacokinetic Drug Interactions		Ref.
			Effect on ARVs (substrate)	Effect on Cancer Drugs (due to enzyme or transporter induction or inhibition)	
Nucleoside reverse-transcriptase inhibitors (NRTIs)					
Abacavir	Renal excretion, ALDH, UGT[1]	None known	Unlikely	Unlikely	9-11
Didanosine	Renal excretion, purine nucleoside phosphorylase	None known	Unlikely	Unlikely	12
Emtricitabine	Renal excretion	None known	Unlikely	Unlikely	13
Lamivudine	Renal excretion	None known	Unlikely	Unlikely	14
Stavudine	Renal excretion	None known	Unlikely	Unlikely	15
Zidovudine	UGT2B7	None known	Possible	Unlikely	16,17
Nucleotide reverse-transcriptase inhibitors (NtRTIs)					
Tenofovir	Renal excretion	Weak inhibitor: CYP1A2	Unlikely	Possible	18
Non-nucleoside reverse-transcriptase inhibitor (NNRTIs)					
Delavirdine	CYP2D6, CYP3A4	Inhibitor: CYP2C9/2C19, CYP2D6, CYP3A4	Possible	Possible (inhibitor)	19,20
Efavirenz	CYP2B6>CYP3A, UGT2B7	Inducer: CYP2B6, CYP3A4 Inhibitor: CYP2C9/2C19. CYP3A4	Possible	Highly likely (inducer)	21-24
Etravirine	CYP2C9/2C19, CYP3A4, UGT[1]	Weak inducer: CYP2B6, CYP3A4 Weak inhibitor: CYP2C9/2C19, ABCB1	Possible	Highly likely (inducer)	25,26
Nevirapine	CYP2B6, CYP3A4, UGT[1]	Potent inducer: CYP2B6, CYP3A4	Possible	Highly likely (inducer)	26-28
Ritonavir or ritonavir–boosted HIV-1 protease inhibitors (PI)					
Amprenavir	CYP3A4>CYP2D6, CYP2C9, ABCB1, UGT[1]	Strong to weak inhibitor: CYP3A Inducer: CYP3A4, ABCB1	Possible	Definite (inhibitor)[2]	29-33
Darunavir	CYP3A4	Inhibitor: CYP3A4	Possible	Definite (inhibitor)[2]	34
Fosamprenavir (prodrug)	Hydrolyzed to amprenavir	See amprenavir	Possible	Definite (inhibitor)[2]	29,35
Indinavir	CYP3A4, ABCB1, ABCC2, UGT[1]	Strong to weak inhibitor: CYP3A>CYP2D6, UGT1A1	Possible	Definite (inhibitor)[2]	29,32,36-41
Lopinavir	CYP3A, ABCC2	Strong to weak inhibitor: CYP3A4>UGT1A1	Possible	Definite (inhibitor)[2]	41-44

Drug	Route of Elimination (Substrate)	Effect on CYP450/Transporters	Potential for Clinically Significant Pharmacokinetic Drug Interactions		Ref.
			Effect on ARVs (substrate)	Effect on Cancer Drugs (due to enzyme or transporter induction or inhibition)	
Ritonavir	CYP3A4 >CYP2D6, ABCB1, ABCC2	Inducer: CYP2B6, CYP2C9/2C19, CYP3A4, UGT[1] Inhibitor: CYP3A>CYP2D6>CYP2C9	Possible	Definite (inhibitor or inducer)	29,32,36, 38,39,45-49
Saquinavir	CYP3A4, ABCB1, ABCC2	Weak inhibitor: CYP3A, CYP2C9>CYP2D6, UGT1A1, ABCB1, ABCC2	Possible	Definite (inhibitor)[2]	29,32,36, 38,39,41, 44
Tipranavir	CYP3A4, UGT[1], ABCB1	Inducer: CYP3A4, ABCB1 Inhibitor: CYP1A2, CYP2C9/2C19, CYP2D6	Possible	Definite (inhibitor or inducer)[2]	50-52
Non-ritonavir boosted HIV-1 protease inhibitors (PI)					
Atazanavir	CYP3A4, ABCB1	Inhibitor: CYP3A4>CYP2C8, UGT1A1, ABCC2	Possible	Possible (inhibitor)	41,44,53-56
Nelfinavir	CYP2C19> CYP3A4 CYP2D6, CYP2C9	Inducer: CYP2C9, CYP3A4, ABCB1 Inhibitor: CYP3A>CYP2D6	Possible	Possible (inhibitor or inducer)	29,31,36, 38,57-59
Integrase strand transfer inhibitors					
Raltegravir	UGT1A1	None known	Possible	Unlikely	60
Fusion inhibitors					
Enfuvirtide	Catabolism	None known	Unlikely	Unlikely	61
Entry inhibitors (Chemokine receptor antagonists)					
Maraviroc	CYP3A4, ABCB1	None known	Possible	Unlikely	62-65

Abbreviations: ABCB1, ATP-binding cassette sub-family B member 1 (a.k.a., P-glycoprotein); ABCC2, ATP-binding cassette sub-family C member 2 (a.k.a., CMOAT, MRP2); ALDH, alcohol dehydrogenase; ARV, antiretroviral; CYP, cytochrome P450; UGT, Uridine 5′-diphospho-glucuronosyltransferase

[1] Isozyme not specified.

[2] When used as a ritonavir-boosted PI.

Table 2

Antiretroviral Drug Interaction Resources

Resource	Website	Source
AIDSinfo	www.aidsinfo.nih.gov	U.S. Department of Health and Human Services (DHHS)
AIDSMeds	aidsmeds.com/	HIV+ patients and physicians
Clinical Care Options	clinicalcareoptions.com/	Clinical Care Options
FDA MedWatch	www.fda.gov/Safety/MedWatch/default	U.S. Food and Drug Administration (FDA)
HIV InSite	www.hivinsite.com	University of California San Francisco
HIVMA	www.hivma.org	HIV Medical Association
HIV medication guide	www.hivmedicationguide.com	J. Antony Gagnon, Pharm.D., B.Pharm., D.P.H., CDE, CAE and Rachel Therrien, Pharm., D.P.H.,MSC
Johns Hopkins POC IT Center: HIV Guide	www.hopkins-hivguide.org	Johns Hopkins University
The Internet's HIV/AIDS Oral Healthcare Resource	www.HIVdent.org	US nonprofit dentists, nurses, pharmacists
Medscape	www.medscape.com	WebMD Health Professional Network
Toronto General Hospital Immunodeficiency Clinic	www.tthhivclinic.com/	Toronto General Hospital
University of Liverpool HIV Drug Interactions Web site	www.hiv-druginteractions.org	University of Liverpool HIV Pharmacology Group