Chapter 7
Drug Interactions in HIV: Protease and Integrase Inhibitors

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7.1 Introduction

Treatment of HIV disease has greatly enhanced our understanding of the molecular basis leading to drug-drug interactions. HIV protease inhibitors (PIs) and nonnucleoside reverse transcriptase inhibitors (NNRTIs), critical components of early antiretroviral therapy (ART), are subject to a number of clinically significant drug-drug interactions. Early effective ART consisted of either a PI- or NNRTI-based regimen in combination with two nucleosides. Although effective, these two therapeutic platforms had major drawbacks, which included a large number of pills, multiple daily dosing, intolerance, and significant impact on metabolic clearance. For example, PIs can alter metabolic clearance by both inhibiting a wide variety of cytochrome P450 (CYP) enzymes and inducing the expression of phase II enzymes such as glucuronidation. In contrast, NNRTIs are well-known inducers of CYP450 isoenzymes that increase the clearance of concomitantly administered drugs.

In the past decade, ART regimens have undergone dramatic improvements in terms of tolerability and simplification (given once or twice daily). Two early changes significantly improved ART tolerability and adherence. One was the development of more tolerable agents such as the NNRTI, efavirenz, and PI, atazanavir, with pharmacokinetic (PK) profiles that also permitted once daily administration. The second was a fortuitous discovery that the PI ritonavir (RTV) could prolong

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Table 7.1 Fixed-dose combinations (FDCs) of antiretroviral agents

Name of FDC	Components	No. of tablets per day	Daily dose
Atripla	600 mg efavirenz, 300 mg tenofovir DF, 200 mg emtricitabine (FTC)	1	Once daily
Combivir	300 mg zidovudine, 300 mg lamivudine	1	Twice daily
Descovy	10 mg tenofovir alafenamide (TAF) and 200 mg emtricitabine (FTC) – Not available in the United States 25 mg tenofovir alafenamide (TAF) and 200 mg emtricitabine (FTC)	1	Once daily Once daily
Eviplera or Complera	25 mg rilpivirine (RPV), 300 mg tenofovir DF (TDF), 200 mg emtricitabine (FTC)	1	Once daily
Epzicom or Kivexa	600 mg abacavir (ABC), 300 mg lamivudine (3TC)	1	Once daily
Evotaz	300 mg atazanavir (ATV), 150 mg cobicistat (COBI)	1	Once daily
Genvoya	150 mg elvitegravir, 150 mg cobicistat, 10 mg tenofovir alafenamide (TAF), 200 mg emtricitabine (FTC)	1	Once daily
Kaletra	200 mg lopinavir (LPV), 50 mg ritonavir (RTV)	2	Twice daily
Odefsey	25 mg rilpivirine, 25 mg tenofovir alafenamide (TAF), 200 mg emtricitabine (FTC)	1	Once daily
Prezcobix or Rezolsta	800 mg darunavir (DRV), 150 mg cobicistat (COBI)	1	Once daily
Stribild	150 mg elvitegravir (EVG), 150 mg cobicistat (COBI), 300 mg tenofovir DF (TDF), 200 mg emtricitabine (FTC)	1	Once daily
Triumeq	50 mg dolutegravir (DTG), 600 mg abacavir (ABC), 300 mg lamivudine (3TC)	1	Once daily
Trizivir	600 mg abacavir (ABC), 300 mg zidovudine (AZT), 300 mg lamivudine (3TC)	1	Twice daily
Truvada	300 mg tenofovir DF (TDF), 200 mg emtricitabine (FTC)	1	Once daily

systemic PK of a concomitantly administered PI, opening the potential to dose PIs once daily with low doses of RTV. The ability to reduce dosing frequency also improved adherence which ultimately improved clinical outcomes. In addition, the development of new ARVs with increased potency meant lower daily dosages could be used and permitted co-formulation of various individual components into a single pill, more commonly referred to as fixed-dose combination tablets or FDC (Table 7.1).

More recently, a potent new class of ART, integrase inhibitors (INIs), has set a new standard as the most potent and well-tolerated agents available with a high genetic barrier to resistance. Raltegravir (RAL) was the first INI approved which

did not require use of RTV as a pharmacoenhancing agent. Subsequently, elvitegravir (EVG) was co-formulated with the first alternative pharmacokinetic booster, cobicistat (COBI), to enable once daily dosing. Elvitegravir is available as a complete, single-tablet regimen (STR) which includes COBI and dual NRTIs, emtricitabine and tenofovir disoproxil fumarate (TDF), in Stribild™ or with another tenofovir prodrug, tenofovir alafenamide (TAF), in Genvoya™. Dolutegravir (DTG) is the first second-generation INI with a PK profile that also supports once daily dosing but without the need for pharmacokinetic boosting agents such as RTV and COBI. Dolutegravir has also been co-formulated as a STR with dual NRTIs, lamivudine (3TC) and abacavir (ABC), in Triumeq™. Among the recently approved INIs, elvitegravir FDC regimens have similar potential for drug-drug interactions as PIs or NNRTIs, as elvitegravir is a CYP3A substrate co-formulated with a potent CYP3A inhibitor. In contrast, raltegravir and dolutegravir have a lower potential for drug-drug interactions because their metabolic pathway involves glucuronidation and thus have lower propensity for being a victim or perpetrator of drug-drug interactions.

This chapter will make extensive use of tables for reference, while the text will provide historical context and discussions about the molecular basis of drug-drug interactions and address key drug-drug interactions issues with PIs and INIs. Internet websites are continually updated with the latest antiretroviral drug-drug interaction information that may be useful to the reader [1–4].

7.2 Pharmacology of ART

7.2.1 Protease Inhibitors

PIs were the first class of antiretrovirals to dramatically improve HIV morbidity and mortality [5]. PIs are potent ARVs that exhibit durable antiretroviral suppression and have a high genetic barrier to resistance. To enhance efficacy, PIs are commonly co-administered with other ARV agents from different therapeutic classes to produce additive to synergistic antiviral activity. The introduction of PIs as part of the antiretroviral regimen led to the term, highly active antiretroviral therapy (HAART), which has since been simplified to antiretroviral therapy (ART). HIV protease inhibitors competitively inhibit HIV protease. PIs are peptidomimetic agents that bind and inhibit viral proteases from liberating the active peptide moieties from a virally produced pro-peptide preventing further viral propagation from infected cells. Numerous PIs have been approved since their introduction in the early 1990s; however, no new agents have been approved in this class since 2006, apart from the new pharmacokinetic boosting agent, cobicistat. Atazanavir, darunavir, and lopinavir are still employed in the treatment of HIV-infected adults and children in combination with a pharmacokinetic enhancer (ritonavir or cobicistat) and other antiretroviral agents, but the use of other HIV PIs has declined.

In general, PIs are large-molecular-weight compounds that often have low water solubility leading to poor oral bioavailability and necessitating large oral doses and concomitant administration of food in many cases to increase bioavailability. Atazanavir has pH-dependent absorption and should be used with caution with gastric-acid modifiers. The majority are highly protein bound and undergo extensive hepatic metabolism via CYP3A and may require multiple daily dosing in the absence of a pharmacoenhancing agent. Hepatic impairment increases PI exposures; however, renal excretion is typically minimal supporting recommendations for no dosage adjustment in renal impairment. PIs are metabolically eliminated by hepatic clearance and are also known to inhibit CYP3A activity or UGT activity [6]. RTV is a potent inhibitor of CYP3A which was a fortuitous discovery that ultimately shifted its use away from a primary ART agent to its use as a low-dose PK-enhancing drug. This boosting effect of RTV was discovered during evaluation of RTV with another PI, saquinavir (SQV), to determine if the combination could enhance antiretroviral activity. Initially, the reduction of circulating HIV was attributed to synergistic antiviral activity but was later found to be the result of RTV's ability to prolong the plasma half-life of SQV and increase its total drug exposure. The added antiviral activities were found to be a drug-drug interaction, whereby RTV potently blocked CYP3A4and reduced the metabolic elimination of the co-administered PI. This strategy was later employed to reduce the pill burden and dosing frequency of other PIs such as indinavir (IDV), lopinavir (LPV), atazanavir (ATV), darunavir (DRV), and tipranavir (TPV) using much lower doses of RTV that still retained potent CYP inhibition but exerted little antiretroviral activity. The majority of DDI studies with PIs have focused on their ability to act as substrates, inhibitors, or inducers of CYP3A4 and P-gp transport; however, PIs are also known to inhibit active transport processes with the most prominent interactions involving OATPs and OCTs. Key drug-drug interactions with protease inhibitors are summarized in Table 7.2.

7.2.2 Integrase Inhibitors

HIV integrase is one of three viral enzymes that are critical for viral replication. Since it is only expressed in virally infected cells, this has been an obvious target to block HIV proliferation and an area of active research for decades. After viral penetration into the host cell and viral DNA replication, the viral DNA integrates into the host genome through a series of DNA cutting and joining reactions. The function of this multipurpose viral enzyme is to remove the 3′-end from the viral DNA to enable the viral DNA strand to be transferred into the host genome. The resultant viral DNA is then joined and inserted into the host genome. After viral DNA insertion, cellular enzymes are activated to repair the single gaps found in the DNA and remove the unpaired nucleotides. HIV integrase inhibitors (INIs) bind to Mg^{+2} within the enzyme catalytic site to effectively disrupt binding to viral DNA, thus blocking the viral strand transfer step [7].

Table 7.2 Drug-drug interactions with HIV protease inhibitors

Concomitant Drugs	PI	Effect	Recommendation
Gastrointestinal agents			
Antacids $Al(OH)_3$, $Mg(OH)_2$	ATV ATV/RTV ATV/COBI	↑ gastric pH will ↓ ATV AUC	Stagger ATV administration for at least 2 h prior or 2 h after antacids
	FPV	↑ gastric pH will ↓ APV AUC 18%	Stagger FPV administration for at least 2 h prior or 1 h after antacids
	TPV/RTV	↑ gastric pH will ↓TPV AUC 27%	Stagger TPV administration for at least 2 h prior or 1 h after antacids
Histamine-2 receptor Antagonists	ATV	↑ gastric pH will ↓ATV AUC	ATV administration must be at least 2 h prior or 10 h after H_2 antagonist administration. H_2 antagonist dosage should not exceed the equivalence of 20 mg famotidine
	ATV/RTV ATV/COBI	↑ gastric pH will ↓ATV AUC	ATV administration must be at least 2 h prior or 10 h after H2 antagonist administration. H2 antagonist dosage should not exceed the equivalence of 40 mg famotidine twice daily for treatment naïve patients If ARV regimen includes TDF with H2 antagonist, use 400 mg ATV/150 mg COBI or 100 mg RTV
	DRV/COBI DRV/RTV LPV/RTV	↑ gastric pH does not significantly affect these PIs	No adjustment needed
	FPV	↑ gastric pH will ↓APV AUC 30%	FPV administration must be at least 2 h prior to H2 antagonist administration. May consider FPV/RTV

(continued)

Table 7.2 (continued)

Concomitant Drugs	PI	Effect	Recommendation
Proton pump inhibitors	ATV ATV/COBI ATV/RTV	↑ gastric will ↓ ATV AUC	PPI dosage should not exceed the equivalence of 20 mg omeprazole daily. PPI should be administered at least 12 h prior ATV/COBI or ATV/RTV
	DRV/COBI	↑ gastric pH does not significant affect these DRV	No adjustment needed
	DRV/RTV	↑ gastric pH does not significant affect these DRV but ↓ omeprazole AUC 42%	No adjustment needed for DRV Dosage adjustment of omeprazole may be necessary
	FPV FPV/RTV LPV/RTV	↑ gastric pH does not significantly affect these PIs	No adjustment needed
	SQV/RTV	↑ gastric pH will ↑AUC 82%	Monitor for signs and symptoms of toxicities
	TPV/RTV	↓ omeprazole AUC	Dosage adjustment of omeprazole may be necessary
Anticoagulants/ antiplatelets agents			
Apixaban	All PIs	↑apixaban	Avoid concomitant use
Dabigatran	All PIs/RTV	↑dabigatran	No dosage adjustment if CrCl >50 mL/min Avoid concomitant use if CrCl < 50 mL/min
Edoxaban	All PIs	↑rivaroxaban	Avoid concomitant use
Ticagrelor	All PIs	↑ticagrelor	Avoid concomitant use
Vorapaxar	PI/RTV	↑vorapaxar	Avoid concomitant use
Warfarin	PI/RTV	↓warfarin	Monitor INR when either initiating or stopping PI/RTV
Warfarin	ATV/COBI DRV/COBI	No data	Monitor INR when either initiating or stopping PI/COBI.

Anti-seizure medications			
Carbamazepine (CBZ)	ATV FPV	↓PI concentrations	Do not combine these PIs with CBZ
	ATV/COBI DRV/COBI	↓COBI concentration ↓PI concentration	Do not combine these PI with CBZ
	ATV/RTV FPV/RTV LPV/RTV SQV/RTV TPV/RTV DRV/RTV	RTV will ↑CBZ concentrations No changes with DRV	Do not combine LPV/RTV or FPV/RTV with CBZ Consider using Keppra as an alternative anticonvulsant
Ethosuximide	All PIs	↑ethosuximide	Monitor for signs and symptoms of ethosuximide toxicities
Lamotrigine	ATV	No effect	No dosage adjustment
	ATV/RTV	↓lamotrigine AUC 32%	
	LPV/RTV	↓lamotrigine AUC 50% No change in LPV	↑lamotrigine dosage is necessary or consider alternative anticonvulsant
	ATV/COBI DRV/COBI	No data	Monitor lamotrigine concentrations
Phenobarbital (PB)	ATV/COBI DRV/COBI	↓COBI ↓PI levels	Do not recommend combining PB with ATV/COBI or DRV/COBI
	PI or PI/RTV	↓PI levels	Do not recommend combining PB with PI

(continued)

Table 7.2 (continued)

Concomitant Drugs	PI	Effect	Recommendation
Phenytoin (PHT)	ATV FPV	↓PI levels	Do not recommend combining PHT with PI Consider ATV/RTV or FPV/RTV Consider alternative anticonvulsants
	ATV/RTV DRV/RTV SQV/RTV TPV/RTV	↓PI levels ↓PHT levels	Do not recommend combining PHT with PI Consider alternative anticonvulsants Assess virologic efficacy
	ATV/COBI DRV/COBI	↓COBI concentration ↓PI concentration	Consider alternative anticonvulsants Assess virologic efficacy
	FPV/RTV	↓PHT AUC 22% ↑APV AUC 20%	Adjust dose according to PHT levels No change in FPV/RTV
	LPV/RTV	↓PHT AUC 31% ↓LPV AUC 33%	Consider alternative anticonvulsant Assess virologic efficacy
Valproic (VPA)	LPV/RTV	↓ or ↔VPA ↑LPV AUC 75%	Monitor VPA concentration and assess virologic efficacy Monitor for LPV toxicities
Antimycobacterial			
Clarithromycin	ATV	↑clarithromycin AUC 94%	Consider alternative macrolide (e.g., azithromycin) ↑risk for QTc prolongation ↑risk for increased liver function test
	PI/RTV ATV/COBI DRV/COBI FPV	↑clarithromycin DRV/RTV ↑Clari AUC 57%	Consider alternative macrolide (e.g., azithromycin) ↑risk for QTc prolongation ↑risk for increased liver function test ↓clarithromycin dose by 50%

Rifabutin	ATV	↑rifabutin	↓Rifabutin to 150 mg daily or 300 mg TIW
	ATV/COBI	↑rifabutin	↓Rifabutin to 150 mg daily or 300 mg TIW
	ATV/RTV	↑rifabutin and ↑rifabutin metabolite AUC 2101%	↓Rifabutin to 150 mg daily or 300 mg TIW Monitor for signs and symptoms of toxicities
	DRV/RTV	Rifabutin ↔ but rifabutin metabolite AUC ↑ 881%	↓Rifabutin to 150 mg daily or 300 mg TIW Monitor for signs and symptoms of toxicities
	FPV	No data	Consider alternative PI or anti-mycobacterial
	FPV/RTV	↑rifabutin and ↑rifabutin metabolite AUC 64%	↓Rifabutin to 150 mg daily or 300 mg TIW Monitor for signs and symptoms of toxicities
	LPV/RTV	↑rifabutin and ↑rifabutin metabolite AUC 473%	↓Rifabutin to 150 mg daily or 300 mg TIW Monitor for signs and symptoms of toxicities
	SQV	↑rifabutin	↓Rifabutin to 150 mg daily or 300 mg TIW Monitor for signs and symptoms of toxicities
	SQV/RTV	Expect ↑rifabutin	↓Rifabutin to 150 mg daily or 300 mg TIW Monitor for signs and symptoms of toxicities
	TPV/RTV	↑rifabutin and ↑rifabutin metabolite AUC 333%	↓Rifabutin to 150 mg daily or 300 mg TIW Monitor for signs and symptoms of toxicities
Rifampin	PI PI/RTV PI/COBI	↓ PI concentration by >75%	Do not co-administer rifampin with PIs. Addition of RTV can overcome drug-interactions but may increase potential for drug-induced hepatotoxicity Addition of COBI is not recommended. Consider substituting rifabutin for rifampin
Rifapentine	PI	↓ PI concentration	Do not co-administer Consider substituting rifabutin for rifapentine

(continued)

Table 7.2 (continued)

Concomitant Drugs	PI	Effect	Recommendation
Steroid contraceptives			
Oral contraceptives	ATV	↑ethinyl estradiol AUC 48%	Recommend contraceptives containing <30 μg ethinyl estradiol Recommend alterative form of contraceptives
	ATV	↑norethindrone AUC 110%	Contraceptives containing ethinyl estradiol or progestins <25 μg have not been studied
	ATV/RTV	↓ethinyl estradiol AUC 19% & C_{min} ↓ 37% Norgestimate ↑ 85% Norethindrone AUC ↑ 51% and C_{min} ↑ 67%	Dosage of oral contraceptives should contain at least 35 μg ethinyl estradiol
	ATV/COBI DRV/COBI	No data	Consider alternatives or change ARV regimen
	FPV	↑ethinyl estradiol ↑norethindrone C_{min} ↓APV C_{min} 20%	Dosage of oral contraceptive should contain <30 μg of ethinyl estradiol
	DRV/RTV FPV/RTV LPV/RTV	↓ethinyl estradiol AUC 37%–48% ↓norethindrone AUC 14%–34% TPV/RTV: Norethindrone AUC↔	Consider alternatives or change ARV regimen
Depo-medroxyprogesterone IM	LPV/RTV	↑MPA AUC 46%; C_{min} ↔	No adjustment needed

Opioid agents			
Buprenorphine	ATV	↑buprenorphine AUC 66% ↑norbuprenorphine AUC 105%	Not recommended
	ATV/RTV	No data	Titrate buprenorphine to effect
	ATV/COBI DRV/COBI	Buprenorphine ↔ ↑norbuprenorphine AUC 46% & C_{min}↑ 71%	Titrate buprenorphine to effect
	DRV/RTV	Buprenorphine ↔ ↓norbuprenorphine AUC 15%	Titrate buprenorphine to effect
	FPV/RTV LPV/RTV	Buprenorphine ↔ LPV/RTV alters Norbuprenorphine	Titrate buprenorphine to effect
	TPV/RTV	↓TPV C_{min} 19–40%	Titrate buprenorphine to effect Monitor TPV levels
Fentanyl	PIs	PIs ↔	Monitor patient for respiratory depression
Methadone	ATV	ATV ↔	No adjustment needed
	ATV/COBI DRV/COBI	No data	Titrate methadone to effect
	FPV	APV ↓ R-methadone C_{min} 21%,	Titrate methadone to effect
	PI/RTV	ATV/RTV, DRV/RTV, & FPV/RTV↓ R-methadone AUC 16–18% LPV: ↓ R-methadone AUC 26–53%	Titrate methadone to effect

Adapted from DHHS Table 19a

The HIV integrase strand transfer inhibitor or integrase inhibitor (INSTI or INI) class of drugs includes raltegravir, elvitegravir, and dolutegravir. Their introduction has revolutionized the management of HIV infection for several reasons. They are characterized as among the most potent and efficacious antiretroviral agents as exemplified by an initial rapid achievement of virologic suppression that is durable over time. They exhibit favorable safety and tolerability profiles, have a high genetic barrier to resistance without cross-resistance to other agents, and have manageable drug-drug interaction profiles (Table 7.3). Most are available in fixed-dose combinations (FDC) with other antiretrovirals to constitute a complete, single-tablet regimen that can be administered once daily (Table 7.1). These features explain why these compounds have transformed how HIV is currently being managed.

7.2.2.1 Raltegravir

Raltegravir (RAL) was the first integrase inhibitor to receive FDA approval for the treatment of HIV. Raltegravir is a small molecule with a beta-diketo acid moiety that selectively inhibits the strand transfer step of viral integration. Its introduction into clinical use was a paradigm changing moment as it was one of the most potent treatment options developed at the time and with a completely new mechanism of action which was especially important for heavily treatment-experienced patients in desperate need for alternative options that were also well tolerated with potential to significantly improve patient adherence.

Raltegravir is approved for twice daily administration (400 mg twice daily) and, more recently, for once daily administration (1200 mg once daily) (Isentress PI). Raltegravir does not require PK boosting with RTV or COBI. It has a low oral bioavailability of 32% with large interindividual variability in exposure. Potential reasons for its high pharmacokinetic variability include whether it is dosed with food, pH-dependent solubility impacting absorption, differences in UGT1A1 expression or polymorphisms, and drug interactions. For example, pharmacokinetic variability increases when RAL is dosed with food, as a high fat meal increased AUC and C_{max} by approximately twofold and increased C12h by 4.1-fold, while T_{max} was delayed for up to 12 h in some healthy volunteers [8]. It has an initial distribution half-life of 1 h, which is followed by a beta terminal half-life that is approximately 9 h. Similar to other INI, raltegravir is eliminated through UGT1A1-mediated metabolism. At clinically achievable concentrations, raltegravir is not a CYP substrate which explains why it has few drug-drug interactions. In addition, raltegravir is not an inhibitor or inducer of CYP expression.

7.2.2.2 Elvitegravir

Elvitegravir (EVG, E) is the second INI that received FDA approval. Similar to raltegravir, EVG is a potent INI with antiviral activity in the subnanomolar range. It is available as a single entity and as part of two complete single-tablet antiretroviral

Table 7.3 Drug-drug interactions with INIs

Concomitant drug	Integrase inhibitor (INI)	Effect	Dosing recommendations and clinical comments
Acid reducers			
Aluminum, magnesium +/– Calcium-containing antacids	DTG	↓DTG AUC (74%) when simultaneously administered ↓DTG AUC (26%) when administered 2 h prior to antacid	Stagger DTG dosing at least 2 hours before or at least 6 hours after antacids containing polyvalent cations
	EVG/COBI EVG plus PI/RTV	↓EVG AUC (40–50%) when simultaneously administered with antacid ↓EVG AUC (15–20%) when administered 2 h before or after antacid	Stagger EVG/COBI/TDF/FTC and antacid administration by more than 2 h No changes when administered 4-h apart
	RAL	Al-mg (OH): ↓RAL C_{min} (54–63%) $CaCO_3$:↓RAL C_{min} 32%	*Do not co-administer RAL and Al-Mg(OH).* Use alternative acid reducing agent No dosing separation necessary when co-administering RAL and $CaCO_3$ antacids
H2-receptor antagonists	EVG/COBI	No significant effect	No dosage adjustment necessary
	EVG plus PI/RTV	↔ EVG	No dosage adjustment necessary for EVG
Proton pump inhibitor	DTG	No significant effect	No dosage adjustment necessary
	EVG/COBI	No significant effect	No dosage adjustment necessary
	EVG plus PI/RTV	No significant effect	No dosage adjustment necessary
	RAL	RAL AUC ↑ 212% and C_{min} ↑ 46%	No dosage adjustment necessary
Anticoagulants and antiplatelets			
Apixaban	EVG/COBI EVG plus PI/RTV	↑apixaban expected	*Avoid concomitant use*

(continued)

Table 7.3 (continued)

Concomitant drug	Integrase inhibitor (INI)	Effect	Dosing recommendations and clinical comments
Dabigatran	EVG/COBI EVG plus PI/RTV	↑dabigatran potential	No dosage adjustment for dabigatran if CrCl >50 mL/min. *Avoid co-administration if CrCl < 50 mL/min*
Edoxaban	EVG/COBI EVG plus PI/RTV	↑edoxaban expected	*Avoid concomitant use*
Rivaroxaban	EVG/COBI EVG plus PI/RTV	↑rivaroxaban expected	*Avoid concomitant use*
Ticagrelor	EVG/COBI EVG plus PI/RTV	↑ticagrelor expected	*Avoid concomitant use*
Vorapaxar	EVG/COBI EVG plus PI/RTV	↑vorapaxar expected	*Avoid concomitant use*
Warfarin	EVG/COBI EVG plus PI/RTV	Warfarin levels may be affected	Monitor INR and adjust warfarin dose accordingly
Anticonvulsants			
Carbamazepine Phenobarbital Phenytoin	DTG	↓DTG expected	Consider alternative anticonvulsant
	EVG/COBI	↑carbamazepine AUC 43% ↓EVG AUC 69% and ↓C_{min} >99% ↓COBI expected	*Contraindicated. Do not co-administer*
	EVG plus PI/RTV	↓EVG	Consider alternative anticonvulsant.
Ethosuximide	EVG/COBI EVG plus PI/RTV	↑ethosuximide potential	Clinically monitor for ethosuximide toxicities

Oxcarbazepine	DTG EVG/COBI EVG plus PI/RTV	↓ INSTI potential	Consider alternative anticonvulsant
Antidepressants/anxiolytics/antipsychotics Also see 'sedative/hypnotics' section below			
Bupropion	EVG/COBI	↑ or ↓ bupropion potential	Titrate bupropion dose based on clinical response
	EVG plus PI/RTV	↓ bupropion potential	Titrate bupropion dose based on clinical response
Buspirone	EVG/COBI EVG plus PI/RTV	↑buspirone potential	Initiate buspirone at a low dose. Dose reduction may be necessary
Fluvoxamine	EVG/COBI EVG plus PI/RTV	↑ or ↓ EVG potential	Consider alternative antidepressant or ARV
Quetiapine	EVG/COBI EVG plus PI/RTV	↑ quetiapine AUC expected	*Initiation of quetiapine in a patient receiving EVG/COBI*: Start quetiapine at the lowest dose and titrate up as needed monitor for quetiapine efficacy and adverse effects *Initiation of EVG/c in a patient receiving a stable dose of quetiapine*: Reduce quetiapine dose to 1/6 of the original dose, and closely monitor for quetiapine efficacy and adverse effects
SSRIs Citalopram Escitalopram Fluoxetine Paroxetine Sertraline	EVG/COBI	↑ SSRI potential	Initiate with lowest dose of SSRI and titrate dose carefully based on antidepressant response
	EVG plus PI/RTV	↑ or ↓SSRI potential	Titrate SSRI dose based on clinical response
	RAL	↔ RAL ↔ citalopram	No dosage adjustment necessary

(continued)

Table 7.3 (continued)

Concomitant drug	Integrase inhibitor (INI)	Effect	Dosing recommendations and clinical comments
TCAs Amitriptyline Desipramine Doxepin Imipramine Nortriptyline	EVG/COBI	↑Desipramine AUC (65%)	Initiate with lowest dose of TCA and titrate dose carefully
	EVG plus PI/RTV	↑ TCA expected	Initiate with lowest dose of TCA and titrate dose carefully based on antidepressant response and/or drug levels
Trazodone	EVG/COBI EVG plus PI/RTV	↑ trazodone potential	Initiate with lowest dose of trazodone and titrate dose carefully
Antifungals			
Isavuconazole	EVG/COBI	↑ isavuconazole expected ↑ EVG and COBI potential	If co-administered, consider monitoring isavuconazole concentrations and assess virologic response
	EVG plus PI/RTV	Changes in isavuconazole and EVG potential	If co-administered, consider monitoring isavuconazole concentrations and assessing virologic response
Itraconazole	EVG/COBI	↑ itraconazole expected ↑ EVG and COBI potential	Consider monitoring itraconazole level to guide dosage adjustments. High itraconazole doses (>200 mg/day) are not recommended unless dose is guided by itraconazole levels.
	EVG plus PI/RTV	↑ EVG potential	Consider monitoring itraconazole level to guide dosage adjustments. Doses >200 mg/day are not recommended with PI/RTV, ATV/COBI, or DRV/COBI unless dosing is guided by itraconazole levels
Posaconazole	EVG/COBI	↑ EVG and COBI potential ↑ posaconazole potential	If co-administered, monitor posaconazole concentrations
	EVG plus PI/RTV	↑ EVG potential	If co-administered, consider monitoring posaconazole concentrations. Monitor for PI adverse effects

Voriconazole	EVG/COBI	↑ voriconazole expected ↑ EVG and COBI potential	Risk/benefit ratio should be assessed to justify use of voriconazole. If administered, consider monitoring voriconazole level. Adjust dose accordingly
	EVG plus PI/RTV	Changes in voriconazole and EVG potential	Do not co-administer voriconazole and RTV or COBI unless benefit outweighs risk. If co-administered, consider monitoring voriconazole concentration and adjust dose accordingly
Antimycobacterials			
Clarithromycin	EVG/COBI	↑clarithromycin potential ↑ COBI potential	CrCl 50–60 mL/min: Reduce clarithromycin dose by 50% CrCl <50 mL/min: EVG/COBI is not recommended
Rifabutin	DTG	Rifabutin (300 mg once daily):↓DTG C_{min} (30%)	No dosage adjustment necessary
	EVG/COBI	Rifabutin 150 mg every other day with EVG/COBI once daily compared to Rifabutin 300 mg once daily alone: ↔ rifabutin AUC 25-o-desacetyl-rifabutin AUC ↑ 625% EVG AUC ↓ 21%, C_{min} ↓ 67%	*Do not co-administer*
	EVG plus PI/RTV	↔ EVG ↔ rifabutin AUC 25-O-desacetyl-rifabutin AUC ↑ 951%	Rifabutin 150 mg once daily or 300 mg three times a week. Monitor for antimycobacterial activity and consider therapeutic drug monitoring PK data reported in this table are results from healthy volunteer studies. Lower rifabutin exposure has been reported in HIV-infected patients than in the healthy study participants
	RAL	↑RAL AUC (19%) and ↓C_{min} (20%)	No dosage adjustment necessary

(continued)

Table 7.3 (continued)

Concomitant drug	Integrase inhibitor (INI)	Effect	Dosing recommendations and clinical comments
Rifampin	DTG	*Rifampin*: ↓DTG AUC (54%), ↓C_{min} (72%)*rifampin*: ↑DTG AUC (33%), ↑C_{min} (22%)	DTG 50 mg BID (instead of 50 mg once daily) for patients without suspected or documented INIs mutation *Alternative to rifampin should be used in patients with certain suspected or documented INI-associated resistance substitutions* *Consider using rifabutin*
	EVG/COBI EVG plus PI/RTV	Significant ↓EVG and COBI expected	*Do not co-administer*
	RAL	*RAL 400 mg*: ↓RAL AUC (40%), ↓C_{min} (61%) *Compared with RAL 400 mg BID alone, rifampin with RAL 800 mg BID*: ↑RAL AUC (27%), ↓C_{min} (53%)	*Dose*: RAL 800 mg BID Monitor closely for virologic response or consider using rifabutin as an alternative rifamycin
Rifapentine	DTG	Significant ↓DTG expected	*Do not co-administer*
	EVG/COBI EVG plus PI/RTV	Significant ↓ EVG and COBI expected	*Do not co-administer*
	RAL	*Rifapentine 600 mg once daily*: ↓RAL C_{min} (41%) *Rifapentine 900 mg once weekly*: RAL AUC ↑ 71%, C_{min} ↓ 12%	*Do not co-administer with once-daily rifapentine* for once-weekly rifapentine, use standard doses

Cardiac medications			
Antiarrhythmics Amiodarone Bepridil Digoxi Disopyramide Dronedarone FlecainideSystemic Lidocaine Mexiletine Propafenone Quinidine	EVG/COBI	↑ antiarrhythmics potential digoxin C_{max} ↑ 41% and AUC no significant change	Use antiarrhythmics with caution. Therapeutic drug monitoring, if available, is recommended for antiarrhythmics
	EVG plus PI/RTV	↑ antiarrhythmics potential	Not recommended
Bosentan	EVG/COBI	↑ bosentan potential	*In patients on EVG/COBI ≥ 10 days*: Start bosentan at 62.5 mg once daily or every other day based on individual tolerability *In patients on bosentan who require EVG/COBI*: Stop bosentan ≥36 h before EVG/COBI initiation. At least 10 days after initiation of EVG/COBI, resume bosentan at 62.5 mg once daily or every other day based on individual tolerability
	EVG plus PI/RTV	↑ bosentan potential	In patients on a PI (other than unboosted ATV) >10 days: Start bosentan at 62.5 mg once daily or every other day In patients on Bosentan who require a PI (other than Unboosted ATV): Stop bosentan ≥36 h before PI initiation and 10 days after PI initiation restart bosentan at 62.5 mg once daily or every other day When switching between COBI and RTV: Maintain same bosentan dose
Beta-blockers (e.g., metoprolol, timolol)	EVG/COBI EVG plus PI/RTV	↑ beta-blockers potential	Beta-blocker dose may need to be decreased; adjust dose based on clinical response consider using beta-blockers that are not metabolized by CYP450 enzymes (e.g., atenolol, labetalol, nadolol, sotalol)

(continued)

Table 7.3 (continued)

Concomitant drug	Integrase inhibitor (INI)	Effect	Dosing recommendations and clinical comments
CCBs	EVG/Cobi EVG plus PI/RTV	↑ CCBs potential	Use with caution. Titrate CCB dose and monitor closely. ECG monitoring is recommended when CCB used with ATV and SQV
Dofetilide	DTG	↑ dofetilide expected	*Do not co-administer*
Eplerenone	EVG/COBI EVG plus PI/RTV	↑ eplerenone expected	*Contraindicated. Do not co-administer*
Ivabradine	EVG/COBI EVG plus PI/RTV	↑ ivabradine expected	*Contraindicated. Do not co-administer*
Corticosteroids			
Dexamethasone (systemic)	EVG/COBI	↓ EVG and COBI potential	Use systemic dexamethasone with caution. Monitor virologic response to ART. Consider alternative corticosteroid
	EVG plus PI/RTV	↓ EVG potential	
Fluticasone Inhaled/intranasal	EVG/COBI EVG plus PI/RTV	↑ fluticasone potential	Co-administration may result in adrenal insufficiency and Cushing's syndrome. Consider alternative therapy (e.g., beclomethasone), particularly for long-term use
Methylprednisolone, prednisolone, triamcinolone Local injections, including intra-articular, epidural, intra-orbital	EVG/COBI EVG plus PI/RTV	↑ glucocorticoids expected	Co-administration may result in adrenal insufficiency and Cushing's syndrome. *Do not co-administer*

Hepatitis C direct-acting antivirals			
Daclatasvir	DTG	daclatasvir ↔	No dosage adjustment necessary.
	EVG/COBI	↑ daclatasvir	Decrease daclatasvir dose to 30 mg once daily
	EVG plus PI/RTV	↑ daclatasvir expected	Decrease daclatasvir dose to 30 mg once daily, regardless of which PI/RTV is used, except for TPV/RTV. *Do not co-administer EVG plus TPV/r with daclatasvir*
	RAL	No data	No dosage adjustment necessary
Dasabuvir plus Ombitasvir/ paritaprevir/r	DTG	No data	No dosing recommendations at this time
	EFG plus PI/RTV EVG/COBI	No data	*Do not co-administer*
	RAL	RAL AUC ↑ 134%	No dosage adjustment necessary
Elbasvir/grazoprevir	DTG	Elbasvir ↔ Grazoprevir ↔ DTG ↔	No dosage adjustment necessary
	EVG plus PI/RTV		Contraindicated. Do not co-administer. May increase the risk of ALT elevations due to a significant increase in grazoprevir plasma concentrations caused by OATP1B1/3 inhibition
	EVG/COBI	↑ elbasvir, grazoprevir expected	*Co-administration is not recommended*
	RAL	Elbasvir ↔ Grazoprevir ↔ RAL ↔ with elbasvir RAL AUC ↑ 43% with grazoprevir	No dosage adjustment necessary

(continued)

Table 7.3 (continued)

Concomitant drug	Integrase inhibitor (INI)	Effect	Dosing recommendations and clinical comments
Ledipasvir/sofosbuvir	EVG/COBI/TDF/FTC	↑ TDF and ↑ ledipasvir expected	*Do not co-administer*
	EVG/COBI/TAF/FTC	↔ EVG/COBI/TAF/FTC expected	No dosage adjustment necessary
	EVG plus PI/RTV	↔ EVG expected	No dosage adjustment necessary Co-administration of ledipasvir/sofosbuvir with TDF and a PI/RTV results in increased exposure to TDF. The safety of the increased TDF exposure has not been established. Consider alternative HCV or ARV drugs to avoid increased TDF toxicities. If co-administration is necessary, monitor for TDF-associated adverse reactions
	DTG RAL	↔ DTG or RAL	No dosage adjustment necessary
Simeprevir	DTG	↔ DTG expected	No dosage adjustment necessary
	EVG/COBI	↑ simeprevir expected	*Co-administration is not recommended*
	EVG plus PI/RTV	↔ EVG expected	*Co-administration is not recommended*
	RAL	No significant effect	No dosage adjustment necessary
Sofosbuvir	All INSTIs	No significant effect expected	No dosage adjustment necessary
Herbal products			
St. John's wort	DTG	↓ DTG potential	*Do not co-administer*
	EVG/COBI EVG plus PI/RTV	↓ EVG and COBI potential	*Do not co-administer*

Hormonal contraceptives			
Hormonal contraceptives	RAL	No clinically significant effect	No dosage adjustment necessary
Norgestimate/ Ethinyl estradiol	DTG	No significant effect	No dosage adjustment necessary
	EVG/COBI	Norgestimate AUC, C_{max}, and C_{min} ↑ >2-fold Ethinyl estradiol AUC ↓ 25% and C_{min}↓ 44%	The effects of increases in progestin (norgestimate) are not fully known and can include insulin resistance, dyslipidemia, acne, and venous thrombosis. Weigh the risks and benefits of the drug, and consider alternative contraceptive method
	EVG plus PI/RTV	↔EVG	Recommendations when used with PI/RTV Refer to Table 7.2
HMG-CoA reductase inhibitors			
Atorvastatin	EVG/COBI	↑ atorvastatin potential	Titrate statin dose slowly and use the lowest dose potential
	EVG plus PI/RTV	↔ EVG expected	Titrate atorvastatin dose carefully and use lowest dose necessary
Lovastatin	EVG/COBI EVG plus PI/RTV	Significant ↑ lovastatin expected	*Contraindicated. Do not co-administer*
Pitavastatin Pravastatin	EVG/COBI	No data	No dosage recommendation
	EVG plus PI/RTV	↔ EVG expected	Use lowest possible starting dose of pravastatin with careful monitoring
Rosuvastatin	EVG/COBI	Rosuvastatin AUC ↑ 38% and C_{max} ↑ 89%	Titrate statin dose slowly and use the lowest dose potential
	EVG plus PI/RTV	↔ EVG expected	Titrate rosuvastatin dose carefully and use the lowest necessary dose while monitoring for toxicities
Simvastatin	EVG/COBI EVG plus PI/RTV	Significant ↑ simvastatin expected	*Contraindicated. Do not co-administer*

(continued)

Table 7.3 (continued)

Concomitant drug	Integrase inhibitor (INI)	Effect	Dosing recommendations and clinical comments
Immunosuppressants			
Cyclosporine Everolimus Sirolimus Tacrolimus	EVG/COBI EVG plus PI/RTV	↑ immunosuppressant potential	Initiate with an adjusted immunosuppressant dose to account for potential increased concentration and monitor for toxicities. Therapeutic drug monitoring of immunosuppressant is recommended. Consult with specialist as necessary
Narcotics/treatment for opioid dependence			
Buprenorphine Sublingual/buccal/ implant	EVG/COBI	Buprenorphine AUC ↑ 35%, C_{max} ↑ 12%, and C_{min} ↑ 66% Norbuprenorphine AUC ↑ 42%, C_{max} ↑ 24%, and C_{min} ↑ 57%	No dosage adjustment necessary. Clinical monitoring is recommended When transferring buprenorphine from transmucosal to implantation, monitor to ensure buprenorphine effect is adequate and not excessive
	EVG plus PI/RTV	↔ EVG expected	Re titrate buprenorphine dose using the lowest initial dose. Dose adjustment of buprenorphine may be needed. It may be necessary to remove implant and treat with a formulation that permits dose adjustments. Clinical monitoring is recommended
	RAL	No significant effect observed (sublingual) or expected (implant)	No dosage adjustment necessary
Methadone	DTG	No significant effect	No dosage adjustment necessary
	EVG/COBI	No significant effect	No dosage adjustment necessary
	EVG plus PI/RTV	↓ methadone	Opioid withdrawal unlikely but may occur. Dosage adjustment of methadone is not usually required. Monitor for opioid withdrawal and increase methadone dose as clinically indicated
	RAL	No significant effect	No dosage adjustment necessary
Neuroleptics			

Perphenazine Risperidone Thioridazine	EVG/COBI	↑ neuroleptic potential	Initiate neuroleptic at a low dose. Decrease in neuroleptic dose may be necessary
PDE5 inhibitors			
Avanafil	EVG/COBI EVG plus PI/RTV	No data	*Co-administration is not recommended*
Sildenafil	EVG/COBI	↑ sildenafil expected	*For treatment of erectile dysfunction*: Start with sildenafil 25 mg every 48 h and monitor for adverse effects of sildenafil *For treatment of PAH*: *Contraindicated*
Tadalafil	EVG/COBI EVG plus PI/RTV	↑ tadalafil expected	*For treatment of erectile dysfunction*: Start with tadalafil 5-mg dose and do not exceed a single dose of 10 mg every 72 h. Monitor for adverse effects of tadalafil *For treatment of PAH* *In patients on EVG/COBI > 7 days*: Start with tadalafil 20 mg once daily and increase to 40 mg once daily based on tolerability *In patients on tadalafil who require EVG/COBI:* Stop tadalafil ≥24 h before EVG/COBI initiation. Seven days after EVG/COBI initiation, restart tadalafil at 20 mg once daily, and increase to 40 mg once daily based on tolerability
Vardenafil	EVG/COBI EVG plus PI/RTV	↑ vardenafil expected	Start with vardenafil 2.5 mg every 72 h and monitor for adverse effects of vardenafil
Sedative/hypnotics			

(continued)

Table 7.3 (continued)

Concomitant drug	Integrase inhibitor (INI)	Effect	Dosing recommendations and clinical comments
Clonazepam Clorazepate Diazepam Estazolam Flurazepam	EVG/COBI EVG plus PI/RTV	↑ benzodiazepines potential	Dose reduction of benzodiazepine may be necessary. Initiate with low dose and clinically monitor Consider alternative benzodiazepines to diazepam, such as lorazepam, oxazepam, or temazepam
Midazolam Triazolam	DTG	*With DTG 25 mg*: Midazolam AUC ↔	No dosage adjustment necessary
	EVG/COBI EVG plus PI/RTV	↑ midazolam expected ↑ triazolam expected	*Do not co-administer triazolam or oral midazolam and EVG/COBI or (EVG plus PI)* Parenteral midazolam can be used with caution in a closely monitored setting. Consider dose reduction, especially if more than one dose is administered
Suvorexant	EVG/COBI EVG plus PI/RTV	↑ suvorexant expected	*Co-administration is not recommended*
Zolpidem	EVG/COBI EVG plus PI/RTV	↑ zolpidem expected	Initiate zolpidem at a low dose. Dose reduction may be necessary
Miscellaneous drugs			
Colchicine	EVG/COBI EVG plus PI/RTV	↑ colchicine expected	*Do not co-administer in patients with hepatic or renal impairment* *For treatment of gout flares*: Colchicine 0.6 mg for 1 dose, followed by 0.3 mg 1 h later. Do not repeat dose for at least 3 days *For prophylaxis of gout flares*: If original dose was colchicine 0.6 mg BID, decrease to colchicine 0.3 mg once daily. If regimen was 0.6 mg once daily, decrease to 0.3 mg every other day *For treatment of familial Mediterranean fever*: Do not exceed colchicine 0.6 mg once daily or 0.3 mg BID

Flibanserin	EVG/COBIEVG plus PI/RTV	↑ flibanserin expected	*Contraindicated. Do not co-administer*
Metformin	DTG	*DTG 50 mg once daily plus metformin 500 mg BID*: Metformin AUC ↑ 79%, C_{max} ↑ 66% *DTG 50 mg BID plus metformin 500 mg BID*: Metformin AUC↑ 2.4 fold, C_{max} ↑ 2 fold	Limit metformin dose to no more than 1000 mg per day When starting/stopping DTG in patient on metformin, dose adjustment of metformin may be necessary to maintain optimal glycemic control and/or minimize GI symptoms
Polyvalent cation supplements Mg, Al, Fe, Ca, Zn, including multivitamins with minerals Note: Please refer to the acid reducers section in this table for recommendations on use with Al-, Mg-, and Ca-containing antacids	All INSTIs	↓ INSTI potential DTG ↔ when administered with Ca or Fe supplement simultaneously with food	If co-administration is necessary, give INSTI at least 2 h before or at least 6 h after supplements containing polyvalent cations, including but not limited to the following products: Cation-containing laxatives; Fe, ca, or mg supplements; and sucralfate. Monitor for virologic efficacy DTG and supplements containing ca or Fe can be taken simultaneously with food Many oral multivitamins also contain varying amounts of polyvalent cations; the extent and significance of chelation is unknown
Salmeterol	EVG/COBIEVG plus PI/RTV	↑ salmeterol potential	*Do not co-administer* due to potential increased risk of salmeterol-associated cardiovascular events

Adapted from DHHS Table 19b

Key to acronyms: *Al* aluminum, *ART* antiretroviral therapy, *ARV* antiretroviral, *ATV/*r atazanavir/ritonavir, *AUC* area under the curve, *BID* twice daily, *Ca* calcium, *CaCO3* calcium carbonate, *CCB* calcium channel blocker, *Cmax* maximum plasma concentration, *Cmin* minimum plasma concentration, *c or COBI* cobicistat, *CrCl* creatinine clearance, *CYP* cytochrome P, *DTG* dolutegravir, *EVG* elvitegravir, *EVG/COBI* elvitegravir/cobicistat, *Fe* iron, *GI* gastrointestinal, *INR* international normalized ratio, *INSTI* integrase strand transfer inhibitor, Mg magnesium, *PAH* pulmonary arterial hypertension, PI protease inhibitor, *PI/RTV* ritonavir-boosted protease inhibitor, PPI proton pump inhibitor, RAL raltegravir, *SQV/r* saquinavir/ritonavir, *SSRI* selective serotonin reuptake inhibitor, *TCA* tricyclic antidepressant, *Zn* zinc

regimens with cobicistat (COBI, C), emtricitabine (FTC, F), and either tenofovir disoproxil fumarate (E/C/F/TDF, Stribild™) or tenofovir alafenamide (E/C/F/TAF, Genvoya™). Since its plasma half-life alone is short, it must be co-administered with a pharmacoenhancer like COBI or RTV to prolong the half-life to approximately 9.5 h to permit once daily dosing [9].

Elvitegravir is metabolized primarily via CYP3A4 with a minor component via UDP-glucuronosyltransferase (UGT) 1A1 and 1A3. As stated earlier, EVG requires pharmacoenhancement by COBI and the presence of food to improve its systemic exposure [10]. Thus, EVG-containing regimens are prone to complex drug interactions via CYP3A similar to those observed with PI and NNRTI classes. EVG is a weak inhibitor of P-gp transport; however, COBI and RTV are both clinically relevant P-gp inhibitors. Additionally, EVG and COBI are substrates and inhibitors of the transporters breast cancer resistant protein (BCRP), organic anionic transporter-B1 (OATP1B1), and OATP1B3 [11, 12]. The use of TAF as an alternative to TDF-based fixed-dose combination tablets of EVG does not generally change the overall drug interaction liability of EVG FDC tablets, rather improved reduction in the incidence of TDF-related renal and bone adverse effects has been reported in some studies.

Elvitegravir has a number of clinically relevant drug-drug interactions. Elvitegravir is contraindicated when used with drugs that are dependent on CYP3A-mediated clearance with a narrow therapeutic index (Table 7.3). In particular, EVG is contraindicated when used together with rifamycins like rifampin and rifapentine. Combining EVG with the potent CYP3A inducers, rifapentine or rifampin, will reduce EVG levels below the threshold required for HIV suppression. When elvitegravir has to be used in combination with a rifamycin, rifabutin may be a good alternative in this scenario since this is a weak CYP3A inducer. In healthy volunteers, rifabutin administered at an adjusted dose of 150 mg every other day significantly reduced elvitegravir C_{min} by 67% with concurrent COBI administration [13]. However, doubling the EVG dose to 300 mg once daily and switching the pharmacokinetic booster to low dose RTV mitigate this interaction and permit co-administration with dose-adjusted rifabutin [14]. However, increased monitoring for rifabutin-associated adverse effects is required as a result of increased rifabutin and desacetyl-rifabutin metabolite concentrations with EVG/r co-administration. Other potent CYP3A enzyme inducers should not be co-administered with EVG, regardless if COBI, within fixed dose tablet regimens, or RTV, with boosted PI regimens, is used for pharmacoenchancement.

In treatment-experienced subjects receiving RTV-boosted PIs with atazanavir or lopinavir, the dose of EVG must be reduced as a result of potent UGT1A1 inhibition by these PIs. In healthy volunteers, EVG exposures increased up to 2.8-fold when co-administered with ATV 300 mg/RTV 100 mg daily and increased by 2.3-fold when co-administered with LPV 400 mg/RTV 100 mg twice daily [15]. Thus, concomitant use with these RTV-boosted protease inhibitors requires a dose reduction in EVG from 150 to 85 mg once daily.

Overall, EVG-containing regimens are prone to complex CYP3A-mediated drug interactions similar to those observed with PI and NNRTI classes but unlike other members of the integrase class. EVG is contraindicated for use with drugs dependent on CYP3A-mediated clearance possessing a narrow therapeutic index and drugs with potent CYP3A induction potential. Healthcare providers are advised to evaluate the potential for drug-drug interactions when prescribing EVG-containing regimens due to potent enzyme and transporter inhibition by RTV and COBI.

7.2.2.3 Dolutegravir

Dolutegravir (DTG) is a potent, second-generation INI with antiviral activity against raltegravir- and elvitegravir-resistant virus. It exhibits low to moderate variability in plasma concentrations and does not require COBI or RTV boosting or food for optimal drug exposures. DTG is available as a single entity and as a component of a STR (Triumeq™) which is combined with two nucleosides abacavir (ABC) and lamivudine (3TC) (Table 7.1).

DTG is primarily metabolized by UGT 1A1 with a minor contribution from CYP3A4 and has a favorable drug interaction profile similar to raltegravir, which also undergoes glucuronidation. Although DTG is a substrate for UGT1A3, UGT1A9, and the efflux transporters P-gp and BCRP, it has a low potential to cause drug-drug interactions. DTG does not induce or inhibit CYP or UGT enzymes. Additionally, it has relatively little impact on major efflux transporters such as P-gp or MRPs [16]. DTG has been shown to potently inhibit renal organic cation transporter, OCT2 and MATE-1, which results in a reduction in creatinine secretion in the renal proximal tubule. This causes a benign increase in serum creatinine concentrations which consequently causes an artificial decline in calculated glomerular filtration rate.

Dolutegravir exposures can be impacted when co-administered with potent CYP3A inducers such as tipranavir, fosamprenavir, efavirenz, and rifampin. When co-administered with moderate to strong UGT1A1 and CYP3A inducers, DTG exposures can be reduced requiring either dose adjustment or employment of mitigating strategies. Rifampin, a potent inducer of CYP and efflux transporters, can significantly decrease dolutegravir plasma concentrations. This interaction can be mitigated by simply increasing the dolutegravir dosage to 50 mg BID. Similar to raltegravir, but unlike elvitegravir, dolutegravir may be administered with rifabutin without dose adjustment [17].

NNRTIs like efavirenz and etravirine are known CYP3A inducers, and both agents are able to reduce DTG plasma concentrations. Efavirenz can significantly reduce DTG plasma C_{min} by 75%; therefore, the dose of DTG must be increased to 50 mg twice daily to overcome this interaction [18]. Surprisingly, etravirine dramatically reduced plasma DTG C_{min} by 88% likely due to combined UGT and CYP3A induction; however, this interaction can be attenuated with the addition of

specific RTV-boosted PIs, either DRV/RTV or LPV/RTV [19]. Therefore, no dose adjustment in DTG is necessary when co-administered with etravirine and RTV-boosted PIs, DRV/RTV and LPV/RTV. Similarly, when DTG is combined with enzyme-inducing PIs like tipranavir or fosamprenavir, even the addition of RTV cannot mitigate the enzyme-inducing effect; therefore, DTG requires dose adjustment when co-administered with these agents.

When DTG is combined with atazanavir (ATV), a potent competitive inhibitor of UGT-mediated metabolism, plasma DTG C_{min} increased by 2.8-fold and AUC by 1.9-fold compared with ATV alone. However, when RTV was added to ATV, the increase in DTG exposure was attenuated possibly via RTV-mediated induction of UGT metabolism [19, 20]. Additionally, there were no safety issues as a result of higher DTG concentrations with atazanavir co-administration in clinical trials; therefore, no dose adjustment of DTG is required.

7.2.3 Drug Interactions to Improve Bioavailability and Dosing

7.2.3.1 Pharmacoenhancement of PIs

As previously mentioned, RTV is a potent CYP3A4 inhibitor found in high levels in the gut wall and liver [21]. These inhibitory properties can be exploited to increase plasma concentrations of co-administered PIs with RTV. The resultant effect is increased PI exposure leading to improved antiviral activity while permitting a lower dosage and dosing frequency of the co-administered PI and potentially reducing the incidence of adverse effects.

RTV is ideally suited to boosting, as it acts both on first-pass metabolism and on hepatic clearance. Thus, CYP3A4 and P-gp found in the intestinal walls can be inhibited using RTV and thus overcome poor intrinsic bioavailability. When RTV 200 mg was co-administered with SQV, a three- to eightfold increase SQV exposure was realized when compared with unboosted SQV [22]. For PIs with good bioavailability but a short half-life, RTV-mediated inhibition of CYP3A4 can decrease hepatic clearance and therefore extend the half-life of a co-administered PI.

Ideally, boosting should maintain drug concentrations that are within the therapeutic window. This means that the C_{min} should fall within a zone above the minimum effective concentration for viral inhibition, while C_{max} should fall below the threshold for toxicity. If an agent has a narrow therapeutic window, boosting is likely to increase the frequency or magnitude of adverse effects, even if boosting has a relatively minor effect on C_{max}. For example, IDV has good bioavailability, but its relatively short half-life requires frequent dosing to prevent suboptimal plasma levels, a shortcoming that can be overcome by boosting with RTV [23]. Although the increase in IDV C_{max} from boosting is small, it is apparently sufficient to substantially increase risk of nephrolithiasis [24]. In contrast, addition of RTV to a PI with low bioavailability, like SQV or LPV, results in greatly increased C_{max} without increased toxicity, probably because these drugs have intrinsically lower toxicity [25].

7.2.3.2 Cobicistat

Cobicistat (COBI, Tybost™) is a structural analog of RTV developed as an alternative pharmacokinetic boosting agent. Although RTV co-administration can improve the pharmacokinetic profile of a co-administered PI, low-dose RTV is also associated with many metabolic side effects including hyperlipidemia and hypercholesterolemia. Advantages of COBI include its lack of antiretroviral activity at the dosage employed, its lower potential to alter lipid metabolism compared with RTV, and its availability as FDC with PIs such as darunavir (DRV) and atazanavir (ATV) and the integrase inhibitor, elvitegravir (EVG), to block CYP3A-mediated metabolism of the parent compound to enable once a day dosing. COBI and RTV share some similarities in pharmacokinetics. For example, COBI has a plasma $t_{1/2}$ of approximately 3 h, which is similar to that found for RTV ($t_{1/2}$ 3–5 h), and COBI inactivates CYP3A enzymes in a time- and concentration-dependent manner similar to RTV. COBI and RTV have both been shown to inhibit the activity of multiple transporters. In vitro, COBI is an inhibitor of Pgp, BCRP, organic anion-transporting polypeptide 1B1 and 1B3 (OATP 1B1 and 1B3), and renal tubular cell drug transporters like multidrug and toxin extrusion protein 1 (MATE-1) and organic cation transporter 1 (OCT1) [26].

In general, COBI and RTV are considered to be equipotent in CYP3A inhibition potential and therefore can be used interchangeably to boost systemic exposures of CYP3A substrates. However, there are notable differences in their ability to inhibit or induce other CYP isoenzymes and glucuronyltransferase activity which can make it difficult to predict the magnitude and direction of drug-drug interactions when using RTV or COBI with concomitant drugs that are metabolized by multiple CYPs or that undergo glucuronidation. Moreover, given that RTV is co-formulated with various other PIs and COBI is co-formulated with EVG, the parent PI, EVG, and the choice of PK boosting agent will all contribute to the net interaction observed with a concomitantly administered agent. COBI is distinct from RTV in that it does not inhibit CYP2C8, is considered a weak 2D6 inhibitor, and does not induce CYP isoenzymes 1A2, 2B6, 2C9, and 2C19 or glucuronyltransferase activity [27]. In addition, other drugs may impact COBI exposures. For example, combining COBI 150 mg BID with tipranavir 500 mg BID resulted in a significantly lower COBI C_{max} and a reduction in COBI $t_{1/2}$ to 2.2 h [13, 28]. These results further support the observation that tipranavir can significantly induce metabolic enzymes leading to enhanced COBI clearance. Therefore, when COBI is combined with tipranavir, a dosage increase of COBI to 200 mg BID may be necessary; however, there is no recommended TPV/COBI dosing regimen approved in current product labeling [26].

Regimens containing 150 mg of cobicistat and darunavir, atazanavir, and elvitegravir are considered to provide bioequivalent exposures compared to these same regimens containing 100 mg of RTV. Drug interaction studies comparing COBI vs RTV-containing regimens and third agents are limited and based on extrapolation

of interaction data with RTV. Relative bioavailability studies have been conducted to compare pharmacokinetic exposures of concomitantly administered PIs and COBI versus RTV. In healthy volunteers receiving DRV 800 mg/COBI 150 mg, DRV C_{max} and AUC_{24} were comparable to those receiving 800 mg DRV/100 mg RTV, as the geometric mean ratio was 1.03, 0.694, and 1.02 for C_{max}, C_{tau}, and AUC_{tau}, respectively. However, both C_0 and C_{24} were approximately 30% lower when DRV was combined with 150 mg COBI as compared to 100 mg RTV [29]. However, DRV $AUC_{0–12}$, C_{max}, and C_{tau} were comparable between the two pharmacoenhancers when DRV/COBI 600/150 mg BID was compared to DRV/RTV 600/100 BID, yet the use of DRV/COBI BID is not considered interchangeable and is not recommended per product labeling [26]. When either EVG or etravirine was added to DRV/COBI 600/150 BID, no changes in DRV PK were noted. Similarly, bioequivalent exposures were demonstrated between ATV 300 mg/COBI 150 mg and ATV 300 mg/RTV 100 mg, as geometric mean ratios (GMR) for C_{max}, C_{tau}, and AUC were 0.923, 0.976, and 1.01, respectively, following a meal in healthy volunteers.

7.3 Issues with ARV Drug-Drug Interactions

Specific interactions with PIs and INIs and concomitant medications are summarized in Tables 7.2 and 7.3. For additional information on interactions with PIs and INIs with antifungals, antimalarials, antimycobacterials, and hepatitis C agents, the reader is referred to Chaps. 12, 15, 17, and 18, respectively.

7.3.1 Interactions with pH-Altering Agents and Polyvalent Cations

Drug-drug interactions exist between ARVs that require low gastric pH for absorption and drugs that raise gastric pH such as proton pump inhibitors (PPI), histamine-2 (H_2) receptor blockers, and antacids. In one study involving 200 HIV patients, 88% reported taking a PPI, H_2-blocker, or antacid, individually or in combination [30]. More importantly, 95% used over-the-counter agents alone or in combination with a prescription drug, underscoring the importance of asking patients about nonprescription medications.

HIV PIs are susceptible to drug-drug interactions with agents that alter gastric pH. When PIs are co-administered with antacids, reductions in atazanavir (ATV), tipranavir (TPV), and amprenavir/fosamprenavir exposure have been noted; therefore, it is recommended to stagger PI doses 2 h before or 1–2 h after antacid dosing. Concomitant H_2 antagonists reduced unboosted atazanavir AUC by 41% with famotidine and reduced amprenavir AUC by 30% with ranitidine. Therefore, it is

recommended that H_2 antagonists should not exceed 20 mg of famotidine or its equivalent with unboosted ATV or 40 mg of famotidine or its equivalent with boosted ATV and that a 2–10-h dose separation strategy is employed [31]. When proton pump inhibitors are used together with PIs, there is generally no significant interaction, except when using atazanavir; therefore, it is not recommended to use PPIs in combination with atazanavir.

HIV INIs demonstrate varying propensities of interaction with concomitant cation-containing products, such as aluminum, magnesium, and calcium-containing antacids, which may be a result of chelation and/or pH-related changes in drug absorption. Cation interactions arise from the ability of INIs to form a complex with divalent cations in the active site of the integrase enzyme, which can effectively reduce the amount of drug available for absorption. Concurrent or staggered administration of aluminum- and/or magnesium-containing antacids is not recommended with RAL because these agents can reduce RAL exposure by greater than 50%. Raltegravir exhibits pH-dependent solubility which may explain why C_{max} and AUC were not significantly altered with concurrent magnesium antacid administration, as increasing pH improves RAL solubility initially; however, the net impact is an overall reduction in RAL exposures, likely a consequence of large quantities of metal cations available for chelation [32–34]. However, the impact on RAL exposures is product dependent as concurrent calcium carbonate antacid administration only modestly reduced RAL C_{min} by 32%. A 2-h dose separation is required between EVG and concomitant aluminum- or magnesium-containing antacid administration to avoid a 40–50% reduction in EVG AUC with simultaneous administration. Dolutegravir requires a 2- to 6-h dose separation with concurrent polyvalent cation administration as simultaneous administration of magnesium- or aluminum-containing antacids reduced DTG AUC by 74%. Alternatively, products containing iron and calcium-containing products may be co-administered at the same time as DTG if also administered with food [35].

7.3.2 Interactions with Anticoagulants

PI interactions with anticoagulants or antiplatelets have been well-established. The co-administration of thrombin inhibitors such as apixaban, dabigatran, edoxaban, and rivaroxaban with any PI will increase thrombin inhibitor concentrations; thus, it is recommended these agents be avoided with PIs. The only exception is dabigatran with PI, when the creatinine clearance is greater than 50 mL/min where no dosage adjustment is required. Similarly, the thrombin receptor antagonist, vorapaxar, should be avoided with PIs. When PI/RTV is co-administered with warfarin, warfarin levels are expected to decrease, and thus titration of warfarin dosage may be necessary to attain targeted anticoagulation levels.

7.3.3 Interactions with Anticonvulsants

As expected, the co-administration of anticonvulsants and HIV PIs will lead to significant drug-drug interactions. In general, PIs cause an increase in levels of anticonvulsants such as carbamazepine and ethosuximide. In contrast, phenytoin and phenobarbital are potent inducers of CYP, and thus co-administration of these anticonvulsants with PIs will lead to reduced PI levels, and the combination may severely impact efficacy of both classes of drugs. It is recommended that other classes of ART such as integrase inhibitors be substituted or a change to a noninteracting anticonvulsant, such as levetiracetam, be considered. All currently marketed integrase inhibitors are substrates for CYP isoenzymes and/or undergo glucuronidation, and therefore anticonvulsants with potent enzyme induction potential, such as phenytoin, phenobarbital, carbamazepine, and oxcarbazepine, are not recommended with concomitant INIs.

7.3.4 Interactions with Steroids

Steroids are widely used immunosuppressive agents for the treatment of inflammation and allergic reactions. HIV patients receiving ART and steroid therapy should be aware of potential drug-drug interactions, particularly when immunosuppressive steroids such as dexamethasone, fluticasone, and methylprednisolone are utilized. Increased fluticasone systemic concentrations have been shown when inhaled fluticasone is co-administered with ART combinations containing COBI or RTV. Thus, chronic use of steroids in combination with RTV- or COBI-containing regimens may enhance the risk for adrenal insufficiency and Cushing's syndrome and is therefore not recommended.

7.3.5 Interactions with Oral Contraceptives

Hormonal contraceptives are frequently co-administered in HIV-infected populations, and drug interactions with various antiretroviral classes have been demonstrated. Hormonal contraceptives consist of steroids that are eliminated by phase I and II metabolic enzymes. Unboosted PI therapy typically results in slightly increased ethinyl estradiol or norethindrone concentrations partly from phase I enzyme inhibition. For example, ATV is a potent inhibitor of UGT that can increase ethinyl estradiol AUC by 48% and norethindrone AUC by 110%. However, many boosted PIs cause a reduction in ethinyl estradiol exposures, and alternative forms of contraception are recommended. RTV alters the expression of the phase II metabolic enzyme, uridine 5′-diphospho-glucuronosyltransferase (UGT).

PI-induced expression of phase II metabolism may partially explain why it is able to interact with nucleosides, steroidal compounds, methadone, and antipsychotic agents. Nucleosides such as abacavir and zidovudine are metabolized via glucuronidation, and thus co-administration of PIs with nucleosides can alter their plasma concentrations. Fortunately, nucleosides have wide therapeutic indices, so no dosage adjustments are necessary.

When PIs are combined with steroid compounds such as components of birth control pills like ethinyl estradiol (EE) and norethindrone (NE), their systemic concentrations can be modified requiring a dose alteration. When an alternative to estradiols is needed, depo-medroxyprogesterone acetate (DMPA) can be utilized. One study evaluating 65 HIV-infected women receiving ART demonstrated no significant interaction between DMPA and EFV, NVP, or NFV [36]. There was no evidence of ovulation, although the study was limited to assessment of interactions with EFV, NVP, and NFV.

Although PIs are most notable in their interaction with oral contraceptives, integrase inhibitors also utilize this pathway for elimination, and thus potential drug-drug interaction between integrase inhibitors and hormonal contraceptives should always be considered. Although both estrogen- and progestin-containing products are available in addition to progestin-only formulations, the progestin component is generally considered to be most important for contraceptive activity.

No significant interaction was seen with either RAL or DTG when co-administered with hormonal contraceptives. However, co-administration of EVG/COBI/FTC/TDF with a norgestimate (NGNM)- and ethinyl estradiol (EE)-containing oral contraceptive resulted in a significant increase in progestin concentrations and reduced EE concentrations. Mean plasma AUC of NGMN increased by 2.26-fold, while the mean plasma AUC of EE was lowered by 0.75-fold. However, increasing the amount of EE to compensate for lower EE concentrations observed with EVG/COBI/FTC/TDF would likely require a higher strength NGNM/EE tablet, further increasing the potential for NGNM-related adverse events. Therefore, caution should be exercised with concomitant administration of NGMN/EE and EVG/COBI/FTC/TDF, and non-hormonal forms of contraception may be considered. However, when EVG was combined with PI/RTV, no change in EVG concentration was noted.

7.3.6 Interactions with Opioid and Psychotropic Agents

Methadone concentrations can be decreased when co-administered with various antiretroviral agents. While EFV and NVP are prominent for their negative interactions with methadone, several PIs, including NFV and LPV/r, also significantly lower methadone levels. This interaction can lead to opioid withdrawal whereby an inability to adjust methadone doses could prompt patients to interrupt or discontinue ART.

When INI are co-administered with methadone, no alteration in methadone levels was observed. However, when INI is combined with PI/RTV, the presence of RTV can induce glucuronidation resulting in lower methadone levels. In this scenario, it is advised that signs and symptoms of opioid withdrawal be closely monitored. Alternative opioids such as buprenorphine can be considered. EVG in combination with COBI increased buprenorphine AUC by 35% and increased buprenorphine metabolite concentrations by 42%. However, despite these PK changes, no adjustment is recommended.

Trazodone is a CYP3A4 substrate, and interactions with IDV and RTV can raise trazodone concentrations. A study in 10 healthy volunteers demonstrated that boosting doses of RTV (200 mg BID for 2 days) led to a 2.4-fold increase in exposure to trazodone. Study participants experienced nausea, hypotension, and syncope [37]. These observations suggest that caution is warranted whenever PIs are used concurrently with trazodone.

7.3.7 Interactions with HMG-Coenzyme a Reductase Inhibitors (Statins)

Limited data are available characterizing ARV drug interactions with HMG-coenzyme A reductase inhibitors (statins). Statins are frequently prescribed in the treatment of dyslipidemias in the HIV population which can be associated to the use of certain ARVs such as protease inhibitors (PIs). In general, statins are predominately metabolized by CYP isoenzymes and can involve drug transport via OATP, P-gP, BCRP, and OAT3 [38]. The majority of PIs inhibit the metabolism of statins through potent CYP3A enzyme inhibition which can increase statin concentrations leading to a clinically significant risk of myopathy and rhabdomyolysis. All PIs, with the exception of fosamprenavir, inhibit the OATP transporter. The degree of interaction varies by PI and statin; however, the potential for statin inhibition is considered greatest with simvastatin and lovastatin followed by atorvastatin and rosuvastatin. Simvastatin and lovastatin are contraindicated with PIs to avoid risk of myopathy. RTV-boosted PIs (ATV/r, DRV/r, and LPV/r) have been documented to increase rosuvastatin AUC from 50% to 200% and C_{max} from 90% to 600%, resulting in cautious use and titrating with the lowest dose possible [39–41] which may be explained by PI-mediated inhibition of OATP transport as rosuvastatin is not metabolized by CYP3A to any significant extent or to inhibition of breast cancer resistance protein (BCRP). Overall, atorvastatin, rosuvastatin, or pravastatin may be considered in patients receiving PI-based regimens; however, dosing adjustments may still be required depending on the components of the ARV regimen. Pitavastatin and fluvastatin do not exhibit significant interactions with PIs and can generally be used without dose adjustments. No dose adjustment of statins is required when co-administered HIV integrase inhibitors, with the exception of elvitegravir co-administered with potent CYP3A inhibitors containing boosted PIs, RTV, or COBI

which is similarly contraindicated with simvastatin and lovastatin, but cautious use with rosuvastatin is permitted [1].

7.3.8 INI Interactions with Renal Transporters

As previously stated, dolutegravir potently inhibits renal organic cation transporter, OCT2, and multidrug and toxin extrusion transporter MATE1. DTG may increase the concentrations of drugs such as metformin and dofetilide or endogenous molecules such as creatinine that are dependent on OCT2-mediated transport for renal excretion. A modest 10–15% increase in serum creatinine observed in DTG clinical trials is attributed to potent OCT2 inhibition by DTG and does not indicate renal toxicity or actual reduction of glomerular filtration [42]. In healthy volunteers, metformin mean AUC increased by 1.8- to 2.5-fold and mean C_{max} by 1.7- to 2.1-fold following metformin 500 mg twice daily administration with either once or twice daily DTG administration; therefore, limiting the total daily dose of metformin and monitoring of blood glucose are recommended [43]. Drugs that have a narrow therapeutic index, such as dofetilide and pilsicainide, which are dependent on OCT2-mediated transport, are contraindicated for use with DTG.

EVG is not known to modulate renal drug transporters; however, it requires pharmacokinetic boosting using either RTV or COBI. RTV demonstrates inhibitory activity for a wide range of transporters, including MATE-1, OAT1, OAT3, MRP2, MRP4, and P-gp, and thus may affect transport of drugs requiring these transporters. COBI is known to inhibit MATE-1 and P-gp drug transporters [44]. Given EVG/COBI is co-formulated with a nucleotide associated with renal toxicity (TDF) or the alternative TFV prodrug, TAF, renal function changes have been reported during use of EVG-containing regimens. COBI has been associated with reports of mild nonprogressive elevations in serum creatinine from inhibition of creatinine active tubular secretion without effecting glomerular filtration or overall renal function in clinical trials [45, 46]. Tenofovir is a substrate for OAT1, OAT3, and MRP4, and therefore inhibition of TFV influx or efflux from renal tubular cells may increase TFV exposure contributing to the observed 10–15% reduction in eGFR among patients receiving TDF and RTV or COBI-boosted PI- or INI-containing regimens [44]. TAF has less nephrotoxic potential when compared to TDF; however, limited long-term data exist on the renal impact of TAF-containing regimens given its recent approval [47–49]. The effect of COBI on creatinine clearance (CrCl) and iohexol-measured GFR demonstrated decreased CrCl but no effect on measured GFR (German) in healthy volunteers, suggesting the observed increase in renal-related adverse events with EVG-containing regimens may be attributed to COBI-mediated inhibition of TDF efflux by P-gp rather than COBI-mediated effects on MATE-1 transport [50, 51]. Overall, the inability to independently evaluate the renal effects of elvitegravir and COBI independently of TAF, TDF, or RTV limits our understanding of the predominant mechanisms that mediated renal function changes in EVG−/COBI-containing regimens.

In summary, although a wide spectrum of co-administered drugs may interact with antiretrovirals, much is presently known about these interactions and how to avoid their effects. A thorough history of prescription and nonprescription drugs, supplements, and herbs should identify key pharmacologic areas where potential interactions may be lurking.

7.4 Summary

Antiretroviral agents with novel mechanisms of action are constantly in development with hopes that these agents may constitute a curative treatment as seen with hepatitis C viral infection. While new classes of ART are expected to provide significant therapeutic benefits, they are also likely to further expand the number of potential drug-drug interactions. Integrase inhibitors have transformed the antiretroviral landscape with their intrinsic high-level potency, rapid attainment of virologic suppression, availability of complete single tablet regimens for once daily dosing, significant improvements in safety and tolerability, and high genetic barriers to resistance affording high efficacy rates. New advances in formulation technology are paving the way for longer-acting medications, including all injectable antiretroviral regimens, as an alternative to daily oral dosing and freedom from the daily reminder of HIV infection. Healthcare providers must remain vigilant in monitoring for drug interactions between antiretrovirals and medications used for the treatment of comorbidities. The vast array of websites and mobile applications are increasingly aiding in rapid identification of potential drug interactions at the bedside; however, the careful management of HIV disease requires a multidisciplinary focus optimized by contributions from experienced practitioners.

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