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REVIEW

Oral oncolytic and antiretroviral therapy administration: dose adjustments, drug interactions, and other considerations for clinical use

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Abstract

The rise in non-AIDS defining cancers (NADCs) is emerging as a leading cause of death for HIV and cancer patients. To address this, current literature and guidelines suggest the continuation of antiretroviral therapy (ART) with oral oncolytic agents to prevent adverse complications associated with HIV disease progression. However, such an approach has the potential for drug–drug interactions and adverse events for patients on such therapy. Further, recommendations on how to adjust these medications, when used concomitantly, are limited. As such, our purpose is to evaluate existing literature through such means as drug databases (e.g. Micromedex, Lexi-Comp, etc.) and package inserts along with PubMed/Medline, Embase, and Google Scholar databases to develop a reference tool for providers to utilize when there is a decision to treat a patient with ART and oral oncolytic agents concurrently. Our findings suggest that there are many drug interactions that should be taken into consideration with dual therapy. Metabolism is a key determinant of dose adjustment, and many oncolytic agents and ART agents must have their dose adjusted as such. Most notably, several tyrosine kinase inhibitors require dose increases when used with non-nucleoside reverse transcriptase inhibitors (NNRTIs) but must be decreased when used concomitantly with protease inhibitors (PIs) and cobicistat. Further findings suggest that certain agents should not be used together, which include, but are not limited to, such combinations as bosutinib with NNRTIs, cobicistat, or PIs; idelalisib with maraviroc or PIs; neratinib with NNRTIs, cobicistat, or PIs; and venetoclax with NNRTIs. Overall, the most prominent oncolytic drug interactions were discovered when such agents were used concomitantly with PIs, cobicistat-boosted elvitegravir, or NNRTIs. Future studies are necessary to further evaluate the use of these agents together in disease therapy to generate absolute evidence of such findings. However, from the studies evaluated, much evidence exists to suggest that concomitant therapy is not without drug interactions. As such, clinical decisions regarding concomitant therapy should be evaluated in which the risk and benefit of dual therapy are assessed. Dose adjustments must be made accordingly and in consultation with both HIV and oncology clinicians and pharmacists to reduce the risk for adverse outcomes and disease progression for those with cancer and HIV/AIDS.

Keywords: adverse events, antiretroviral therapy, antiretrovirals, cancer, dosage adjustments, drug–drug interactions, HIV/AIDS, oral oncology agents, oral oncolytics.

Citation

Badowski ME, Burton B, Shaeer KM, Dicristofano J. Oral oncolytic and antiretroviral therapy administration: dose adjustments, drug-interactions, and other considerations for clinical use. Drugs in Context 2019; 8: 212550. DOI: 10.7573/dic.212550

Introduction

Significant advances in both antiretroviral (ARV) therapies and anticancer therapies have afforded patients longer life expectancies than ever in HIV and cancer, respectively. Over the past 20 years, the discovery and availability of antiretroviral therapy (ART) has significantly reduced human immunodeficiency virus (HIV)- and acquired immunodeficiency syndrome (AIDS)-related morbidity and mortality. Concurrently, advances in cancer treatment (e.g. targeted therapies) have resulted in sustained cancer and survival rates potentially years to decades longer than ever before. As a result, the number of AIDS-defining cancers has significantly decreased. Despite this, there has been a rise in non-AIDS defining cancers (NADCs), which have become one of the leading causes of death.[1] Clinical practice guidelines and other literature recommend initiation

of ART with anticancer therapy in patients newly diagnosed with HIV and cancer concurrently. They also recommend a continuation of ART in patients receiving chemotherapy to prevent a decrease in CD4 count, and subsequent opportunistic infections, and an increase in viral load. The presence of a malignancy should not delay the initiation of ART nor should initiation of ART delay the treatment and management of a malignancy due to potentially imminent, adverse implications on cancer outcomes.[2] Unfortunately, concomitant ART and chemotherapy also increases the risk of drug interactions related to reduced efficacy and increased toxicity of anticancer agents.[1]

Historically, ART was suspended in patients who were to receive high-dose myeloablative chemotherapy and in patients who underwent chemotherapy to manage certain AIDS-related lymphomas due to myelosuppressive effects of zidovudine as well as the use of protease inhibitors (PIs), which were responsible for increasing concentrations of chemotherapy agents and their subsequent risk of toxicity. The intent of this practice was to ensure that patients obtained the maximum benefit of chemotherapy without overlapping toxicity or drug interactions that could limit the total amount of chemotherapy patients could ultimately receive. Notably, these studies only evaluated patients with AIDS-associated lymphomas. The consequences of chemotherapy dose reduction, suspension, or discontinuation can adversely affect overall survival and curative intent. The studies supporting the aforementioned recommendations do have their limitations, which require very careful consideration. As many of these studies were published in a very narrow subset of oncology patients at a time before oral targeted therapies were widely utilized, they lack the external validity to apply these conclusions to larger oncology populations. Additionally, the impact of the toxicities of chemotherapy make it difficult to draw the best conclusions with regards to the efficacy of ARVs in this setting. For example, patients with significant mucositis, nausea, vomiting, or mechanical gastrointestinal (GI) obstructions who may require concomitant oral anticancer therapy may also be unable to receive their ART, or could potentially receive less than optimal amounts via non-oral enteral routes of administration.

Because of these important limitations, it is necessary that patients thoroughly understand the prognosis of their cancer and that providers discuss and carefully weigh the clinical intent of chemotherapy (curative versus palliative) with appropriate administration of ART. Furthermore, seamless communication with their interdisciplinary team regarding potential toxicities, medication access, and modifications in therapy is essential. As of December 2018, the National Cancer Institute reported over 250 oncolytic agents, of which 80 are oral. With new agents being approved approximately every 4 months in 2018 and more than 40 ARVs and combination therapies, the need to identify clinically significant drug–drug interactions between these two disease states is of utmost importance.[2,3] The objective of this review was to highlight clinically significant drug–drug interactions of oral oncolytic agents in the presence of ART and provide recommendations for those requiring concomitant treatment.

Methods

All US Food and Drug Administration (FDA) approved ARVs and oral oncolytic agents were determined through internet and primary literature searches. The list of drugs was updated with new drug approvals through verification with the FDA website through December 1, 2018. Antiretroviral and oral oncolytic agents were segmented into their respective classes (e.g. integrase inhibitors [INSTIs], nucleoside reverse transcriptase inhibitors [NRTIs], non-nucleoside reverse transcriptase inhibitors [NNRTIs], protease inhibitors [PIs], tyrosine kinase inhibitors [TKIs]), although some agents were not grouped due to the unique properties. To create a comprehensive table listing the metabolism profile for each of the agents, drug databases such as Micromedex and Lexi-Comp along with medication package inserts were utilized. Literature searches were performed using databases such as PubMed/Medline, Embase, and Google Scholar. Search terms included oral oncology and antiretroviral medications by name. Although studies were not limited, all identified studies were case reports, case studies, or case series. Studies were identified that evaluated drug–drug interactions between oral oncolytic agents and ART, thereby providing dosing recommendations for concomitant treatment. The metabolism profiles and studies were consolidated to generate a reference tool for providers when adjusting doses for those requiring concomitant oral oncolytic agents in the presence of ART. Various tables were created to assist the practitioner in identifying documented treatment recommendations for clinically significant drug–drug interactions (Table 1), circumstances where potential interactions are expected, but the practitioner should use clinical judgment and monitor (Table 2), the metabolism profiles of oral oncology and ARVs (Table 3), oral oncology agents with no expected interactions with ARVs (Box 1), and QTc prolongation risk potential for oral oncology agents and ARVs (Box 2). The following sections explain our results.

Entry/fusion inhibitors

Both enfuvirtide and maraviroc exert their mechanisms of action extracellularly on the CD4 cell. Maraviroc is a CCR5 chemokine coreceptor antagonist used for the treatment of CCR5-tropic HIV-1 infection. The CCR5-tropic receptor has been shown to be responsible for the entry process of the HIV virus into host CD4 cells.[2] Maraviroc is metabolized primarily by CYP3A4, and to a lesser extent P-glycoprotein (P-gp), into metabolites that are inactive against HIV infection.[4] The metabolite of maraviroc is a secondary amine formed by N-dealkylation and lacks significant activity. As a result

Table 1. Interactions for which dosing recommendations exist in literature and/or package labeling.[1]

Oncology drugs	Maraviroc	NRTIs	NNRTIs	INSTIs	PIs and COBI	Specific dosing recommendation
Abemaciclib			↓ Abemaciclib		↑ Abemaciclib	• Contraindicated with EFV, NVP, ETR • Avoid with PIs and COBI • Abemaciclib dose reduction to 100 mg twice daily with PIs or COBI if concomitant use unavoidable • If unable to tolerate 100 mg twice daily, can further reduce to 50 mg twice daily
Acalabrutinib					↑ Acalabrutinib	• Contraindicated with PIs and COBI
Afatinib					↑ Afatinib	• Avoid with PIs and COBI • If adverse events occur, reduce dose by 10 mg with PIs or COBI if concomitant use unavoidable
Alectinib					↑ Alectinib	• Alectinib dose reduction with PIs if symptomatic bradycardia observed • If starting dose is 600 mg twice daily, reduce to 450 mg twice daily for first occurrence, then 300 mg twice daily for second occurrence. Discontinue if patient is unable to tolerate 300 mg twice daily
Apalutamide	↓ MVC		↓ NNRTIs	↓ BIC, EVG	↓ PIs and COBI	• Contraindicated with NNRTIs • Avoid with MVC, EVG, PIs, and COBI • Increase dose of MVC to 600 mg twice daily (in the absence of a strong CYP3A4 inhibitor)
Axitinib			↓ Axitinib		↑ Axitinib	• Contraindicated with EFV, ETR, PIs, and COBI
Bosutinib			↓ Bosutinib		↑ Bosutinib	• Contraindicated with EFV, ETR, PIs, and COBI
Brigatinib					↑ Brigatinib	• Brigatinib dose reduction by 50% with PIs and COBI (round to nearest tablet strength)
Cabozantinib					↑ Cabozantinib	• Avoid with PIs and COBI • If concomitant use unavoidable, dose reduction based on formulation and indication
Ceritinib			↓ Ceritinib		↑ Ceritinib	• Avoid with PIs and COBI if possible • Reduce ceritinib dose with PIs and COBI by one-third and round to nearest 150 mg
Cobimetinib			↓ Cobimetinib		↑ Cobimetinib	• Contraindicated with EFV, ETR, PIs, and COBI
Crizotinib			↓ Crizotinib		↑ Crizotinib	• Avoid with PIs and COBI • If concomitant use of PIs or COBI unavoidable, dose reduce crizotinib to 250 mg daily
Dabrafenib	↓ MVC		↓ NNRTIs	↓ EVG	↓ PIs ↑ Dabrafenib	• Contraindicated with PIs and COBI • Avoid with EVG, MVC, and NNRTIs

(Continued)

Table 1. (*Continued*)

Oncology drugs	Maraviroc	NRTIs	NNRTIs	INSTIs	PIs and COBI	Specific dosing recommendation
Dasatinib					↑ Dasatinib	• Reduce dose of dasatinib with strong CYP3A inhibitor depending on starting daily dose from: 140 to 40 mg 100 to 20 mg 70 to 20 mg
Duvelisib					↑ Duvelisib	• Reduce dose of duvelisib with strong CYP3A4 inhibitors from 25 mg BID to 15 mg BID
Encorafenib					↑ Encorafenib	• Contraindicated with EFV, ETR • Avoid use with PIs and COBI • Decrease encorafenib dose to one-third of usual dose by rounding to the nearest 50 or 75 mg tablet size
Erlotinib					↑ Erlotinib	• Avoid with PIs and COBI • If severe adverse events occur, reduce erlotinib dose in 50 mg decrements
Everolimus					↑ Everolimus	• Contraindicated with PIs and COBI
Gilteritinib					↑ Gilteritinib	• Avoid with PIs and COBI
Glasdegib			↓ Glasdegib		↑ Glasdegib	• Avoid with EFV, ETR, PIs, and COBI
Idelalisib	↑ MVC				↑ PIs ↑ Idelalisib	• Contraindicated with MVC and PIs • Reduce idelalisib dose if unavoidable with strong CYP3A4 inhibitors
Ibrutinib					↑ Ibrutinib	• Contraindicated with PIs and COBI
Ketoconazole	↑ MVC		↓ Ketoconazole	↑ INSTIs	↑ PIs ↑ Ketoconazole	• Contraindicated with EFV and ETR • Avoid with PIs and EVG • Ketoconazole dose should not exceed 200 mg/day if concomitant use unavoidable with PIs and COBI • Reduce MVC dose to 150 mg twice daily
Lapatinib			↓ Lapatinib		↑ Lapatinib	• Contraindicated with PIs and COBI • Reduce dose of lapatinib when used with PIs to 500 mg/day of lapatinib • Increase dose with NNRTIs from 1250 mg/day up to 4500 mg/day (HER2-positive metastatic breast cancer indication) or from 1500 mg/day up to 5500 mg/day
Lorlatinib	↓ MVC		↓ NNRTIs ↓ Loratinib	↓ EVG	↓ PIs and COBI ↑ Lorlatinib	• Avoid with NNRTIs, EVG, MVC, PIs, and COBI
Midostaurin					↑ Midostaurin	• Avoid with PIs, and COBI
Mitotane	↓ MVC		↓ NNRTIs	↓ BIC, DTG, EVG	↓ PIs	• Avoid with MVC, NNRTIs, EVG, PIs, and COBI
Neratinib			↓ Neratinib		↑ Neratinib	• Contraindicated with EFV, ETR, PIs, and COBI

(Continued)

Table 1. (*Continued*)

Oncology drugs	Maraviroc	NRTIs	NNRTIs	INSTIs	PIs and COBI	Specific dosing recommendation
Nilotinib	↑ MVC		↓ NNRTIs ↓ Nilotinib	↑ INSTIs	↑ PIs ↑ Nilotinib	• Avoid with RPV, PIs, and COBI • Reduce dose of nilotinib with PIs and COBI to 300 mg daily for resistant or intolerant Ph+ CML or 200 mg daily for newly diagnosed Ph+ CML in chronic phase
Olaparib			↓ Olaparib		↑ Olaparib	• Contraindicated with EFV and ETR • Avoid with PIs or COBI • Reduce dose of olaparib from 300 mg twice daily to 100 mg twice daily with PIs or COBI
Palbociclib	↑ Palbociclib		↓ Palbociclib		↑ Palbociclib	• Contraindicated with PIs and COBI • If PI or COBI use unavoidable, reduce palbociclib to 75 mg/day • Avoid with EFV and ETR
Panobinostat			↓ Panobinostat		↑ Panobinostat	• Avoid with PIs and COBI • If PI or COBI use unavoidable, reduce panobinostat dose to 10 mg
Pazopanib			↓ Pazopanib		↑ Pazopanib	• Contraindicated with COBI and RTV • Avoid with PI • Reduce dose of pazopanib to 400 mg if use is unavoidable
Ponatinib					↑ Ponatinib	• Avoid with PI and COBI • Reduce dose of ponatinib from 45 mg daily to 30 mg once daily with PIs and COBI
Regorafenib					↑ Regorafenib	• Contraindicated with PIs and COBI
Ribociclib					↑ Ribociclib	• Avoid with PIs and COBI • Reduce dose of ribociclib to 400 mg daily if PI and COBI use unavoidable
Sonidegib			↓ Sonidegib		↑ Sonidegib	• Contraindicated with EFV, ETR, PIs, and COBI
Sunitinib					↑ Sunitinib	• Avoid with PIs and COBI
Tamoxifen					↑ Tamoxifen	• Avoid with PIs and COBI
Topotecan					↑ Topotecan	• Contraindicated with COBI and RTV
Toremifene					↑ Toremifene	• Avoid with PIs and COBI
Vemurafenib					↑ Vemurafenib	• Avoid with PIs and COBI
Venetoclax			↓ Venetoclax		↑ Venetoclax	• Contraindicated at initiation and during ramp-up phase with PIs and COBI • Contraindicated with EFV and ETR • Reduce dose of venetoclax by 75% if PI or COBI if use is unavoidable after ramp-up

[1]All data derived from Lexi-comp, Micromedex, and package insert for each medication.
ATV, atazanavir; BIC, bictegravir; CML, chronic myeloid leukemia; COBI, cobicistat; DRV, darunavir; EFV, efavirenz; ETR, etravirine; EVG, elvitegravir; INSTIs, integrase inhibitors; LPV/RTV, lopinavir/ritonavir; MVC, maraviroc; NNRTIs, non-nucleoside reverse-transcriptase inhibitors; NRTIs, nucleoside reverse-transcriptase inhibitors; NVP, nevirapine; PIs, protease inhibitors; RPV, rilpivirine; RTV, ritonavir; SQV, saquinavir.

Table 2. Interactions for which potential interactions are expected, but the practitioner should use clinical judgment and monitor.[1]

Oncology drugs	Maraviroc	NRTIs	NNRTIs	INSTIs	PIs and COBI
Abemaciclib			↓ Abemaciclib		↑ Abemaciclib
Abiraterone			↓ Abiraterone		↑ PIs
Acalabrutinib			↓ Acalabrutinib		↑ Acalabrutinib
Afatinib					↑ Afatinib
Apalutamide	↓ MVC		↓ NNRTIs	↓ INSTIs	↓ PIs, COBI
Bicalutamide	↑ MVC		↑ NNRTIs ↓ or ↑ Bicalutamide		↑ PIs ↑ Bicalutamide
Brigatinib			↓ Brigatinib		↑ Brigatinib
Busulfan			↓ Busulfan		↑ Busulfan
Cabozantinib		↑ Cabozantinib	↓ Cabozantinib		↑ Cabozantinib
Ceritinib	↑ MVC		↓ Ceritinib	↑ BIC, DTG, EVG	↑ PIs, COBI
Cyclophosphamide			↓ Cyclophosphamide		↑ Cyclophosphamide
Dasatinib			↓ Dasatinib		↑ Dasatinib
Duvelisib	↑ MVC		↓ Duvelisib		↑ Duvelisib
Encorafenib			↓ Encorafenib		↑ Encorafenib
Enzalutamide	↓ MVC		↓ NNRTIs ↓ Enzalutamide	↓ BIC, EVG	↓ PIs, COBI ↑ Enzalutamide
Erlotinib			↓ Erlotinib		↑ Erlotinib
Etoposide			↓ Etoposide		↑ Etoposide
Everolimus	↑ MVC		↓ Everolimus		↑ Everolimus
Exemestane			↓ Exemestane		↑ Exemestane
Gefitinib			↓ Gefitinib		↑ Gefitinib
Glasdegib			↓ Glasdegib		↑ Glasdegib
Ibrutinib			↓ Ibrutinib		↑ Ibrutinib
Idelalisib	↑ MVC		↑ NNRTIs ↓ Idelalisib	↑ BIC, EVG	↑ PIs, COBI ↑ Idelalisib
Imatinib	↑ MVC		↓ Imatinib		↑ Imatinib
Ixazomib			↓ Ixazomib		
Ketoconazole	↑ MVC		↑ NNRTIs ↓ Ketoconazole	↑ BIC, DTG, EVG	↑ PIs, COBI ↑ Ketoconazole
Lapatinib			↓ Lapatinib		↑ Lapatinib
Letrozole			↓ Letrozole		↑ Letrozole
Lorlatinib	↓ MVC		↓ NNRTIs		↓ PIs and COBI
Methotrexate					↑ Methotrexate
Midostaurin			↓ Midostaurin		↑ Midostaurin
Nilotinib			↓ NNRTIs ↓ Nilotinib		↑ Nilotinib
Osimertinib			↓ Osimertinib		↑ Osimertinib
Palbociclib	↑ MVC		↓ Palbociclib		↑ Palbociclib
Panobinostat			↓ Panobinostat		↑ Panobinostat
Pazopanib			↓ Pazopanib		↑ Pazopanib
Pomalidomide					↑ Pomalidomide

(Continued)

Table 2. ***(Continued)***

Oncology drugs	Maraviroc	NRTIs	NNRTIs	INSTIs	PIs and COBI
Ponatinib			↓ Ponatinib		↑ Ponatinib
Regorafenib			↓ Regorafenib		↑ Regorafenib
Ribociclib	↑ MVC		↓ Ribociclib		↑ Ribociclib
Sorafenib					↑ Sorafenib
Sunitinib			↓ Sunitinib		↑ Sunitinib
Talazoparib					↓ Talazoparib (with RTV or COBI)
Tamoxifen			↓ Tamoxifen		↑ Tamoxifen
Toremifene			↓ Toremifene		↑ Toremifene
Vandetanib			↓ Vandetanib		↑ Vandetanib
Vemurafenib	↓ MVC		↓ Vemurafenib		↑ Vemurafenib

[1]All data derived from Lexi-comp, Micromedex, and package insert for each medication.
BIC, bictegravir; COBI, cobicistat; DTG, dolutegravir; EVG, elvitegravir; INSTIs, integrase inhibitors; MVC, maraviroc; NNRTIs, non-nucleoside reverse-transcriptase inhibitors; NRTIs, nucleoside reverse-transcriptase inhibitors; PIs, protease inhibitors; RTV, ritonavir.

Table 3. Metabolism profiles of oral oncology and antiretroviral agents.[1]

Oral oncology agent	Substrate	Inhibitor	Inducer
Abemaciclib	CYP3A4, P-gp, BCRP	P-gp, BCRP, OCT2, MATE1, MATE2-K	
Abiraterone	CYP3A4	CYP2D6, CYP2C8, OATP	
Acalabrutinib	P-gp, BCRP, CYP3A4	CYP3A4/5, CYP2C8, CYP2C9, CYP2C19	CYP1A2, CYP2B6, CYP3A4
Afatinib	P-gp, BCRP	P-gp, BCRP	
Alectinib	CYP3A4	P-gp, BCRP	
All-trans retinoic acid (atra)	CYP2A6 (minor), CYP2B6 (minor), CYP2C8 (minor), CYP2C9 (minor)		CYP2E1 (weak)
Anastrozole	N-dealkylation, hydroxylation, glucuronidation	CYP1A2, CYP2C8 CYP2C9, CYP3A4	
Apalutamide	CYP2C8, CYP3A4	CYP2B6, CYP2C8 (moderate); CYP2C9, CYP2C19, CYP3A4, (weak), OCT2, OAT3, MATEs	CYP2B6, CYP3A4, CYP2C19, UGT (strong); CYP2C9, P-gp, BCRP, OATP1B1 (weak)
Axitinib	CYP3A4/5 (major); CYP1A2, CYP2C19, UGT1A1		CYP1A2, CYP2C8 (weak)
Bicalutamide	UGT1A9	CYP3A4 (major); CYP2C9, 2C19, 2D6 (minor)	
Binimetinib	UGT1A1, (major); CYP1A2, CYP2C19, P-gp, BCRP (minor)		
Bosutinib	CYP3A4		
Brigatinib	CYP2C8, CYP3A4, P-gp, BCRP	P-gp, BCRP, OCT1, MATE1, MATE2K	CYP3A, CYP2C
Busulfan	Glutathione S-transferase		
Cabozantinib	CYP3A4, MRP2	P-gp	

(Continued)

Table 3. ***(Continued)***

Oral oncology agent	Substrate	Inhibitor	Inducer
Capecitabine	CEs, thymidine phosphorylase	CYP2C9	
Ceritinib	CYP3A4, P-gp	CYP3A, CYP2C9	
Cobimetinib	CYP3A, UGT2B7		
Crizotinib	CYP3A4/5	CYP2B6, P-gp, OCT1, OCT2	
Cyclophosphamide	CYP2B6 (major); CYP2C9, CYP3A4, 3A5, 2C9, 2C18, 2C19 (minor)		
Dabrafenib	CYP2C8, CYP3A4, P-gp, BCRP	OATP1B1, OATP1B3, OAT1, OAT3, OCT2, BCRP	CYP3A4, CYP2B6, CYP2C
Dacomitinib	2D6 (minor)	2D6 (major)	
Dasatinib	CYP3A4, UGT, FMO-3	CYP3A4	
Duvelisib	CYP3A4, P-gp, BRCP		
Enasidenib	CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4, UGT1A1, UGT1A3, UGT1A4, UGT1A9, UGT2B7, UGT2B15	CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4, and UGT1A1, P-gp, BCRP, OAT1, OATP1B1, OATP1B3, OCT2	CYP2B6, CYP3A4
Encorafenib	UGT1A1, CYP1A2, CYP2B6, CYP2C8/9, CYP2D6, CYP3A, P-gp	P-gp, BCRP, OCT2, OAT1, OAT3, OATP1B1, OATP1B3	CYP2B6, CYP2C9, CYP3A4
Enzalutamide	CYP2C8 (major), CYP3A4 (major)	CYP2B6, 2C8, 2C9, 2C19, 2D6, 3A4/5 P-gp, BCRP	CYP2B6, CYP3A4 (strong), CYP2C9/19 (moderate)
Erlotinib	CYP3A4 > CYP1A2		
Etoposide	CYP3A4	CYP3A4, CYP2D6	
Everolimus	CYP3A4, P-gp		
Exemestane	CYP3A4		
Flutamide	CYP1A2 (major), CYP3A4 (minor)	CYP1A2	
Gefitinib	CYP3A4 (major); P-gp, CYP2D6 (minor)		
Gilteritinib	3A4, P-gp	BCRP, OCT1	
Glasdegib	CYP3A4, P-gp, BRCP (major); CYP2C8, UGT1A9 (minor)	P-gp, BRCP, MATE1, MATE2K	
Ibrutinib	CYP3A (major); 2D6 (minor)	BCRP, P-gp	
Idelalisib	Aldehyde oxidase, CYP3A (major); UGT1A4 (minor)	CYP2C8, CYP2C19, UGT1A1	CYP2B6
Imatinib	CYP3A (major); CYP1A2, CYP2D6, CYP2C9, CYP2C19 (minor)	CYP2C9, CYP2D6, CYP3A4/5	
Ixazomib	3A4, 1A2, 2B6 (major), 2C8, 2D6, 2C19, 2C9 (<1%) (minor)		
Ketoconazole	CYP3A4, P-gp	CYP3A4, P-gp (major); CYP1A1, 1A2, 2A6, 2C9, 2E1 (minor)	
Lapatinib	CYP3A4, P-gp	P-gp	
Lenalidomide	P-gp/ABCB1		
Lenvatinib	CYP3A, aldehyde oxidase, P-gp, BCRP	CYP2C8, CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP3A, UGT1A1	CYP3A
Letrozole	CYP3A4, CYP2A6	CYP2A6, CYP2C19	

(Continued)

Table 3. ***(Continued)***

Oral oncology agent	Substrate	Inhibitor	Inducer
Lorlatinib	CYP3A4, UGT1A4 (major); CYP2C8, CYP2C19, CYP3A5, and UGT1A3 (minor)	CYP3A, P-gp, OCT1, OAT3, MATE1, BCRP	CYP3A, CYP2B6
Mercaptopurine	HGPRT	6-TGNs	
Methotrexate	BCRP, OAT1, OAT3		
Midostaurin	CYP3A4	CYP1A2, CYP2C8, CYP2C9, CYP2D6, CYP2E1 and CYP3A, P-gp, BCRP, OATP1B1	CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP3A
Mitotane	CYP2C9		CYP3A4
Neratinib	CYP3A4 (major); FMO (minor)	P-gp	
Nilotinib	CYP3A4, P-gp (major); CYP2C8 (minor)	CYP2C8, CYP2D6, UGT1A1, P-gp	CYP2B6, CYP2D8
Nilutamide	CYP2C19		
Niraparib	CEs, UGT, P-gp, BCRP	BCRP (minor)	
Olaparib	CYP3A	CYP3A,P-gp, UGT1A1, BCRP, OATP1B1, OCT1, OCT2, OAT3, MATE1, MATE2K (minor)	CYP3A4, CYP2B6
Osimertinib	CYP3A4, P-gp, BCRP	BCRP	CYP1A2
Palbociclib	CYP3A, SULT2A1	CYP3A	
Panobinostat	CYP3A, P-gp (major); 2D6, 2C19 (minor) , UGT1A1, UGT1A3, UGT1A7, UGT1A8, UGT1A9, and UGT2B4	CYP2D6, CYP2C19, CYP3A4, OAT3, OCT1, OCT2, OATP1B1 and OATP1B3	
Pazopanib	CYP3A4, P-gp, BCRP (major); CYP1A2, CYP2C8 (minor)	CYP1A2, 3A4, 2B6, 2C8, 2C9, 2C19, 2D6, and 2E1	CYP3A4
Pomalidomide	CYP1A2, CYP3A4, P-gp (major); CYP2C19 and CYP2D6 (minor)		
Ponatinib	CYP3A4 (major); CYP2C8, CYP2D6 and CYP3A5 (minor)	P-gp, ABCG2, BSEP	
Regorafenib	CYP3A4, UGT1A9	CYP2C8, CYP2C9, CYP2B6, CYP3A4 and CYP2C19, CYP2D6, UGT1A9, UGT1A1, BRCP	
Ribociclib	CYP3A4	CYP1A2, CYP2E1 and CYP3A4/5, BCRP, OCT2, MATE1	
Rucaparib	CYP2D6, P-gp, BCRP (major); CYP1A2 and CYP3A4 (minor)	CYP2C8, CYP2D6, UGT1A1, P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, MATE1, MATE2K, OCT1, OCT2, MRP3	CYP1A2
Sonidegib	CYP3A	CYP2B6, CYP2C9, BCRP	
Sorafenib	CYP3A4, UGT1A9	UGT1A1, UGT1A9, P-gp	
Sunitinib	CYP3A4		
Talazoparib	P-gp, BCRP		
Tamoxifen	CYP3A (major), CYP2D6, CYP2C9, CYP2C19, CYP2B6, SULT1A1, UGT2B7, UGT1A4		
Temozolomide	Spontaneously hydrolyzes		
Thalidomide	Unchanged		
Thioguanine	TPMT		
Topotecan	P-gp, BCRP		

(Continued)

Table 3. ***(Continued)***

Oral oncology agent	Substrate	Inhibitor	Inducer
Toremifene	CYP3A4	CYP2C9 (minor)	
Trametinib	CEs, Glucoronidiation (major); P-gp, BSEP (minor)	CYP2C8	CYP3A
Trifluridine-tipiracil	Thymidine phosphorylase		
Vandetanib	CYP3A4, FMO1, FMO3	OCT2, P-gp	
Vemurafenib	CYP3A4, P-gp, BCRP	CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4/5P-gp, BCRP	
Venetoclax	CYP3A, P-gp, BCRP	P-gp, BCRP (major); OATP1B1 (minor)	
Vismodegib	98% unchanged; CYP2C9, CYP3A4/5 (minor)	CYP2C8, CYP2C9, CYP2C19, BCRP (minor)	
Vorinostat	UGT		
Antiretroviral agent	**Substrate**	**Inhibitor**	**Inducer**
Abacavir		MRP2	
Atazanavir	CYP3A4 (major)	BCRP/ABCG2, CYP3A4 (strong), OATP1B1/SLCO1B1, UGT1A1	
Bictegravir	P-gp, UGT1A1, CYP3A4	OCT2, MATE1	
Cobicistat	CYP3A4 (major)	BCRP/ABCG2, CYP2D6 (weak), CYP3A4 (strong), OATP1B1/SLCO1B1, OATP1B3/SLCO1B3	
Darunavir	CYP3A4 (major), P-gp/ABCB1	CYP2D6 (moderate), CYP3A4 (strong)	
Dolutegravir	BCRP/ABCG2, CYP3A4 (minor), P-gp/ABCB1, UGT1A1, UGT1A3, UGT1A9	OCT2, MATE1	
Doravirine	CYP3A4 (major)		
Efavirenz	CYP2B6 (major), CYP3A4 (major)		CYP2B6 (moderate), CYP2C19 (weak), CYP3A4 (moderate), UGT1A1
Elvitegravir	CYP3A4 (major), UGT1A1, UGT1A3		
Emtricitabine		MRP2	
Enfuvirtide	NONE		
Etravirine	CYP2C19 (major), CYP2C9 (major), CYP3A4 (major)	CYP2C19 (weak)	CYP3A4 (moderate)
Fosamprenavir	CYP2C9 (minor), CYP2D6 (minor), CYP3A4 (major), P-gp/ABCB1	CYP3A4 (moderate)	
Ibalizumab-uiyk		NONE	
Lamivudine		MRP2	
Lopinavir/ritonavir	CYP3A4	CYP3A4, P-gp (strong), OATP	
Maraviroc	CYP3A4 (major), P-gp/ABCB1		
Nelfinavir	CYP2C19 (major), CYP2C9 (minor), CYP2D6 (minor), CYP3A4 (major), P-gp/ABCB1	BCRP/ABCG2, CYP3A4 (strong)	CYP1A2 (weak), CYP2B6 (weak)
Nevirapine	CYP2B6 (minor), CYP2D6 (minor), CYP3A4 (major)	MRP2	CYP2B6 (moderate), CYP3A4 (weak)

(Continued)

Table 3. ***(Continued)***

Antiretroviral agent	Substrate	Inhibitor	Inducer
Raltegravir	UGT1A1		
Rilpivirine	CYP3A4 (major)		
Ritonavir	CYP1A2 (minor), CYP2B6 (minor), CYP2D6 (minor), CYP3A4 (major), P-gp/ABCB1	BCRP/ABCG2, CYP3A4 (strong), MRP2, OATP1B1/SLCO1B1, P-gp/ABCB1	CYP1A2 (weak), CYP2B6 (moderate), CYP2C19 (weak), CYP2C9 (weak)
Saquinavir	CYP2D6 (minor), CYP3A4 (major), P-gp/ABCB1	BCRP/ABCG2, CYP3A4 (strong), MRP2, OATP1B1/SLCO1B1	
Tenofovir alafenamide	BCRP/ABCG2, P-gp/ABCB1	MRP2	
Tenofovir disoproxil fumarate	BCRP/ABCG2, P-gp/ABCB1	MRP2	
Tipranavir	CYP3A4 (major)	BSEP/ABCB11, CYP2D6 (strong)	
Zidovudine	CYP2A6 (minor), CYP2C9 (minor), CYP2C19 (minor), CYP3A4 (minor), OAT3		

[1]All data derived from Lexi-comp, Micromedex, and package insert for each medication.
ABCG2, ATP-binding cassette G2; BSEP, bile salt export pump; CEs, carboxylesterases; FMO-3, flavin-containing monooxygenase 3; HGPRT, hypoxanthine-guanine phosphoribosyl transferase; MATE, multidrug and toxin extrusion protein; MRP, multidrug resistance-associated protein 2; OAT, organic anion transporter; OATP, organic anion transporting polypeptide; OCT, organic cation transporter; P-pg, P-glycoprotein; 6-TGNs, 6-thioguanine nucleotides; SULT, sulfotransferase; TPMT, Thiopurine S-methyltransferase; UGT1A1, uridine diphosphate-glucuronosyltransferase 1A1.

Box 1. Oral oncology agents with no expected interactions with antiretrovirals.

Anastrozole
Bicalutamide
Binimetinib
Dacomitinib
Enasidenib
Flutamide
Lenalidomide
Letrozole
Mercaptopurine
Nilutamide
Niraparib
Rucaparib
Tamoxifen
Temozolomide
Thioguanine
Trametinib
Tretinoin
Trifluridine/tipiracil
Vismodegib
Vorinostat

of maraviroc's metabolic profile, drugs that inhibit CYP3A4 and/or P-gp can lead to an increase in maraviroc concentration. Specifically, the use of idelalisib is contraindicated with maraviroc, as idelalisib may increase the serum concentration of maraviroc. It is recommended to avoid the use of maraviroc with enzalutamide, dabrafenib, or mitotane, as the oral oncology agents act as CYP3A4 inducers and potentially decrease serum concentrations of maraviroc, resulting in loss of virologic suppression of HIV-1 and development of resistance. If these combinations cannot be avoided, the dose of maraviroc should be increased to 600 mg twice daily with therapeutic drug monitoring (TDM) of maraviroc concentrations, if possible. If enzalutamide, dabrafenib, or mitotane are used in combination with a strong CYP3A4 inhibitor, then the maraviroc dose should be reduced to 150 mg twice daily, as the net effect will be inhibition, resulting in increased concentrations of maraviroc. Again, TDM of maraviroc concentrations should be obtained, if possible. It is noteworthy that in the presence of severe renal impairment, creatinine clearance (CrCl) <30 mL/minute, concomitant use of potent CYP3A4 inhibitors and/or potent CYP3A4 inducers is contraindicated with the use of maraviroc.

Although void of drug–drug interactions, the use of enfuvirtide is limited by its twice daily subcutaneous formulation and potential for injection site reactions. Enfuvirtide binds to the viral envelope glycoprotein and inhibits the fusion of HIV-1 with the CD4 cells by blocking a conformational change that is necessary for membrane fusion and entry into the cells.[5]

Box 2. QTc prolongation according to risk potential (oral oncology agents and antiretroviral agents).

Highest
Nilotinib
Ribociclib
Toremifene
Vandetanib
Vemurafenib
Moderate
Ceritinib
Crizotinib
Efavirenz
Glasdegib
Lenvatinib
Midostaurin
Osimertinib
Panobinostat
Pazopanib
Saquinavir
Indeterminate
Bosutinib
Capecitabine
Dasatinib
Lapatinib
Rilpivirine
Sorafenib
Sunitinib
Vorinostat

Post-attachment inhibitor

The newest advance in HIV therapy is ibalizumab-uiyk, a CD4-directed post-attachment HIV-1 inhibitor that, when used in combination with other ARVs, is used in the management of adults with multidrug resistant HIV-1 infection failing their current ARV regimen. This intravenous formulation lacks any significant drug–drug interactions.[6] Therefore, this agent is expected to be safe when given in combination with all oral oncolytics.

Ibalizumab, maraviroc, and enfuvirtide are reserved for use in heavily treatment-experienced patients living with HIV-1, but with the advent of newer agents with high genetic barriers to resistance, the need for these agents is not commonplace.

Nucleoside/nucleotide reverse transcriptase inhibitors

Dual NRTIs remain the backbone of therapy for many patients living with HIV/AIDS. NRTIs are analogs of nucleobases of DNA (adenine, cytosine, guanine, and thymine). Drugs of this class include abacavir, emtricitabine, lamivudine, tenofovir alafenamide, tenofovir disoproxil, and zidovudine.[2] Cellular enzymes convert NRTIs to their active triphosphate forms, which act as a competitive inhibitor of HIV reverse transcriptase, leading to a subsequent viral DNA termination. The majority of NRTIs are not substrates, inhibitors, or inducers of the CYP450 isoenzyme system.[2] Tenofovir disoproxil fumarate (TDF) is the single exception whereby *in vitro* concentrations have been substantially higher (~300-fold) than those observed *in vivo* and demonstrated a minor (e.g. 6%), reduction in metabolism of a CYP1A2 substrate.[7] Based on this information, the potential for a TDF-CYP-mediated interaction is unlikely. A recently approved TDF prodrug, tenofovir alafenamide (TAF), is unique in that it is the only NRTI that is a substrate of the P-gp and Breast Cancer Resistance Protein (BCRP) transporter.[8] Drugs that greatly affect P-gp and BCRP activity will likely alter the absorption, concentration, and efficacy of TAF. The use of strong P-gp inducers is not recommended with TAF. Abacavir, TAF, and TDF act as multidrug resistance-associated protein 2 (MRP2) inhibitors and should be used with caution in patients receiving cabozantinib due to cabozantinib acting as a substrate based on *in vitro* data. MRP2 inhibitors may increase cabozantinib concentrations thereby leading to toxicity.[8–10] While there are minimal drug–drug interactions with NRTIs and oral chemotherapy agents, a clinician should also mindfully evaluate a patient's renal function. All NRTIs except for abacavir are primarily eliminated from the body by renal excretion. In an evaluation of the pharmacokinetics of high-dose methotrexate in people living with HIV on ARTs, various NRTI backbones did not affect methotrexate elimination half-life despite the potential competition for active renal tubular transporters among NRTIs and methotrexate.[11] The use of concomitant agents eliminated via the renal route will need to be monitored closely, as further dosage adjustments may be warranted.

It is important to consider that with the use of other ARVs, such as bictegravir, dolutegravir, cobicistat, and rilpivirine, that inhibit renal transporters organic cation transporter 2 (OCT2) and/or multidrug and toxin extrusion 1 (MATE1), may cause a sustained increase in serum creatinine via inhibition of creatinine secretion. However, actual renal function is not impaired. Although outside the scope of this manuscript, it is worth noting this is an important consideration, as this should not be mistaken as a sign of renal toxicity. In general, only changes in SCr of >0.3 mg/dL from baseline warrant further investigation for renal toxicity.[12]

Integrase inhibitors

INSTIs exert their mechanism of action by preventing the insertion of HIV DNA into host CD4 cell DNA. Members of this drug class include raltegravir, elvitegravir, dolutegravir, and bictegravir.[2] The first FDA-approved integrase strand transfer inhibitor (INSTI), raltegravir, is neither a substrate, inhibitor, nor an inducer of CYP450 enzymes, which makes it

a preferred agent to use, if possible, when a patient requires chemotherapy.[13] Both *in vivo* and *in vitro* studies demonstrated that raltegravir is eliminated mainly by metabolism via a uridine glucuronyl transferases (UGT)1A1-mediated glucuronidation pathway. Co-administration of raltegravir with chemotherapy agents that inhibit or induce UGT1A1 may alter plasma levels of raltegravir. However, the oral chemotherapy agents reviewed in this manuscript are neither major substrates nor inhibitors of UGT1A1 (Table 1). Literature published has demonstrated success with a raltegravir-containing regimen used concomitantly with oral multi-kinase inhibitors, alkylating agents (e.g. cyclophosphamide), and epidermal growth factor receptor-TKIs (e.g. erlotinib).[14–17]

Another first generation INSTI, elvitegravir, is coformulated with cobicistat, a pharmacokinetic enhancer that helps maintain an adequate elvitegravir concentration to allow for once-daily administration. Elvitegravir is a substrate of CYP3A4 (major) and UGT1A1/3 (minor) as well as an inducer of CYP2C9, where cobicistat is a substrate and an inhibitor of CYP3A4 and CYP2D6 and inhibits numerous drug transporters (e.g. P-gp, BCRP, organic-anion transporting polypeptides (OATP)1B1, and OATP1B3).[18,19] Patients will have to be monitored closely for signs and symptoms of toxicities while taking cobicistat-boosted elvitegravir concomitantly with an oral chemotherapy agent that is a substrate, inducer, or inhibitor of these same CYP isoenzymes or drug transporters (Tables 1 and 2). Cabozantinib and tamoxifen concentrations may be reduced if given in conjunction with elvitegravir-based therapy due to CYP2C9 induction.[9,10,18,20] Co-administration of tamoxifen or cabozantinib with elvitegravir has not been studied. Tamoxifen metabolism occurs via two pathways that involve many CYP450 isoenzymes including CYP3A4 and CYP2C9, leading to an active metabolite responsible for most of its oncolytic activity.[20] As such, co-administration with elvitegravir-cobicistat-containing regimens may lead to failure of achieving adequate chemotherapeutic agent concentrations. Enzalutamide is a CYP3A4 inducer that may lead to subtherapeutic INSTI concentrations leading to virologic failure.[21] To date, no publications exist that provide guidance on whether or not elvitegravir, cobicistat, or oral chemotherapy agents require dosage adjustments if administered concomitantly. These plausible interactions are theoretical and have unknown clinical significance.

A second generation INSTI, dolutegravir, is primarily a substrate of UGT1A1 followed by CYP3A4.[22] *In vitro*, dolutegravir is a substrate of additional drug transporters (e.g. UGT1A3, UGT1A9, BCRP, and P-gp). Drugs that induce CYP3A4 or UGT1A1 and drug transporters may decrease dolutegravir plasma concentration and reduce the therapeutic effect of dolutegravir, leading to HIV virologic failure and the potential for resistance. Oral chemotherapeutic agents that inhibit CYP3A4 may increase dolutegravir concentrations, leading to adverse effects, but this is likely not clinically significant, as only a minor portion of dolutegravir (10–15%) undergoes metabolism via CYP3A4.[22] To date, no publications exist that provide guidance on whether or not dolutegravir or oral chemotherapy agents require dosage adjustments if administered concomitantly. These plausible interactions are theoretical with an unknown clinical significance. The recently approved second-generation INSTI, bictegravir, has a similar metabolic profile to dolutegravir in that it too acts as a substrate for UGT1A1 and CYP3A4, yet unlike dolutegravir, CYP3A4 and UGT1A1 have a similar contribution to the metabolism of bictegravir.[23] Both dolutegravir and bictegravir uniquely inhibit OCT2 and MATE1); therefore, drug–drug interactions can be expected with concomitant agents that impact these pathways.

The absorption of INSTIs and many oral chemotherapy agents may be impaired with concomitant administration of metal-containing antacids. Metal-containing antacids such as calcium carbonate, aluminum hydroxide, and magnesium hydroxide are commonly taken to minimize chemotherapy-induced GI upset. Staggered or co-administration of raltegravir with aluminum and/or magnesium hydroxide–containing antacids is not recommended.[2] However, raltegravir 400 mg tablets may be administered without dose adjustment or separation from calcium carbonate–containing antacids. Conversely, the current recommendation is to avoid co-administration of raltegravir 600 mg tablets with calcium carbonate–containing antacids.[2,13] The appropriate duration of separation has yet to be proposed or determined. Elvitegravir as well as bictegravir and antacid administration must be separated by at least 2 hours.[2,18,23] Dolutegravir must be administered at least 2 hours before or 6 hours after antacids.[2,22] An antacid must also be administered 2 hours before or after dasatinib, erlotinib, nilotinib, and vismodegib and 6 hours before or after gefitinib, respectively.[24–28] Antacids may reduce the bioavailability of ponatinib, but the changes are not clinically significant to promote avoidance of co-administration.[29]

NNRTIs, PIs, and pharmacokinetic enhancers

NNRTIs, including etravirine, nevirapine, efavirenz, doravirine, and rilpivirine exert their mechanism of action by directly binding to HIV reverse transcriptase and causing a conformational change in the catalytic site and preventing viral DNA synthesis. PIs inhibit the function of HIV protease enzyme, consequently preventing proper protein formation, leading to a termination in the final step of the replication cycle. Agents in this class include atazanavir, lopinavir, and darunavir. Use of NNRTIs, PIs, and pharmacokinetic enhancers (e.g. ritonavir and cobicistat) are associated with the highest likelihood of drug–drug interactions with oral oncolytic agents. NNRTIs induce CYP3A isoenzymes, with the exception of rilpivirine and doravirine, which may result in decreased exposure and efficacy of concomitant agents metabolized through this pathway. Additionally, all NNRTIs serve as substrates of CYP3A4. In addition, efavirenz induces CYP2B6 and UGT1A1, etravirine inhibits CYP2C19, and nevirapine induces CYP2B6.[2] On the other hand, PIs and

pharmacokinetic enhancers act as substrates and inhibitors of CYP3A4 and P-gp.[2] A majority of oral oncolytics are substrates for CYP3A4 and/or P-gp. As a result, numerous drug–drug interactions are expected to occur when NNRTIs and PIs are administered concurrently. Ritonavir is a nonselective CYP450 and P-gp substrate, inhibitor, and inducer. At currently used pharmackokinetic boosting doses, ritonavir has similar inhibiting properties as cobicistat – that is, inhibition of CYP3A4, P-gp, and possibly 2D6. Ritonavir is distinct from cobicistat in that it also possesses inducing properties, and can induce UGT, CYP1A2, 2C9, 2C19 and 2B6.[2] This may result in many clinically significant drug–drug interactions and adverse effects. Cobicistat, a novel pharmacokinetic enhancer, is a CYP3A4, CYP2D6, and P-gp inhibitor. It is generally considered an equipotent inhibitor of CYP3A4 and P-gp. In many instances, dosage reductions or avoidance of oral oncolytics are needed (Tables 1 and 2). Although limited data exist in this population, drug–drug interactions are based on expected or documented interactions seen with potent CYP3A4 substrates, inhibitors, and inducers such as ketoconazole, clarithromycin, itraconazole, and carbamazepine. Caution should be observed, and close monitoring should occur if combining oral oncology agents and ARVs that carry this potential, if concomitant therapy is unavoidable.

Kinase inhibitors

Small molecule kinase inhibitors interfere with intracellular signaling pathways that provide a host of functions critical for normal cellular function, division, and survival. These agents comprise over half of all orally administered oncologic agents and are associated with drug interactions related to CYP450 metabolism. Clinicians should be cognizant of the high likelihood for potential interactions between these agents ARVs, and other medications. The following summarize commercially available classes as well as their interaction potentials with ARV agents (Tables 1–3).

Anaplastic lymphoma kinase (ALK) inhibitors

ALK inhibitors are indicated specifically for ALK rearrangement positive (ALK+) non-small cell lung cancer that comprises roughly 5% of all cases.[30] These agents are preferred over cytotoxic infusional chemotherapy for patients with ALK+ tumors in the first-line setting and after failure of prior ALK inhibitor therapy.[31]

Crizotinib is a major substrate for CYP3A4/5 as well as P-gp and moderately inhibits CYP3A4.[32] When compared with crizotinib alone, co-administration with strong CYP3A4 inhibitors and inducers showed over a 3-fold increase and 82% decrease in the area under the curve (AUC), respectively.[33] Co-administration of crizotinib with midazolam, a major CYP3A4 substrate, resulted in a 3.7-fold increase in midazolam AUC.[34] Therefore, use of crizotinib with PIs and cobicistat is contraindicated. Co-administration of crizotinib with efavirenz, nevirapine, or etravirine could theoretically result in reduced systemic exposure to crizotinib, as these NNRTIs are both moderate CYP3A4 inducers, and rilpivirine and doravirine are the least likely to interact, as it is neither an inhibitor nor an inducer of CYP450 enzymes.[32,35] Unboosted INSTIs such as bictegravir, dolutegravir, and raltegravir would be appropriate options for use with crizotinib.

Ceritinib is associated with a higher interaction potential when compared with crizotinib. In addition to being a major substrate for CYP3A4 and P-gp, it is also a moderate inhibitor of CYP2C9 and strong inhibitor of CYP3A4.[36,37] Ceritinib co-administration with ketoconazole, a strong CYP3A4 inhibitor, resulted in a 2.9-fold increase in AUC. Co-administration with PIs or cobicistat is contraindicated, but if concomitant therapy cannot be avoided, the dose of ceritinib should be reduced by one-third and rounded to the nearest 150 mg dose.[36] Co-administration of ceritinib with rifampin, a strong CYP3A4 inducer, resulted in a 70% decrease in ceritinib AUC. When administered with CYP3A and CYP2C9 substrates, ceritinib has been shown to result in time-dependent inhibition at clinical concentrations based on *in vitro* data. Ceritinib has the potential to increase the systemic exposure to maraviroc and all agents within the NNRTI drug class. As such, etravirine may decrease serum concentrations of ceritinib, as it acts as a major substrate for both CYP3A4 and CYP2C9. As efavirenz and etravirine are moderate CYP3A4 inducers, it is possible that reduced systemic exposure of ceritinib could ensue. Unboosted INSTIs such as bictegravir, dolutegravir, and raltegravir would be appropriate options for use with ceritinib.

Alectinib is a minor substrate of CYP3A4 and does not induce or inhibit any CYP450 enzymes.[38] Although alectinib is a CYP3A4 substrate, drug interaction studies have found that co-administration with CYP3A4 inducers and inhibitors do not result in significant changes in total alectinib systemic exposure. Hence, no pharmacokinetic interactions with alectinib requiring dosage adjustment have been identified. However, clinicians should be mindful of potential adverse effects associated with alectinib and concomitant drugs that may contribute to symptomatic bradycardia and hepatotoxicity. Bradycardia can develop in up to 18% of patients receiving alectinib; thus caution is advised when alectinib is prescribed with PIs, which are agents also associated with bradycardia.[38,39] Dosage modification of alectinib is not required in asymptomatic cases; however, for symptomatic bradycardia (e.g. dizziness, lightheadedness, syncope), the manufacturer recommends withholding alectinib until recovery to asymptomatic bradycardia or to a heart rate ≥60 bpm.[38] Evaluation of concomitant medications known to cause bradycardia and all antihypertensive medications is necessary in which dose adjustments or discontinuation of concomitant medications must be assessed. In addition, co-administration of alectinib with other agents known to induce hepatotoxicity may potentiate the risk of liver injury. Hepatotoxicity is a risk with most NNRTIs. Among NNRTIs, the risk of hepatotoxicity

is greatest with nevirapine, particularly in the first few months of therapy and greater for women than for men. Also, before starting nevirapine, the risk is greatest for women who have CD4 counts above 250 cells/mm^3 and for men who have CD4 counts above 400 cells/mm^3.[2] Efavirenz has been associated with hepatotoxicity during postmarketing use. In addition, all PIs can increase the risk of hepatotoxicity, but the risk is greatest with tipranavir/ritonavir. Maraviroc has also been reported to cause hepatotoxicity.[2] Among reported cases of hepatic failure, a few occurred in patients with no pre-existing hepatic disease or other identifiable risk factors. It is, therefore, prudent to monitor patients closely for signs and symptoms of hepatotoxicity. Monitoring of liver function tests should be performed before and during treatment, especially in patients with underlying hepatic disease (including hepatitis B or C co-infection) or marked transaminase elevations. The benefit of continued therapy with efavirenz should be considered against the unknown risks of significant hepatotoxicity in patients who developed persistent elevations of serum transaminases greater than five times the upper limit of normal.[40]

Brigatinib is metabolized by CYP3A4 and to a lesser extent by CYP2C8, BCRP/ATP-binding cassette (ABC) G2, and P-gp/ABCB1. The AUC of brigatinib increased by an average of 101% when co-administered with itraconazole and was reduced by 80% when administered with rifampin.[41] PIs or elvitegravir/cobicistat should not be administered concomitantly with brigatinib, but if co-administration is unavoidable, brigatinib should be dose reduced by 50%. It is possible that the NNRTIs may result in reduced systemic exposure of brigatinib; however, recommendations for dose adjustments have not been published to date. As is the case with alectinib, bradycardia has been reported with brigatinib. Similar recommendations for bradycardia management and dose modifications previously summarized for alectinib can be applied to brigatinib.[41] The use of bictegravir, dolutegravir, and raltegravir would be appropriate for co-administration with brigatinib.

Lorlatinib is primarily metabolized by CYP3A4 and UGT1A4 and to a lesser extent by CYP2C8, CYP2C19, CYP3A5, and UGT1A3.[42] When combined with itraconazole, the AUC and maximum concentration (Cmax) were increased by an average of 42 and 24%, respectively. Therefore, it is recommended to avoid lorlatinib with the use of PIs and elvitegravir/cobicistat. If this combination is unavoidable, the dose of lorlatinib should be reduced from 100 to 75 mg once daily. Further reduction to 50 mg daily may be required in the presence of adverse effects (e.g. peripheral neuropathy, weight gain, mood effects, diarrhea, fatigue). Baseline and periodic cholesterol screening is also strongly advised, as PIs may exacerbate hyperlipidemia caused by lorlatinib, which has been shown to occur in >90% of patients.[42] When lorlatinib 150 mg was combined with a single dose of midazolam, the AUC and Cmax of midazolam were reduced by an average of 64 and 50%, respectively.[42] Concomitant use of lorlatinib and CYP3A4 substrates should be avoided based on the potential loss of therapeutic effect in ARVs such as maraviroc, NNRTIs, PIs, and COBI. Additionally, when combined with a strong CYP3A4 inducer such as rifampin, severe hepatotoxicity occurred in 10 of 12 patients. Therefore, lorlatinib use is contraindicated with strong CYP3A4 inducers and should be avoided with moderate inducers such as efavirenz, nevirapine, and etravirine.[42] If concomitant use in unavoidable, ALT, AST, and bilirubin should be monitored 48 hours after initiation and at least three times during the first week of therapy.[42]

In summary, alectinib is the least likely of the ALK inhibitors to interact pharmacokinetically with ARVs; however, concomitant therapy may cause or potentiate bradycardia. Brigatinib also carries this risk. As each of these therapies have the potential for significant interactions, close patient monitoring and/or dosage adjustments are necessary to avoid potentially serious toxicities.

BCR-ABL tyrosine kinase inhibitors

After oral administration, bosutinib is extensively metabolized by CYP3A4.[43] Abbas et al. conducted an open-label, randomized, two-period crossover study where patients received either bosutinib 100 mg once as a single dose or in combination with a potent CYP3A4 inhibitor (ketoconazole, 400 mg every 12 hours starting 12 hours before the bosutinib dose for five doses). Ketoconazole co-administration was associated with a 5.2-fold increase in bosutinib Cmax and 8.6-fold increase in bosutinib AUC. The mean terminal half-life was significantly increased in the ketoconazole arm, as well.[44] Therefore, concomitant use of bosutinib with PIs or cobicistat is contraindicated and should be avoided. Abbas et al. conducted a similar study assessing the effect of rifampin, a potent CYP3A4 inducer on bosutinib. Rifampin administration was associated with an 86% reduction in Cmax, 92% reduction in AUC, and a significant reduction in half-life for bosutinib.[45] With respect to NNRTIs, efavirenz, nevirapine, and etravirine moderately induce CYP3A4 while nevirapine weakly inhibits this enzyme. Co-administration of bosutinib with all moderate or strong CYP3A4 inhibitors or inducers should be avoided.[43,46] Thus, rilpivirine and doravirine are the preferred NNRTIs to use if co-administration with bosutinib is necessary. Bosutinib can be safely administered with unboosted INSTIs.

Nilotinib is metabolized by CYP3A4 and P-gp; is a moderate inhibitor of CYP2D6, CYP3A4, P-gp, UGT1A1; and is a weak to moderate inducer of CYP2B6. In addition, nilotinib is both a weak to moderate inducer and inhibitor of the CYP2C8/9 enzyme system.[26,47,48] Ketoconazole co-administration with nilotinib resulted in a 1.8- and 3-fold increase in Cmax and AUC, respectively.[49] When co-administered as a single or repeated dose with midazolam, nilotinib resulted in weak and moderate inhibition of the CYP3A enzyme, respectively.[50] It is recommended to avoid co-administration of strong inhibitors of CYP3A4 such as PIs and cobicistat. All of the NNRTIs may be subject to weak to moderate CYP inhibition when co-administered with nilotinib, causing increased concentrations of NNRTIs. Generally, co-administration of these agents with

nilotinib can proceed with monitoring of toxicities from the NNRTIs and efficacy or toxicity of nilotinib (e.g. rash, nausea/vomiting, fatigue, diarrhea, constipation, and headache).[26,47] Rilpivirine and doravirine neither induce nor inhibit any CYP enzyme system and are not expected to affect systemic exposure of nilotinib. An *in vitro* study of nilotinib metabolism was conducted by Pillai et al. using human hepatocytes alone or treated with ketoconazole or ritonavir and efavirenz or rifampin. As expected, nilotinib treatment with ketoconazole or ritonavir was associated with a significantly higher AUC when compared to nilotinib alone. Efavirenz treated cells exhibited a 1.6-fold reduction in AUC and 2.1-fold reduction in half-life compared with vehicle control.[51] Although there is the potential for increased bictegravir, and possibly dolutegravir, via CYP3A4 inhibition by nilotinib, they are not considered clinically significant. Therefore, unboosted INSTIs may be safely administered with nilotinib.

Dasatinib is metabolized through the CYP3A4 isoenzyme and has inhibitory activity against CYP2C8 and 3A4.[24] In a pharmacokinetic study in healthy volunteers, systemic exposure was increased five-fold when dasatinib was administered with ketoconazole.[52] When co-administered with midazolam or repaglinide (CYP3A4, CYP2C8), dasatinib inhibition properties were responsible for increasing midazolam and repaglinide concentrations.[52] Concurrent use of strong CYP3A4 inhibitors should be avoided, but if this is not possible, a dosage reduction of 20 mg once daily is recommended if the optimal dose is 100 mg once daily. If the recommended dose is 140 mg once daily, a dosage reduction of 40 mg once daily is recommended.[24] In another pharmacokinetic study in healthy volunteers, the AUC of dasatinib was reduced by 82% when given in combination with the potent CYP3A4 inducer, rifampin.[53] With the exception of rilpivirine and doravirine, efavirenz, nevirapine, and etravirine may reduce dasatinib concentrations. The use of unboosted INSTIs may safely be administered with dasatinib.

Imatinib is metabolized primarily by CYP3A4. Area under the curve increased by 40% in healthy volunteers receiving concomitant ketoconazole.[54,55] Theoretically, PIs and cobicistat could result in added toxicity from imatinib with manifestations such as edema, rash, and GI distress. Imatinib is a potent inhibitor of CYP3A4 and 2D6 and, therefore, may increase the Cmax and AUC of drugs metabolized through this pathway. Further, drugs that induce CYP3A4, efavirenz, nevirapine, and etravirine, will lower the systemic level of imatinib. As such, it is recommended to increase the imatinib dose by at least 50% if concomitant use cannot be avoided.[56]

Ponatinib is a substrate of CYP3A4, 2C8, and 2D6.[29] Use with CYP3A4 inhibitors such as PIs and cobicistat should be avoided, as using these agents together will increase the AUC and Cmax of ponatinib by 78 and 47%, respectively, based on a study in healthy volunteers receiving concomitant ketoconazole.[57] If use is unavoidable, the dose of ponatinib should be lowered to 30 mg once daily as opposed to the standard dosing of 45 mg once daily.[29] Concomitant use of CYPinducers will theoretically lower systemic concentrations of ponatinib; however, clinical evidence is not abundant to support this. Ponatinib inhibits the P-gp transport system and, therefore, has a theoretical effect on drugs utilizing this pathway including maraviroc.

The BCR-ABL inhibitors are used most widely in various lines of therapy of chronic myeloid leukemia (CML). As these agents are instrumental in inducing long-term responses in patients, concomitant therapy with ARVs is often unavoidable in patients co-infected with HIV. Given the high likelihood of interactions associated with these agents, it is imperative that clinicians carefully modify ART or select regimens with the least potential to interact and/or dose adjust these agents as clinically necessary.

Bruton tyrosine kinase (BTK) inhibitors

Ibrutinib and acalabrutinib are both major substrates of CYP3A4.[58,59] Acalabrutinib also acts as a BCRP and P-gp substrate. Serum concentration and AUC of acalabrutinib were increased by 3.9- and 5.1-fold, respectively, in healthy volunteers receiving itraconazole 200 mg once daily for 5 days. Similar results have been documented when ibrutinib is co-administered with strong CYP3A4 inhibitors. It is for this reason that concomitant use of PIs or cobicistat are contraindicated. If concomitant therapy is unavoidable, ibrutinib and acalabrutinib dose reductions are necessary, as toxicity to these agents (e.g. diarrhea, cardiac arrhythmias, profound myelosuppression) may otherwise result. Although there are recommendations to interrupt acalabrutinib treatment with short-term use of strong CYP3A inhibitors, ARVs are commonly given long term, and it would not be a feasible option. These agents have not been shown to inhibit or induce CYPenzymes.[60,61] The use of efavirenz, nevirapine, and etravirine may reduce concentrations of the CYP3A4 substrates ibrutinib and acalabrutinib. Therefore, monitoring for decreased clinical effects of ibrutinib and acalabrutinib should be considered in patients requiring concomitant therapy.

BRAF and MEK inhibitors

BRAF inhibitors (dabrafenib, vemurafenib, and encorafenib) and MEK inhibitors (trametinib, cobimetinib, and binimetinib) are used most widely for melanoma but can also be used in other malignancies harboring BRAF V600E and/or BRAF V600K mutations (e.g. non-small cell lung cancer, anaplastic thyroid cancer).

Dabrafenib and encorafenib are both substrates for CYP3A4 and P-gp where increased systemic exposure is expected to occur with concomitant strong CYP3A4 inhibitor administration.[62,63] A study in BRAF V600 mutated cancer patients demonstrated that ketoconazole increased dabrafenib AUC and Cmax by 71 and 33%, respectively.[64] Similarly, encorafenib co-administration with posaconazole and diltiazem (moderate CYP3A4 inhibitor) increased AUC three-fold and two-fold, respectively.[63] Strong CYP3A4 inhibitors such as ritonavir or

cobicistat-boosted regimens should be avoided in combination with dabrafenib, and therapy should be closely monitored in patients receiving inducers or moderate inhibitors of this isoenzyme. If co-administration of encorafenib with strong or moderate CYP3A4 inhibitors is unavoidable, the encorafenib dose should be reduced to one-third of the prior dose or one-half of the prior dose, respectively. As dabrafenib is a moderate inducer of CYP3A4 and all NNRTIs are substrates, NNRTIs are unlikely to reduce dabrafenib concentrations.[65] Consequently, the use of encorafenib with efavirenz, nevirapine, or etravirine is contraindicated, as moderate CYP3A4 inducers may reduce serum concentrations of encorafenib although pharmacokinetic data is lacking, yet clinical trials suggested possible CYP3A4 auto-induction of encorafenib.[66]

Dabrafenib is extensively metabolized by the liver by CYP2C8 and CYP3A4 to hydroxyl-dabrafenib. Dabrafenib also exhibits moderate CYP3A4 induction properties which could result in reduced systemic exposure to NNRTIs, PIs, cobicistat, elvitegravir, bictegravir, and possibly dolutegravir, although no recommendations for dosage adjustments exist.[62] Conversely, encorafenib is an inhibitor of CYP3A4, CYP2C19, and CYP2D6, which could result in increased systemic exposure of the previously mentioned ARV classes, yet clinical significance is unknown.

Dabrafenib is often administered in combination with trametinib; however, trametinib is not metabolized by CYP450 isoenzymes and is not expected to interact with members of the NNRTI, PI, INSTI, or pharmacokinetic enhancer drug classes.[67] Similarly, encorafenib and binimetinib are FDA approved to be utilized in combination; however, binimetinib is not expected to interact with ARV agents.[68]

Vemurafenib can be administered as monotherapy in metastatic melanoma; however, its off-label label use in combination with cobimetinib is also prescribed in clinical practice.[69,70] It is anticipated that PIs and cobicistat may result in increased vemurafenib exposure given that vemurafenib is a substrate of CYP3A4 and P-gp, yet specific data regarding these interactions is not available. Although no specific dose adjustments guidance for managing vemurafenib with CYP3A4 inhibitors exist, therapy should be avoided if possible. Concomitant use of strong CYP3A inducers should also be avoided, but if absolutely necessary, it is recommended that the vemurafenib dose be increased by 240 mg (one tablet) daily while weighing patient tolerability.[71]

Cobimetinib is a substrate of CYP3A4 (major) and P-gp. It is not known to affect the metabolism of other drugs via CYP450 pathway. As cobimetinib is primarily metabolized by CYP3A4, co-administration of strong CYP3A4 inhibitors may significantly increase the plasma concentrations of cobimetinib and occurrence of GI distress, rash, liver enzyme abnormalities, and rhabdomyolysis.[72] In a pharmacokinetic study of 15 healthy volunteers given a single 10 mg dose of cobimetinib with the potent CYP3A4 inhibitor itraconazole (200 mg once daily for 14 days), the mean cobimetinib peak plasma concentration (Cmax) and systemic exposure (AUC) increased by 3.2- and 6.7-fold, respectively, compared to cobimetinib administered alone.[73] Physiologically based pharmacokinetic modeling (PBPK) simulations suggested that erythromycin and diltiazem (moderate CYP3A inhibitors) can increase cobimetinib exposure (AUC) by 3- to 4-fold. PBPK modeling with CYP3A4 inducers predicted that rifampin and efavirenz can decrease cobimetinib exposure by 83 and 73%, respectively.[73] Concomitant use with strong or moderate CYP3A inhibitors and inducers (e.g. carbamazepine, cobicistat, efavirenz, etravirine, nevirapine, phenytoin, rifampin, ritonavir, and St. John's wort) should be avoided.[72,74] If concurrent short-term use (less than 14 days) of a moderate CYP3A4 inhibitor cannot be avoided, one may reduce the cobimetinib dose from 60 mg to 20 mg. Upon discontinuation of moderate CYP3A4 inhibitor therapy, one may resume the previous dose of 60 mg. In the event that patient is already receiving a reduced dose of 40 or 20 mg daily, alternatives to the strong or moderate CYP3A4 inhibitor are highly recommended.[72,74] Published recommendations for adjustments with concurrent CYP3A4 inducers are not available to date.

Cyclin-dependent kinase 4 and 6 (CDK 4/6) inhibitors

Palbociclib, ribociclib, and abemaciclib are used for the treatment of advanced and/or metastatic HER2+ breast cancer and are CYP3A substrates along with abemaciclib being a P-gp substrate. As such, caution is advised when they are used in conjunction with CYP3A4 inducers and inhibitors. Specific recommendations for dose adjustments have been published when these agents are co-administered with CYP3A4 inhibitors. Clinicians should also be aware that these agents can be combined with aromatase inhibitors. It is preferable to use letrozole or anastrozole in lieu of exemestane, as the latter is also primarily metabolized by CYP3A4.[75]

Palbociclib exposure increases significantly in the setting of concomitant itraconazole administration, and the dose should be reduced to 75 mg once daily instead of the traditional dosing regimen consisting of 125 mg once daily when given in combination with strong CYP3A4 inhibitors such as ritonavir or cobicistat. It has been shown that co-administration with rifampin decreased plasma concentration of palbociclib in healthy subjects by 85%. As such, use with strong CYP3A inducers should be avoided.[76]

Abemaciclib co-administration with PIs or cobicistat requires a dose reduction to 100 mg twice daily if the initial dose was 200 or 150 mg twice daily. If toxicities, such as bone marrow suppression, diarrhea, or hepatotoxicity still exist, the dose of abemaciclib can further be reduced to 50 mg twice daily.[77] This recommendation was based on a pharmacokinetic study between clarithromycin 500 mg twice daily co-administered with a single dose of abemaciclib 50 mg. The AUC of abemaciclib and its active metabolites increased 1.7-fold in

patients with cancer. In the presence of CYP3A4 inducers, efavirenz, nevirapine, and etravirine, co-administration is contraindicated based on data in healthy subjects receiving abemaciclib (200 mg as a single dose) and rifampin 600 mg daily, as the AUC of abemaciclib and its active metabolites, M2, M18, and M20 were reduced by 70%. Even with moderate CYP3A4 inducers, such as efavirenz, nevirapine, and etravirine, the AUC of M2, M18, and M20 are predicted to be reduced by 53, 41, and 29%, respectively.[77]

When ribociclib was co-administered with ritonavir 100 mg twice daily for 14 days, the AUC of ribociclib increased, on average, by 3.2-fold.[78] In the presence of a moderate inhibitor, erythromycin is predicted to increase the AUC of ribociclib 1.9-fold. Based on this data, it is recommended to avoid concomitant use with strong CYP3A4 inhibitors. If co-administration cannot be avoided, the dose of ribociclib should be reduced to 400 mg once daily to reduce the risk of toxicities (e.g. neutropenia, QTc prolongation, and hepatobiliary effects). Subsequently, ribociclib should not be used with efavirenz and should be avoided with rilpivirine due to an increased risk of QTc prolongation.

Hedgehog inhibitors

Vismodegib is indicated for patients with metastatic basal cell carcinoma and is primarily excreted as an unchanged drug with only minor metabolites produced through CYP enzymes.[27] Vismodegib has been shown to have minimal CYP2C8, 2C9, and 2C19 inhibitor properties; however, this has not been deemed clinically significant. Further, vismodegib does not appear to induce CYP1A2, 2B6, 3A4, in which case dose adjustments during concomitant therapy with substrates for these enzymes is not necessary. In addition, CYP inhibition and induction as well as P-gp inhibition are not expected to affect the systemic concentration of vismodegib.

Sonidegib binds to smoothened homologue (SMO), the transmembrane protein involved in Hedgehog signal transduction, to inhibit cell growth and differentiation through this pathway. Basal cell cancer can activate this pathway, resulting in unrestricted proliferation of skin basal cells. Sonidegib is currently indicated for locally advanced basal cell carcinoma following recurrent post-surgery or radiation and for patients who are not candidates for surgery or radiation.[79,80] Sonidegib is metabolized predominantly by CYP3A4 and does not inhibit or induce any other CYP3A4 enzyme systems to any great extent. Clinical studies included in the package labeling demonstrate co-administration with moderate or strong CYP3A4 inhibitor increased sonidegib AUC by 1.8- and 2.2-fold, respectively.[79,81] Therefore, concomitant use with PIs or cobicistat should be avoided. In the setting of co-administration with a strong CYP3A4 inducer, sonidegib AUC was reduced by 72%. Efavirenz was co-administered with sonidegib to assess its effect on sonidegib exposure. After 14 days and 4 months, sonidegib AUC was reduced by 56 and 65%, respectively. It is for this reason that sonidegib administration with strong or moderate CYP3A4 inhibitors or inducers should be avoided.[79] Rilpivirine, doravirine, as well as unboosted INSTIs, can be safely co-administered with sonidegib.

Glasdegib was recently approved for use in combination with low-dose cytarabine for patients with newly diagnosed acute myelogenous leukemia (AML). Glasdegib is primarily metabolized by the CYP3A4 with minor contributions from CYP2C8 and UGT1A9.[82] When co-administered with ketoconazole, AUC and Cmax of glasdegib increased by an average of 2.4- and 1.4-fold, respectively. Therefore, use with PIs and COBI should be avoided. If co-administration is unavoidable, patients should be closely monitored for adverse effects, including QTc prolongation. The use of glasdegib and rifampin reduced both AUC and Cmax of glasdegib by 70 and 35%, respectively. Therefore, use with other inducers such as efavirenz, nevirapine, and etravirine should be avoided.

Human epidermal growth factor (HER2 and EGFR) pathway inhibitors

Erlotinib is a CYP3A4 substrate and demonstrates significant alterations in erlotinib exposure due to CYP3A4 inhibition when co-administered with ritonavir.[25] A preclinical study in mice revealed a 3-fold increase in AUC in the presence of ritonavir and erlotinib.[83] Pharmacokinetic models revealed that ritonavir was associated with significant inhibition of erlotinib metabolism by increasing the AUC 4.2-fold.[84] There was also an observed 6.8-fold increase in AUC when used in combination with darunavir 800 mg/ritonavir 100 mg.[85] Co-administration of these agents should be avoided; however, if not possible, it is recommended to reduce erlotinib by 50 mg decrements until tolerated.[25] Based on pharmacokinetic modeling, optimal dosing of erlotinib may be as low as 25 mg orally daily or every other day.[83,85] Efavirenz, nevirapine, and etravirine have the potential to reduce serum concentrations of the CYP3A4 substrate erlotinib based on their inducing properties. Therefore, monitor for decreased clinical efficacy of erlotinib or use rilpivirine, doravirine, or an unboosted INSTI.

Gefitinib undergoes extensive metabolism by the CYP450 enzymes, particularly CYP3A4, CYP3A5, CYP2D6, and CYP1A1.[28,86,87] In the absence of pharmacokinetic studies to describe the extent of the drug–drug interactions with gefitinib, it is expected that PIs, cobicistat, and NNRTIs are drugs of concern when co-administered with gefitinib. PIs and cobicistat are postulated to inhibit the CYP3A4 pathway and may result in an increased gefitinib concentration. When a single dose of 250 or 500 mg of itraconazole was combined with gefitinib in healthy volunteers, the AUC of gefitinib increased, on average, by 61–78%. Therefore, concomitant use of PIs and cobicistat with gefitinib should be closely monitored for gefitinib-related adverse effects (e.g. skin reactions, diarrhea).[88] Etravirine is a substrate of CYP450 enzymes and has moderate inducing and inhibiting characteristics on CYP

subfamilies. As such, etravirine may have limited interactions with oncolytic drugs metabolized through the CYP450 pathway and may be considered if administration is unavoidable.[88] In addition, if co-administration of CYP3A4 inducer is unavoidable, in the absence of severe adverse reactions associated with gefitinib, it is recommended to increase gefitinib dose to 500 mg daily in patients receiving strong CYP3A4 inducers. It is also suggested that the dose be decreased to the original starting dose of 250 mg daily 7 days after discontinuation of a strong CYP3A4 inducer.[28]

Afatinib is not a substrate of any of the CYP450 isoenzymes; however, it is known to be a substrate and inhibitor for P-gp, which has clinically relevant implications on concomitant PI or cobicistat-based therapy.[89] Wind et al. demonstrated that ritonavir increased afatinib Cmax and AUC by 39 and 48%, respectively.[90] This interaction is hypothesized to be due to the ritonavir-mediated inhibition of P-gp efflux of afatinib. As this study only evaluated up to 3 days of co-administration with either agent, the results reported from this study likely underestimate the severity and significance of the true interaction. It is possible that this interaction could occur with other PIs and elvitegravir/cobicistat, so patients receiving concomitant therapy with afatinib should be closely monitored for signs and symptoms of afatinib toxicity (e.g. diarrhea, acneiform rash, nausea/vomiting). If toxicity occurs, the daily afatinib dose should be reduced by 10 mg in patients and perhaps further as clinically necessary. If concomitant P-gp inhibitor therapy is discontinued, patients may be escalated back to their previous maintenance dose. No significant interactions are expected with afatinib and NNRTIs or unboosted INSTIs.[89,91]

Osimertinib is known to be a substrate of CYP3A4 (major) and P-gp.[92,93] Based on a phase I study, osimertinib is principally metabolized by CYP3A4/5 and produces two circulating active metabolites, AZ5104 and AZ7550.[94] In a separate phase I AURA study of the pharmacokinetics of osimertinib, patients who had concomitant therapy with CYP3A4 inhibitors/inducers were excluded from the study.[95] Although pharmacokinetic data is lacking, this highlights theoretical concerns regarding drug–drug interactions associated with osimertinib, particularly with PIs, elvitegravir/cobicistat, and NNRTIs. There is no dose adjustment recommendation for osimertinib when co-administered with a strong CYP3A4 inhibitor. If a strong CYP3A4 inhibitor is administered concurrently with osimertinib, clinicians are advised to monitor the adverse effects associated with supratherapeutic levels of osimertinib (e.g. diarrhea, rash, dry skin, and nail toxicity).[92] On the other hand, if concomitant use of a strong CYP3A4 inducer with osimertinib is unavoidable, clinicians may increase osimertinib dose from 80 to 160 mg daily. However, among the NNRTIs, efavirenz, nevirapine, and etravirine are moderate CYP3A4 inducers; hence a higher dose of osimertinib may be warranted.[92] In addition to drug–drug interactions with osimertinib through the CYP3A4 pathway, clinicians should also be mindful of concomitant drugs that may cause QTc prolongation as well. Osimertinib may cause dose-related prolongation of the QT interval. Theoretically, co-administration with other agents that can prolong QT interval, such as rilpivirine and PIs may result in additive effects and increase the risk of ventricular arrhythmias including torsade de pointes and sudden death. PIs, such as atazanavir and lopinavir, have been reported to cause cardiac abnormalities and should be avoided or monitored closely.[92,96] The risk of this is highest when lopinavir/ritonavir is used.

Lapatinib is indicated for patients with advanced or metastatic breast cancer who overexpress the HER2 receptor.[97] This drug undergoes extensive liver metabolism primarily through CYP3A4 and CYP3A5. Lapatinib inhibits CYP3A4, CYP2C8, and P-gp, thereby increasing concentrations of drugs that utilize these metabolic pathways. The use of lapatinib with strong CYP3A4 inhibitors such as PIs or cobicistat is contraindicated based on data derived from healthy volunteers. When ketoconazole was combined with lapatinib, the Cmax and AUC increased by 2.1- and 3.6-fold, respectively.[98] Lapatinib also serves as a substrate of the P-gp transporter, and concentrations of lapatinib will increase if used with inhibitors of this efflux transport system. Further, lapatinib should be used with caution in agents that serve as CYP3A4 inducers – efavirenz, nevirapine, and etravirine – as the clinical efficacy of lapatinib may be reduced. Lapatinib may be safely used in combination with rilpivirine, doravirine, and unboosted INSTIs.[99]

Neratinib is a kinase inhibitor indicated for extended adjuvant treatment of HER2-breast cancer after adjuvant treatment with trastuzumab.[100] Neratinib acts as a major substrate for the CYP3A4 isoenzyme. When ketoconazole 400 mg once daily for 5 days was combined with neratinib 240 mg as a single dose on day 2, AUC and maximum serum concentrations increased by 4.8-fold and 3.2-fold, respectively, in 22 healthy volunteers, which has the potential to lead to an increased risk of diarrhea or other toxicities.[100,101] Subsequently, when 24 healthy volunteers received concomitant neratinib and rifampin, AUC and Cmax were reduced by 87 and 76%, respectively. As this can lead to reduced efficacy of neratinib, co-administration with strong or moderate inhibitors or inducers should be avoided when PIs, cobicistat, efavirenz, nevirapine, and etravirine are concomitantly used.

Dacomitinib is indicated in the first-line setting for patients with metastatic non-small cell lung cancer harboring either the EGFR exon 19 deletion or the exon 21 L858R substitution.[102] It is metabolized by CYP2D6 to O-desmethyl dacomitinib, which has been shown *in vitro* to have similar activity to dacomitinib. Cobicistat is known to have weak CYP2D6 inhibitory properties, although the clinical significance of this interaction is unclear and therefore does not warrant dose modifications to either agent.[103] In summary, erlotinib, gefitinib, afatinib, osimertinib, and dacomitinib are used primarily in various lines of advanced and metastatic NSCLC and are preferred over traditional cytotoxic agents in patient who express various subtypes of EGFR sensitizing mutations. Co-administration with ARVs

may be unavoidable in this population due to clear efficacy results of these agents in patients expressing these genetic features. Dacomitinib is least likely to interact with ARVs and can be considered over other agents, if clinically indicated. Lapatinib and neratinib are approved for metastatic breast cancer, although many alternatives exist in this treatment setting if patients are also receiving agents that strongly induce or inhibit CYP3A4. Nevertheless, empiric dose reductions and early detection and monitoring of dermatologic toxicities and diarrhea are necessary to ensure that patients attain maximal therapeutic benefit while limiting potential toxicities.

Phosphatidylinositol 3-kinase (PI3K-δ) inhibitors

Idelalisib is a potent inhibitor of the delta isoform of phosphatidylinositol 3-kinase (PI3Kδ) and is indicated for relapsed chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma, and follicular B-cell non-Hodgkin's lymphoma (NHL).[104] It is metabolized by aldehyde oxidase (AO) to its major circulating inactive metabolite, GS-563117. Other metabolic pathways include CYP3A4 (major substrate), P-gp, and UGT1A4. Although some *in vitro* data suggest that idelalisib or its metabolite weakly inhibit metabolizing enzymes CYP2C8, CYP2C19, and UGT1A1, these interactions are not thought to be significant at clinically relevant concentrations. However, GS-563117 is a potent CYP3A4 inhibitor and harbors the most concern with regard to drug interaction potential.[104–106] Co-administration of idelalisib with rifampin or ketoconazole in two separate studies resulted in a 75% reduction and 79% increase in idelalisib AUC, respectively.[106,107] The use of idelalisib, CYP3A4 substrate, with CYP3A4 inducers such as efavirenz, nevirapine, or etravirine may result in reduced concentrations of idelalisib. In addition, co-administration of strong CYP3A4 inhibitors, such as PIs and cobicistat, may increase the concentration of idelalisib. Patients experiencing increased adverse effects (e.g. diarrhea, rash, nausea, fatigue) may require a reduced dose of idelalisib, but dosing recommendations are not established.

When midazolam was co-administered with idelalisib, a 437% increase in midazolam AUC was observed in clinical trials. Package labeling recommends avoiding idelalisib co-administration with strong CYP3A4 inducers and inhibitors, as well as CYP3A4 substrates, due to competition for elimination.[104] Therefore, the use of PIs, cobicistat, and maraviroc should not be co-administered with idelalisib due to the risk of increased systemic exposure of ARVs. Additionally, as idelalisib is a strong CYP3A inhibitor, concomitant use of bictegravir or rilpivirine may result in increased serum concentrations of ARVs, and monitoring for adverse effects should occur.

Duvelisib, another inhibitor of this pathway, has inhibitory activity against both delta and gamma (γ) kinase isoforms and is also indicated in the relapsed and refractory CLL, small lymphocytic lymphoma (SLL), or follicular lymphoma settings.[108] It is metabolized hepatically by CYP3A4 and is also a substrate of P-gp and BCRP *in vitro*. In a study of 16 adults, Cmax and AUC of duvelisib were increased by 1.7- and 4-fold, respectively, in the setting of concomitant ketoconazole. At steady state, the magnitude of increased exposure is approximately 2-fold based on PBPK modeling and simulation. Of note, PBPK studies assessing the impact of concomitant administration of mild or moderate CYP3A4 inhibitors revealed no effect on the exposure of duvelisib. In 13 adults, duvelisib Cmax and AUC were reduced by 66 and 82%, respectively, when duvelisib was co-administered with rifampin.[108] Duvelisib is also postulated to act as a moderate CYP3A4 inhibitor. In a study of 14 adults, duvelisib increased AUC and Cmax of midazolam by 4.3- and 2.2-fold, respectively.[109] For patients receiving strong CYP3A4 inhibitors such as ritonavir and cobicistat, duvelisib should be reduced from 25 mg twice daily to 15 mg twice daily while clinicians should monitor patients for duvelisib-associated toxicities (e.g. diarrhea, transaminitis, rash). Dose reduction is especially important with these specific ARVs, as they also act as strong P-gp inhibitors. Further duvelisib dose reductions may be necessary. Co-administration of duvelisib with CYP3A4 inducers should be avoided, as its efficacy may be significantly reduced. When duvelisib is co-administered with CYP3A4 substrates, patients should be monitored for increased toxicity of substrates.[108,109] This guidance applies to NNRTIs, PIs, cobicistat, and maraviroc, although the clinical significance of this interaction is equivocal given the lack of confirmatory studies.

Vascular endothelial growth factor (VEGF) inhibitors

Cabozantinib is metabolized by CYP3A4, and a study assessing the effect of co-administration with ketoconazole and rifampin found a 38% increase and 77% decrease in cabozantinib AUC, respectively.[110] Therapy modification is recommended in the presence of CYP3A4 inhibitors. When these therapies cannot be avoided, it is recommended to reduce the daily dose of the cabozantinib capsule formulation of cabozantinib by 40 mg and the tablet formulation by 20 mg in the presence of a strong CYP3A4 inhibitor.[9,10] Although *in vitro* studies show that cabozantinib is a noncompetitive inhibitor of CYP2C8, a mixed-type CYP2C9 and CYP2C19, and a weak competitive inhibitor of CYP3A4, these are not thought to be clinically significant interactions. When subjects receiving chronic cabozantinib were given rosiglitazone, a CYP2C8 substrate, no significant effects on plasma Cmax or AUC were observed.[9,110] Efficacy of cabozantinib should be monitored in patients receiving concomitant therapy with efavirenz, nevirapine, and etravirine, as these agents have the potential to result in reduced cabozantinib systemic exposure due to CYP3A4 induction. Doravirine, rilpivirine, and unboosted INSTIs are unlikely to interact with cabozantinib and are the preferred agents to co-administer in patients requiring cabozantinib therapy.

Sunitinib is a major substrate of CYP3A4.[111] One study evaluated concomitant use of ritonavir and sunitinib and found that

the maximum tolerated dose in these patients needed to be reduced to 37.5 mg daily, as toxicities (e.g. grade 3 neutropenia and grade 1/2 diarrhea, fatigue, and mucositis) were comparable in the non-ritonavir based group of 50 mg/day.[112] Additionally, there is the potential for efavirenz, nevirapine, and etravirine to induce sunitinib metabolism, which may reduce sunitinib concentrations.[111]

Regorafenib, also a major substrate of CYP3A4, resulted in an increased AUC of 33% in 18 healthy volunteers who received a single 160 mg dose 5 days after the initiation of ketoconazole 400 mg daily for 18 days.[113] It is recommended that regorafenib not be used in combination with PIs or cobicistat, as they are strong CYP3A4 inhibitors. As regorafenib is a CYP3A4 substrate, its concentration may be reduced in the presence of efavirenz, nevirapine, or etravirine. Clinical progression should be closely monitored, but the combination should only be used if absolutely necessary.

Pazopanib is another agent that is primarily metabolized by CYP3A4 with minor contributions by CYP2C8 and CYP1A2. Pazopanib is also a substrate of P-gp. As such, the degree of liver metabolism of vandetanib remains unknown with the majority of metabolism thought to be due to CYP3A4 and monooxygenase enzymes.[114] The use of atazanavir, lopinavir, ritonavir, and cobicistat is contraindicated with pazopanib, as these agents inhibit P-gp and can thus increase pazopanib serum concentrations of pazopanib. PIs and cobicistat act as strong CYP3A4 inhibitors and are also responsible for raising serum concentrations of pazopanib.[114] A pharmacokinetic study in healthy volunteers was performed using a single dose of ketoconazole with pazopanib eye drops, which increased pazopanib AUC, on average, by 220% and maximum serum concentration (Cmax) by 150%. If co-administration cannot be avoided, the dose of pazopanib should be reduced to 400 mg once daily.[114] Antiretroviral therapy with efavirenz, nevirapine, or etravirine, CYP3A4 inducers, can potentially decrease the concentration of pazopanib, as it acts as a CYP3A4 substrate. Although dosage adjustments are not recommended, clinical monitoring should occur.

The use of vandetanib is contraindicated in the presence of efavirenz and should be used with caution in patients receiving rilpivirine due to its risk of QTc prolongation. Although nevirapine and etravirine act as moderate CYP3A4 inducers to the substrate vandetanib, no empiric dosage adjustment is recommended, yet decreased effects of vandetanib should be monitored. Again, in the presence of a strong CYP3A4 inhibitor such as PIs or cobicistat, the concentration of vandetanib may increase, but there was little clinical significance demonstrated when combined with itraconazole.[115,116]

Lenvatinib is considered a minor substrate of CYP3A4 and P-gp.[117] Although there have not been any reported drug interactions between lenvatinib and CYP3A4 or P-gp inhibitors and inducers, caution should be exerted in the presence of efavirenz and rilpivirine due to their risk to prolong QTc. No dose adjustment is necessary, but QTc monitoring should occur if combined with efavirenz or rilpivirine. In addition to monotherapy for select indications, lenvatinib is FDA approved in combination with everolimus for renal cell carcinoma (RCC); however, this regimen should be avoided due to the high likelihood that everolimus will interact with PIs and cobicistat.

As sorafenib is extensively metabolized through CYP3A4 and glucuronidation pathways, the concentration of sorafenib may be increased by CYP3A4 inhibitors, such as PIs and cobicistat; howevever, such agents as ketoconazole (400 mg once daily) did not significantly alter sorafenib (50 mg) pharmacokinetics in healthy volunteers.[118,119] Although no dosage changes are recommended, the presence of side effects with sorafenib should still be monitored (e.g. diarrhea, rash, fatigue). The use of NNRTIs and unboosted INSTIs may be safely used with sorafenib, as they lack strong CYP3A4 inducing properties.

Axitinib is an inhibitor against intracellular tyrosine kinases targeting the vascular endothelial through factor receptors (VEGFR)-1, VEGFR-2, and VEGFR-3 and is indicated for RCC after failure of one prior therapy. Axitinib is a major metabolic substrate of CYP3A4 and CYP3A5 and metabolized by a lesser extent through CYP1A2, CYP2C19, and UDP1A1. Axitinib is neither an inhibitor nor an inducer of any cytochrome P450 or other enzymes.[120] In the setting of ketoconazole, co-administration with axitinib, axitinib was associated with an approximately two-fold increased AUC compared with axitinib alone.[121] Avoidance of PIs and cobicistat is recommended; however, if a strong CYP3A4 inhibitor must be used concomitantly with axitinib, the dose of axitinib should be reduced by 50%.[120] Another study investigating the effect of rifampin co-administration with axitinib showed that axitinib AUC was reduced by 70–80%. Notably, this study included only Japanese and Caucasian subjects and found that, despite potential differences in frequency in UGT1A1*28 genotype between the two groups, no differences in axitinib pharmacokinetics were observed regardless of rifampin co-administration.[121] Specific recommendations for efavirenz, nevirapine, and etravirine guide against co-administration, as these agents, classified as moderate CYP3A4 inducers, could result in significantly reduced systemic exposure of axitinib.[122] Administration with nevirapine may proceed with close monitoring, where rilpivirine, doravirine, and unboosted INSTIs are least likely to interact with axitinib.

Other agents

Alkylating agents

Busulfan is most commonly used in conditioning regimens for hematopoietic stem cell transplantation.[123] Although studies have not definitively proven that busulfan is a substrate for CYP450 isoenzymes, metabolism through CYP3A4 has been hypothesized, a small study demonstrated that concomitant itraconazole reduced busulfan clearance by 20% in 13 patients undergoing bone marrow transplantation.[124] Of note, many centers assess appropriateness of busulfan therapy by

monitoring AUC values, as reduced systemic exposure could result in failed engraftment and poor survival outcomes while exposure above its therapeutic range could result in serious and sometimes fatal toxicities (e.g. prolonged neutropenia, hepatic sinusoidal obstructive syndrome, pulmonary toxicity).[125] The CYP-inducing characteristics of the NNRTIs could result in reduced concentrations of busulfan, and inhibiting characteristics of PIs and cobicistat could increase busulfan concentrations. Clinicians should consider this information in patients requiring concomitant busulfan and ARV therapy and adjust busulfan levels accordingly if they deviate from target AUC concentrations.

Cyclophosphamide is used in a wide variety of malignancies and is considered a major substrate for CYP2B6 and a minor substrate for CYP3A4.[126,127] A study conducted by Bower et al. compared neutropenia in patients receiving PI-based or non-PI based ART regimens and demonstrated significantly lower neutrophil counts in patients receiving PIs with concomitant cyclophosphamide/doxorubicin/etoposide (CDE) chemotherapy.[128] This finding is hypothesized to be caused by PI mediated CYP3A4 inhibition of cyclophosphamide.[117] Efavirenz and nevirapine are known CYP2B6 inducers and thus the most likely NNRTIs to interact, resulting in decreased cyclophosphamide concentrations if administered concomitantly.[127] It should be noted that the limited data available on cyclophosphamide and interactions with ARVs only include patients receiving intravenous cyclophosphamide in combination with other antineoplastics, prophylactic antimicrobials, and other medications that might interact with NNRTIs and PIs.

Temozolomide is not known to be metabolized by or otherwise affect CYP450 enzymes; however, it is associated with lymphopenia in patients receiving concomitant radiation therapy.[129] This could be especially problematic in HIV/AIDS patients experiencing already low CD4 counts. Prophylaxis against *Pneumocystis jirovecii* pneumonia is recommended in these patients as well as those receiving concomitant corticosteroids.[118]

Anti-androgens and other androgen deprivation therapies

Bicalutamide, flutamide, and nilutamide are androgen receptor inhibitors utilized in advanced and metastatic prostate cancer to prevent tumor flare associated with the initiation of luteinizing-hormone releasing hormone (LHRH) agonists or are used in combination with LHRH agonists after progression on LHRH agonist monotherapy.[130–133] Bicalutamide does not have any evidence in clinical studies of being a hepatic enzyme inducer and its primary metabolism is thought to be that of glucuronidation of both stereoisomers. However, *in vitro* studies have shown bicalutamide to be an inhibitor of CYP3A4; therefore, caution should be taken when using bicalutamide with CYP3A4 substrates. Flutamide is considered a minor CYP3A4 substrate, so although theoretical interactions may exist with NNRTIs, PIs, and cobicistat, the severity is likely not to be clinically significant.[130] Nilutamide is metabolized by CYP2C19 and is unlikely to interact with NNRTIs, PIs, or cobicistat.[134]

Enzalutamide and apalutamide are the newest anti-androgen therapies approved for use specifically in castration-resistant prostate cancer and are both metabolized by CYP3A4 and CYP2C8.[21,135] Enzalutamide inhibits BCRP and MRP2 and induces CYP2C9/19 (moderate) and CYP3A4 (strong) while apalutamide acts as a moderate to strong inducer of CYP3A4 isoenzymes. A trial assessing co-administration of itraconazole, a CYP3A4 inhibitor, with enzalutamide revealed a 1.3-fold increase in composite enzalutamide/N-desmethyl enzalutamide AUC with no appreciable change to Cmax.[136] When co-administered with rifampin, enzalutamide/N-desmethyl enzalutamide, AUC was shown to be reduced by 37%. Based on these data, NNRTIs may theoretically decrease the effectiveness of enzalutamide while PIs and cobicistat would theoretically increase the risk of toxicities. Both enzalutamide and apalutamide were shown in *in vitro* studies to reduce the AUC of a single dose of midazolam by 86 and 92%, respectively. Although theoretically this translates to reduced exposure to PIs, NNRTIs, and INSTIs (except raltegravir), confirmatory studies are lacking. Generally, co-administration of enzalutamide or apalutamide with these ARV classes should be avoided, when possible, or done in conjunction with ARV TDM. Of note, the manufacturer recommends dose escalation of enzalutamide in the setting of concomitant therapy with strong CYP3A4 inducers; however, this guidance does not apply to ARV therapies.[21]

Ketoconazole and abiraterone, both metabolized extensively through CYP3A4, inhibit CYP17, the enzyme that enzyme catalyzes the formation of androgens and estrogens in the adrenal and adipose tissues.[137,138] Ketoconazole should be avoided in patients receiving NNRTIs and PIs, as it is both a major substrate and a strong inhibitor of CYP3A4.[137] Doravirine is the safest in terms of NNRTI to use with ketoconazole, and the maximum daily dose of ketoconazole is 200 mg daily with PIs and cobicistat. Historically, this agent was used for the management of castration-resistant prostate cancer, although it has fallen out of favor for other agents with more favorable tolerability and improved efficacy. Abiraterone inhibits CYP2D6 and as such can increase the concentrations of drugs that are CYP2D6 substrates. Co-administration should be undertaken with caution in which the concomitant drug dose should be lowered. Abiraterone is a substrate of CYP3A4; therefore, its use with strong CYP3A4 inhibitors (such as atazanavir, ritonavir, and cobicistat) or inducers should be done with caution.[138]

Antimetabolites

Capecitabine, methotrexate, mercaptopurine, thioguanine, and trifluridine/tipiracil are the orally available antimetabolite agents.[139–143] These agents are not known to be metabolized by or otherwise affect any CYP isoenzymes associated with NNRTI

or PI metabolism and are thus not expected to interact with these agents.[139–143] Although lopinavir, ritonavir, and cobicistat act as inhibitors of P-gp, no major interaction is expected with the P-gp substrate, methotrexate. These agents can be safely administered in the presence of NNRTIs, PIs, and cobicistat.

Aromatase inhibitors

Exemestane, anastrozole, and letrozole are indicated for hormone-receptor (HR) positive breast cancer. Exemestane is a major substrate of CYP3A4, so it is possible that concentrations may be reduced with concomitant NNRTI therapy and increased with PI or cobicistat therapy.[75] These same effects are possible, but less likely, with letrozole, as it is a weak substrate of CYP3A4 and not expected with anastrozole, as it is not metabolized through CYP enzymes.[75,144–148] These agents are occasionally combined with other oral antineoplastic agents that also serve as CYP450 substrates in the metastatic setting.[149]

Histone deacetylase (HDAC) inhibitors

Panobinostat is a major substrate of CYP3A4 as well as P-gp.[150] With concomitant NNRTI therapy, therapeutic concentrations of panobinostat may be reduced. Although patients should be monitored closely, no studies have been published evaluating the severity of this interaction, and dose modifications should be based on clinical judgement. In the presence of ketoconazole, panobinostat Cmax and AUC were found to be increased 1.6- and 1.8-fold, respectively, after only one dose.[151] Thus, it is recommended that the panobinostat dose be reduced from 20 to 10 mg in patients receiving concomitant PIs or cobicistat.[150] Vorinostat, another HDAC inhibitor, is not known to interact with any CYP450 isoenzymes.[152] Both panobinostat and vorinostat are associated with QTc prolongation. EKG monitoring is recommended specifically with lopinavir, ritonavir, saquinavir, efavirenz, rilpivirine, and etravirine if used in combination with either of these agents.[150,152–154]

Immunomodulatory agents

Pomalidomide is indicated in refractory multiple myeloma and is primarily metabolized by CYP1A2 and 3A4. Of note, ritonavir is a potent 3A4 inhibitor but induces 1A2. Although no drug interaction studies, to date, have been published assessing the 3A4 interaction specifically, monitoring of both pomalidomide efficacy and toxicity is advised for NNRTIs and PIs if they are co-administered.[155]

Thalidomide, mechanism of metabolism in humans is not fully established, and lenalidomide, minimally metabolized in human studies, is not associated with clinically significant interactions with NNRTIs, PIs, or cobicistat.[156,157] Of note, thalidomide is contraindicated in the presence of efavirenz due to the risk of both agents acting as CNS depressants.

Poly (ADP-ribose) polymerase (PARP) inhibitors

The PARP inhibitors (olaparib, talazoparib, rucaparib, niraparib) are a relatively new class of anticancer agents with known activity in HER-2 negative and BRCA-mutated breast cancer, as well as BCRA-mutated ovarian cancer. Niraparib, however, is unique, as it can be used in recurrent ovarian, fallopian tube, or primary peritoneal cancer regardless of BRCA status.

Olaparib is metabolized by the CYP3A enzyme system.[158] When olaparib was co-administered with itraconazole or rifampin, olaparib AUC was increased 2.7-fold and reduced by 87%, respectively.[159] In the setting of moderate CYP3A4 inhibition modeled by fluconazole co-administration, olaparib AUC was increased approximately 2-fold. Although, concomitant therapy with moderate or strong CYP3A inhibitors should be avoided, olaparib should be dose reduced to 100 mg twice daily (tablets) or 150 mg twice daily (capsules) in the presence of a strong inhibitor and 150 mg twice daily (tablets) or 200 mg twice daily (capsules) in the presence of a moderate inhibitor, if co-administration is necessary. With concomitant CYP3A inducers, co-administration should be avoided for the potential of reduced efficacy of olaparib; however, no recommendations for dose-escalating olaparib to counteract this interaction exist.[145] Etravirine, nevirapine, and efavirenz co-administration with olaparib should be avoided, as these NNRTIs have the potential to reduce the efficacy of olaparib. Doravirine and rilpivirine are the preferred NNRTIs to select if co-administration with olaparib is necessary.

Talazoparib is a substrate for BCRP and P-gp; thus co-administration of agents that inhibit or induce the activity of these transporters will increase or decrease talazoparib concentrations, respectively. Cobicistat inhibits BCRP, and ritonavir inhibits both BCRP and P-gp; thus co-administration with talazoparib may theoretically increase its systemic exposure, yet no drug interaction studies, to date, have been published. If co-administration is unavoidable, clinicians should monitor patients closely for toxicities of talazoparib (e.g. diarrhea, myelosuppression).[160]

Rucaparib, primarily metabolized by CYP2D6, and niraparib, metabolized through carboxylesterases, are not associated with significant interactions with NNRTIs, PIs, cobicistat, or INSTIs and may be safely co-administered.[161,162]

Selective estrogen receptor modulators (SERMs)

Toremifene and tamoxifen act as SERMs for the management of breast cancer in postmenopausal women with estrogen-receptor positive tumors.[164] Toremifene is primarily metabolized through CYP3A4 whereas tamoxifen's main route of metabolism is glucuronidation.[20] The use of PIs and cobicistat are not recommended with toremifene due to an increase in toremifene concentrations secondary to reduced

metabolism of toremifene. This data was generated from healthy volunteers receiving ketoconazole 200 mg twice daily and toremifene 80 mg once daily. This combination produced a 2.9-fold increase in toremifene AUC and a 1.4-fold increase in Cmax.[163,164] No major drug interaction is expected between CYP3A4 inducers or substrates. Toremifene also carries a black box warning for prolonged QTc, and also for this reason, it is recommended that co-administration with PIs is avoided. Tipranavir may decrease the serum concentration of active metabolites found in tamoxifen, producing reduced efficacy of tamoxifen. Furthermore, CYP3A4 inhibitors such as the PIs and cobicistat should also be avoided with tamoxifen because the metabolism of tamoxifen may be decreased putting the patient at risk for increased toxicities (e.g. rash nausea, fluid retention).[20]

Toremifene is no longer widely used in clinical practice given the availability of agents with less toxicity, less potential for drug interactions, and similar efficacy outcomes in the metastatic setting (e.g. CDK 4/6 inhibitors, aromatase inhibitors). Although tamoxifen is used much more commonly than toremifene, specifically in the premenopausal setting, it is associated with drug interactions and carries a black box warning for uterine or endometrial cancer when used for breast-cancer risk reduction or ductal carcinoma *in situ*. These agents can generally be avoided, as several alternative hormonal therapies (e.g. injectable LHRH agonists, aromatase inhibitors, etc.) with less potential to interact can be utilized to circumvent complications in patients receiving concurrent ARV therapy.[20,163]

Topoisomerase inhibitors

Topotecan is a topoisomerase I inhibitor approved for the use of a variety of labeled and unlabeled indications.[165] It is a substrate of P-gp, and concentrations may be increased in the presence of PIs and cobicistat, which act as inhibitors. If concomitant therapy is unavoidable, the patient should be monitored for increased presence of adverse events. In addition, topotecan is a substrate of BCRP/ABCG2 and, when combined with cobicistat, a BCRP/ABCG2 inhibitor, serum concentrations of topotecan may increase. Therefore, the combination of cobicistat and topotecan is contraindicated and should be avoided.

Etoposide is a topoisomerase II inhibitor that is not associated with major drug–drug interactions with ARVs. Although etoposide acts as a CYP3A4 and P-gp substrate, there are no dosage adjustments needed in the presence of inducers or inhibitors, but clinical monitoring should occur especially in the presence of efavirenz, nevirapine, and etravirine, as these inducers may reduce the serum concentration of etoposide.[166,167]

Miscellaneous

All trans retinoic acid (ATRA) is approved for the treatment of acute promyelocytic leukemia. Through a mechanism not fully understood, it induces differentiation of immature promyelocytes. Although this agent is not associated with CYP or P-gp interactions, hyperlipidemia (e.g. hypertriglyceridemia, hypercholesterolemia) has been reported in up to 60% of patients.[168,169] As this could be exacerbated even further by PI or cobicistat co-administration, clinicians should consider baseline and periodic cholesterol screening as necessary.

Enasidenib is an isocitrate dehydrogenase (IDH) 2 inhibitor used in relapsed or refractory AML patients with an IDH2 mutation.[170] It is a substrate for and an inhibitor of many CYP450 enzyme systems, including 3A4 and P-gp. Clinical significance of interactions is unclear, as the drug interaction data is based on a small number of *in vitro* studies without published results.

Everolimus is a major CYP3A4 substrate, so as expected, its use is contraindicated in the presence of PIs and cobicistat due to increased serum concentrations of everolimus. This was demonstrated in healthy volunteers as well as patients receiving ketoconazole, voriconazole, and clarithromycin.[171–174] With moderate CYP3A4 inducers within the NNRTI class, reductions in everolimus concentrations and systemic exposure could theoretically occur, but no published literature has evaluated these interactions, and therefore, dose adjustment recommendations are not available at this time. In breast cancer, everolimus is combined with exemestane. This combination should be avoided, as exemestane is also a CYP3A4 substrate and subject to similar effects as everolimus when given with CYP3A4 inducers and inhibitors.[149]

Ixazomib is a proteasome inhibitor approved for relapsed or refractory multiple myeloma. Ixazomib is a major substrate for 3A4 and is also a substrate for P-gp.[175] A study by Gupta et al. showed that rifampin decreased ixazomib Cmax and AUC by 54 and 74%, respectively, although co-administration with clarithromycin, a strong CYP3A4 inhibitor, did not show any meaningful increase in ixazomib concentrations.[176] Although the potential for more clinically significant interactions might be mitigated by this agent's unique dosing regimen (one dose on days 1, 8, and 15 every 28 days), patients should nevertheless be closely monitored. Other ixazomib-sparing combination regimens can also be considered.

Midostaurin is a TKI approved for FLT3 positive AML and is extensively metabolized by CYP3A4. As seen in other pharmacokinetic studies, when given with ketoconazole, midostaurin AUC increased 10.4-fold.[177,178] Similarly, when combined with itraconazole, serum concentrations of midostaurin increased.[177] Ideally, combinations containing ritonavir or cobicistat should be avoided, but if this is not possible, close monitoring for toxicities (e.g. nausea/vomiting, diarrhea, myalgia/arthralgia) is essential.

Gilteritinib is another TKI recently approved for FLT3 positive AML. Gilteritinib is metabolized by CYP3A4 *in vitro*.[179] Although pharmacokinetic studies are still underway, it is recommended to avoid gilteritinib in the presence of strong CYP3A4 inhibitors such as PIs and COBI. If concomitant use is unavoidable, frequent monitoring for adverse effects associated with

gilteritinib (e.g. myalgia/arthralgia, rash, transaminitis, hypotension, nausea/vomiting, and diarrhea) should be performed. Concomitant use should also be avoided in the presence of combined P-gp and strong CYP3A4 inducers, which are currently not associated with any ARVs currently on the market. The effects on moderate inducers such as efavirenz, nevirapine, and etravirine are unknown at this time.

Mitotane is an adrenolytic agent used exclusively for adrenocortical carcinoma.[180] As a CYP3A4 substrate and strong CYP3A4 inducer, it reduces serum concentrations of CYP3A4 substrates, including PIs, NNRTIs, INSTIs, such as elvitegravir and bictegravir, and cobicistat, which could potentially decrease the efficacy of these agents. Therefore, patients receiving ART with these agents may be vulnerable to loss of virologic suppression and increased risk of HIV resistance. It is for these reasons that PIs, NNRTIs, certain INSTIs, and cobicistat should be avoided with mitotane. Mitotane can also result in a plethora of metabolic and hormonal derangements that could complicate or exacerbate those experienced with PIs and other ARV therapies.

Venetoclax is a BCL-2 inhibitor approved in CLL in patients with del 17p. This agent is a substrate of CYP3A4 and P-gp/ABCB1.[181] The use of venetoclax is contraindicated in combination with moderate or strong CYP3A4 inducers based on a pharmacokinetic study with rifampin, which decreased the AUC and Cmax of venetoclax by 71 and 42%, respectively. Therefore, efavirenz, nevirapine, and etravirine should not be co-administered with venetoclax.[182] A single dose of rifampin 600 mg increased the maximum concentration and AUC through the inhibition of the P-gp-mediated efflux of venetoclax. As cobicistat and ritonavir acts as a P-gp inhibitor, it is recommended that the dose of venetoclax be reduced by at least 50% if concomitant administration is required. The same dosage adjustment should occur with moderate CYP3A4 inhibitors. The use of strong CYP3A4 inhibitors is contraindicated with venetoclax based on an observed increase in maximum concentration and AUC when co-administered with either ketoconazole or ritonavir. If there are no alternatives to a strong CYP3A4 inhibitor, the dose of venetoclax should be reduced by 75%.[181]

Conclusion

Alone in 2017, there were eight new oral oncolytic agents approved by the FDA. The speed at which oral agents for the management of cancers are being approved is rapid. Therefore, it is essential to be familiar with both oral oncolytic agents and their interactions and dosage adjustments in the presence of ART, as patients living with HIV are living longer and carry an increased risk for developing non-AIDS defining cancers. It is possible to modify ART to a combination that does not interact with an oral oncolytic agent. However, this should only be done in consultation with a clinician experienced in the management of HIV. It is important to work with a strong interdisciplinary team including physicians and pharmacists experienced in the management of both HIV and oncology and drug interaction management. The use of PIs, cobicistat, efavirenz, nevirapine, and etravirine tend to have the most drug–drug interactions where NRTIs, unboosted INSTIs, rilpivirine, and doravirine tend to be the safest ARVs when oral oncology medications are part of the patient's management. Enzalutamide, apalutamide, and TKIs tend to have the most drug–drug interactions with ARVs. More clinical studies are needed to demonstrate the safety and tolerability of oral oncolytic drugs in the presence of ARVs.

Contributions: All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Disclosure and potential conflicts of interest: The authors declare that there is no conflict of interest in preparing this article. The International Committee of Medical Journal Editors (ICMJE) Potential Conflicts of Interests form for the authors are available for download at http://www.drugsincontext.com/wp-content/uploads/2018/12/dic.212550-COI.pdf

Acknowledgments: None.

Funding declaration: There was no funding associated with the preparation of this article.

Article URL: https://www.drugsincontext.com/oral-oncolytic-and-antiretroviral-therapy-administration:-dose-adjustments,-drug-interactions,-and-other-considerations-for-clinical-use

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Provenance: invited; externally peer reviewed.

Submitted: 4 July 2018; **Peer review comments to author:** 7 September 2018; **Revised manuscript received:** 3 December 2018; **Accepted:** 4 December 2018; **Publication date:** 13 February 2019.

Drugs in Context is published by BioExcel Publishing Ltd. Registered office: Plaza Building, Lee High Road, London, England, SE13 5PT.

BioExcel Publishing Limited is registered in England Number 10038393. VAT GB 252 7720 07.

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