HIV Protease-Inhibitors-based regimens: Darunavir/cobicistat (Prezcobix), Atazanavir/cobicistat (Evotaz) and Cobicistat (Tybost)

Abbreviated Drug Monograph

June 2015

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a comprehensive drug review for making formulary decisions. Updates will be made when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

FDA Approval Information[1-3]

Description/Mechanism of Action	**Darunavir/cobicistat:** Fixed-dose combination of Protease Inhibitor and pharmacokinetic booster (i.e. CYP3A inhibitor) to increase systemic exposure. Darunavir has previously been approved by the FDA as an individual agent that requires co-administration with ritonavir. **Atazanavir/cobicistat:** Fixed-dose combination of Protease Inhibitor and pharmacokinetic booster to increase systemic exposure. Atazanavir has previously been approved by the FDA as an individual agent that can be administered with or without ritonavir. **Cobicistat:** Strong CYP3A inhibitor for co-administration with darunavir or atazanavir to increase systemic exposure (i.e., pharmacokinetic booster). Cobicistat lacks antiviral activity against HIV-1. The FDA had previously approved cobicistat as part of elvitegravir/cobicistat/emtricitabine/tenofovir quadruple combination product.
Indication(s) Under Review in this document (may include off label)	**Darunavir/cobicistat** is indicated for use in combination with other antiretroviral agents for the treatment of HIV-1 infection in treatment-naïve and treatment-experienced adults without darunavir resistance-associated substitutions. **Atazanavir/cobicistat** is indicated for use in combination with other antiretroviral agents for the treatment of HIV-1 infection in treatment-naïve and treatment-experienced adults. **Cobicistat** is indicated to increase systemic exposure of atazanavir or darunavir (once daily dosage regimen) in combination with other antiretroviral agents in the treatment of HIV-1 infection. Limitations of Use: • Cobicistat is not interchangeable with ritonavir to increase exposure of darunavir 600mg twice daily, fosamprenavir, saquinavir, or tipranavir due to lack of exposure data. Thus, cobicistat is not recommended for co-administration with these agents. • Cobicistat and ritonavir when administered with atazanavir or darunavir may result in different drug interactions when used with concomitant medications.
Dosage Form(s) Under Review	Darunavir/cobicistat 800mg/150mg tablet Atazanavir/cobicistat 300mg/150mg tablet Cobicistat 150mg tablet
REMS	☐ REMS ☒ No REMS ☐ Postmarketing Requirements
Pregnancy Rating	Darunavir/cobicistat: Category C Atazanavir/cobicistat: Category B Cobicistat: Category B

Executive Summary[1-8]

Efficacy	**Darunavir/cobicistat:** • Approval of darunavir/cobicistat was based upon clinical trials for the approval

	of darunavir co-administered with ritonavir. **Atazanavir/cobicistat** • Approval of atazanavir/cobicistat was based on one Phase 3 randomized, double-blinded clinical trial (Study 114) evaluating adult patients who were treatment naïve with eGFR of ≥ 70 mL/min. • The primary efficacy endpoint in the Phase 3 atazanavir/cobicistat trial compared proportion of patients with HIV-1 viral load <50 copies/mL at 48 weeks between atazanavir/cobicistat co-administered with tenofovir/emtricitabine and atazanavir/ritonavir co-administered with tenofovir/emtricitabine. The atazanavir/cobicistat group was non-inferior to atazanavir/ritonavir, 85% v. 87%, respectively. **Cobicistat** • Approval of cobicistat was primarily based on two pharmacokinetic studies along with clinical efficacy data from phase 3 trial of atazanavir/cobicistat (Study 114) and darunavir co-administered with ritonavir. • The two pharmacokinetic studies compared darunavir/cobicistat to darunavir/ritonavir and atazanavir/cobicistat to atazanavir/ritonavir. Steady state pharmacokinetic parameters were comparable for the cobicistat-containing and ritonavir-containing regimens.
Safety	**Darunavir/cobicistat** • Common adverse events observed for darunavir co-administered with ritonavir were diarrhea, nausea, rash, headache, abdominal pain and vomiting. Adverse events reported from single arm clinical trial with darunavir/cobicistat did not differ greatly. **Atazanavir/cobicistat** • Common adverse events observed when co-administered with atazanavir were jaundice, ocular icterus, and nausea. **Cobicistat** • Common adverse events observed when co-administered with atazanavir were jaundice, ocular icterus, and nausea
Potential Impact	• Darunavir/cobicistat is approved as a fixed-dose combination to be used in combination with other antiretrovirals for the treatment of HIV-1 infections and is designated in the DHHS guidelines as an alternative regimen for antiretroviral-naïve patients. • Atazanavir/cobicistat is approved as a fixed-dose combination to be used in combination with other antiretroviral agents for the treatment of HIV-1 infections and is designated in the DHHS guidelines as an alternative treatment for antiretroviral-naïve patients. • Cobicistat is approved for co-administration with darunavir or atazanavir in combination with other antiretrovirals in the treatment of HIV-1 infections.

Background

Purpose for review

Recent FDA approvals: Darunavir/cobicistat (January 29, 2015), atazanavir/cobicistat (January 29, 2015) and cobicistat (September 24, 2014)

Issues to be determined:

- ✔ Evidence of need
- ✔ Do darunavir/cobicistat, atazanavir/cobicistat and cobicistat offer advantages over current VANF agents?
- ✔ What safety issues need to be considered?

Other therapeutic options

Formulary Alternatives for HIV Protease Inhibitors	Other Considerations
Atazanavir	QD dosing. Co-administration with acid reducing agents can significantly reduce absorption. DHHS recommended "alternative" regimen for treatment-naïve
Darunavir	QD or BID dosing in treatment experienced patients with darunavir resistance. DHHS "recommended "regimen for treatment-naïve
Fosamprenavir	QD or BID dosing in protease inhibitor experienced patients.
Lopinavir/ritonavir	QD or BID dosing in experienced patients with lopinavir resistance. DHHS recommended as "other" regimen for treatment-naïve
Indinavir	DHHS does not position as recommended, alternative or other regimen for treatment-naïve
Saquinavir	DHHS does not position as recommended, alternative or other regimen for treatment-naïve
Nelfinavir	DHHS does not position as recommended, alternative or other regimen for treatment-naïve
Ritonavir	Only recommended to be co-administered with other protease inhibitors as PK booster
Tipranavir	DHHS does not position as recommended, alternative or other regimen for treatment-naïve

Efficacy (FDA Approved Indications)

Literature Search Summary

A literature search was performed on PubMed/Medline (1966 to April 2015) using the search terms <Atazanavir> <Evotaz>, <Darunavir>, <Prezcobix>, <Cobicistat>, and <Tybost>. The search was limited to studies performed in humans and published in the English language. Key randomized controlled trials published in peer-reviewed journals were included.

Review of Efficacy[1-7]

Darunavir/cobicistat: The FDA indication for darunavir/cobicistat was primarily based clinical trials conducted for the approval of darunavir formulated as a single agent while co-administered with ritonavir in combination with other antiretrovirals. Of note, a bioequivalence study found that darunavir co-administered with cobicistat was bioequivalent to darunavir co-administered with ritonavir. In addition, a Phase IIIb open-label trial (NCT01440569) with a primary outcome of safety and a secondary outcome of efficacy was conducted. Darunavir/cobicistat co-administered with two non-reverse transcriptase inhibitors resulted in 260/313 patients (83%) achieving VL <50 c/mL at 48 weeks. Overall quality of evidence: Low (Refer to Appendix A); please note that all trials were funded by Janssen Pharmaceuticals

Atazanavir/cobicistat: The FDA indication for atazanavir/cobicistat was based on a Phase 3 randomized, double-blinded clinical trial. The study population was primarily male and white.

Table 2: Clinical Trials Supporting Atazanavir/cobicistat FDA Indications and Results

Clinical Trials	Study	Population	Regimen	Results	Primary Efficacy Endpoint Results
Phase 3	Study 114	Treatment-naïve adults with an eGFR of	Cobicistat + atazanavir with TDF/FTC compared to	Cobicistat was non-inferior to ritonavir when co-administered with atazanavir and	Proportion of patients with HIV-1 viral load <50 copies/mL at 48 weeks: Cobicistat group 85%

		≥ 70 mL/min	ritonavir + atazanavir with TDF/FTC	TDF/FTC	(292/344) v. ritonavir group 87% (303/348) 95% CI (-7.4% to 3%)

Overall quality of evidence: Moderate (Refer to Appendix A); please note that all trials were funded by Gilead Sciences
FTC=emtricitabine; TDF=tenofovir

Cobicistat:
The FD approval of cobicistat was primarily based on two pharmacokinetic studies along with clinical efficacy data from phase 3 trial of atazanvir/cobicistat (Study 114) and darunavir co-administered with ritonavir. Two pharmacokinetic studies evaluated the systemic exposures of atazanavir or darunavir when co-administered with cobicistat 150mg compared to ritonavir 100mg once daily. The steady-state pharmacokinetic parameters were comparable between cobicistat and ritonavir when co-administered with atazanavir or darunavir. Overall quality of evidence: Moderate (Refer to Appendix A); please note that all trials were funded by Gilead Sciences

Potential Off-Label Use

Cobicistat is only indicated to increase systemic exposure of atazanavir or darunavir; therefore, potential off-label use when co-administered with other protease-inhibitors.

Safety [1-7]

(for more detailed information refer to the product package insert)

	Comments
Boxed Warning	• None

Contraindications	• **Darunavir/cobicistat:**
	  ○ Co-administration with certain drugs for which altered plasma concentrations are associated with serious and/or life-threatening events or loss of therapeutic effect.
	• **Atazanavir/cobicistat:**
	  ○ Co-administration with certain drugs for which altered plasma concentrations are associated with serious and/or life-threatening events or loss of therapeutic effect.
	  ○ In patients with previously demonstrated hypersensitivity (Stevens-Johnson syndrome, erythema multiforme, or toxic skin eruptions) to any of the components of atazanavir/cobicistat.
	• **Cobicistat:**
	  ○ Co-administration with certain drugs for which altered plasma concentrations are associated with serious and/or life-threatening events or loss of therapeutic effect.

Warnings/Precautions	• **Darunavir/cobicistat:**
	  ○ Drug-induced hepatitis, liver injury, including some fatalities can occur with darunavir/cobicistat. Monitor liver function before and during therapy, especially in patients with underlying chronic hepatitis, cirrhosis, or in patients who have pre-treatment elevations of transaminases.
	  ○ Skin reactions ranging from mild to severe, including Stevens-Johnson Syndrome, toxic epidermal necrolysis, drug rash with eosinophilia and systemic symptoms and acute generalized exanthemotous pustulosis, con occur with darunavir/cobicistat. Discontinue if severe reaction develops.
	  ○ Assess creatinine clearance before initiating treatment.
	  ○ When darunavir/cobicistat is used in combination with tenofovir containing regimens: Cases of acute renal failure and Fanconi syndrome have been reported. Assess urine glucose and urine protein at baseline. Monitor serum phosphorus in patients with or at risk for renal impairment.
	  ○ Drug interactions need to be assessed prior to initiation and on-going during therapy.
	  ○ Darunavir/cobicistat is not recommended in combination with other

antiretroviral drugs that require pharmacokinetic boosting.
    - Monitor in patients with a known sulfonamide allergy
    - Patients receiving darunavir/cobicistat may develop new onset or exacerbations of diabetes mellitus/hyperglycemia, redistribution/accumulation of body fat, and immune reconstitution syndrome.
    - Patients with hemophilia may develop increased bleeding events.
- **Atazanavir/cobicistat:**
    - Cardiac conduction abnormalities (PR interval prolongation) may occur in some patients. Consider ECG monitoring in patients with preexisting conduction system disease or when co-administered with other drugs that may prolong PR interval.
    - Discontinue if severe rash develops.
    - Assess creatinine clearance before initiating treatment.
    - When atazanavir/cobicistat is used in combination with tenofovir containing regimens: Cases of acute renal failure and Fanconi syndrome have been reported. Assess urine glucose and urine protein at baseline. Monitor serum phosphorus in patients with or at risk for renal impairment. Co-administration with tenofovir is not recommended in patients with creatinine clearance below 70 mL/min or in patients also receiving a nephrotoxic agent.
    - Nephrolithiasis and cholelithiasis have been reported. Consider temporary interruption or discontinuation.
    - Patients with Hepatitis B or C co-infection are at risk of increased transaminases or hepatic decompensation. Monitor hepatic laboratory tests prior to therapy and during treatment.
    - Consider potential for drug interactions prior to and during atazanavir/cobicistat therapy.
    - The following antiretrovirals are not recommended for co-administration with atazanavir/cobicistat:
        - Ritonavir or products containing ritonavir
        - Other protease inhibitors or elvitegravir
    - Most patients experience asymptomatic increases in indirect bilirubin, which is reversible upon discontinuation. If concomitant transaminase increase occurs, evaluate for alternative etiologies.
    - Patients receiving atazanavir/cobicistat therapy may develop immune reconstitution syndrome. New onset or exacerbations of diabetes mellitus/hyperglycemia and redistribution/accumulation of body fat.
    - Patients with hemophilia may develop increased bleeding events.
- **Cobicistat:**
    - Assess creatinine clearance before initiating treatment.
    - When cobicistat is used in combination with tenofovir containing regimens: Cases of acute renal failure and Fanconi syndrome have been reported. Assess urine glucose and urine protein at baseline. Monitor serum phosphorus in patients with or at risk for renal impairment. Co-administration with tenofovir is not recommended in patients with creatinine clearance below 70 mL/min or in patients also receiving a nephrotoxic agent.
    - Co-administration with more than one antiretroviral requiring pharmacokinetic enhancement (i.e., two protease inhibitors or elvitegravir in combination with a protease inhibitor) is not recommended.
    - Use with HIV-1 protease inhibitors other than atazanavir or darunavir administered once daily are not recommended.
    - Co-administration with drugs or regimens containing ritonavir is not recommended.

Safety Considerations

Darunavir/cobicistat: The safety assessment is based upon data from two Phase 3 trials. The first trial (ARTEMIS) assessed for adverse events grades 2-4 with darunavir formulated as a single agent while co-administered with ritonavir and TDF/FTC in 343 patients for 192 weeks. The second study (NCT01440569) assessed for adverse effects regardless of causality with darunavir/cobicistat administered to 313 patients for 48 weeks.

Atazanavir/cobicistat: The safety assessment is based upon data from the pooled analysis of one Phase 2 trial (atazanavir/ritonavir) and one Phase 3 trial (atazanavir/cobicistat) both co-administered with TDF/FTC. There were a total of 771 patients that received treatment for at least 48 weeks.

Cobicistat: The safety assessment is based upon the same data used for atazanavir/cobicistat therapy. Please refer to the above for trial details.

Adverse Reactions

Common adverse reactions	**Darunavir/cobicistat:** NCT01440569 trial (*Incidence ≥10%*): diarrhea (27%), nausea (23%), URTI (15%), headache (12%) **Atazanavir/cobicistat** (*Incidence ≥10%*): Jaundice (13%), ocular icterus (15%), nausea (12%) for atazanavir/cobicistat (study 114) **Cobicistat** (*Incidence ≥10%*): Jaundice (13%),ocular icterus (15%), nausea (12%) for atazanavir/cobicistat (study 114)
Death/Serious adverse reactions	**Darunavir/cobicistat**: • There were 4 deaths observed in patients exposed to darunavir coadministered with ritonavir. The study investigators indicated that these deaths were not related to treatment. **Atazanavir/cobicistat:** • There were no reported deaths in either arm for the pooled Phase 2 and Phase 3 trial safety analysis. **Cobicistat:** Safety results based on atazanavir/cobicistat trials as above
Discontinuations due to adverse reactions	**Darunavir/cobicistat:** 7.6% in darunavir/ritonavir (vs. 14.5% in lopinavir/ritonavir) **Atazanavir/cobicistat:** 7% in atazanavir/cobicistat **Cobicistat:** Discontinuation results based on atazanavir/cobicistat trials as above

Drug-Drug Interactions[1-3, 8]

- Darunavir/cobicistat is primarily metabolized by CYP3A. Drug interaction trials have been conducted with darunavir co-administered with ritonavir and with cobicistat.
    - Co-administration of darunavir/cobicistat with the following medications is contraindicated: alfuzosin, ranolazine, dronedarone, colchicine (in renal or hepatic impairment), rifampin, lurasidone, pimozide, dihydroergotamine, ergotamine, methylergonovine, cisapride, st. john's wort, lovastatin, simvastatin, sildenafil (for treatment of pulmonary arterial hypertension), midazolam (oral), and triazolam.
    - Co-administration of the following agents with darunavir/cobicistat should be avoided: efavirenz, etravirine, nevirapine, apixaban, rivaroxaban, boceprevir, simeprevir, telaprevir, everolimus, salmeterol, and avanafil.
    - Didanosine should be administered one hour before or two hours after darunavir/cobicistat.
    - Maraviroc should be dosed 150mg BID when co-administered with darunavir/cobicistat.
    - Clinical monitoring is recommended when darunavir/cobicistat is co-administered with the following: amiodarone, disopyramide, flecainide, lidocaine (systemic), mexiletine, propafenone, quinidine, digoxin, warfarin, clonazepam, itraconazole, ketoconazole, artemether/lumefantrine, carvedilol, metoprolol, timolol, amlodipine, diltiazem, felodipine, nifedipine, verapamil, cyclosporine, sirolimus, tacrolimus, fentanyl, and oxycodone.
    - Benefit/risk assessment should be performed and alternatives should be considered to the following when co-administered with darunavir/cobicistat: clarithromycin, erythromycin, telithromycin, carbamazepine, oxcarbazepine, phenobarbital, phenytoin, voriconazole, budesonide, fluticasone, dexamethasone, budesonide, prednisolone, progestin/estrogen, and fentanyl .
    - Dose adjustments may be necessary for the following when co-adminstered with darunavir/cobicistat: paroxetine, tricyclic antidepressants, trazodone, colchicine, rifabutin, bosentan, atorvastatin,

rosuvastatin, buprenorphine, buprenorphine/naloxone, methadone, tramadol, perphenazine, risperidone, thioridazine, midazolam (parenteral), buspirone, and diazepam.

- Atazanavir/cobicistat is primarily metabolized by CYP3A. Drug interaction trials have been conducted with atazanavir co-administered with ritonavir and with cobicistat alone. The same drug interactions for darunavir/cobicistat apply with the addition of the following:
  - Antacids should be administered a minimum of 2 hours apart from atazanavir/cobicistat.
  - H_2-receptor antagonists are not recommended with atazanavir/cobicistat co-administered with tenofovir in treatment experienced patients. Atazanavir/cobicistat should be administered either at the same time or at a minimum of 10 hours after a dose of a H_2-receptor antagonist. The H2-receptor antagonist should not exceed a dose comparable to famotidine 40 mg twice daily for treatment-naïve patients or 20 mg twice daily for treatment-experienced patients.
  - Proton pump inhibitors should be administered at a minimum 12 before atazanavir/cobicistat. The dose of proton pump inhibitor should not exceed 20 mg daily. Co-administration of atazanavir/cobicistat and proton pump inhibitors is not recommended in treatment-experienced patients.
- Cobicistat is an inhibitor of CYP3A and to a lesser extent CYP2D6. Cobicistat also inhibits transporters p-glycoprotein, BCRP, OATP1B1 and OATP1B3. Table 4 is adapted from DHHS HIV guidelines to compare difference of potential drug interactions between ritonavir and cobicistat.

Table 4. Role of cobicistat compared to ritonavir for potential drug interactions

	P-glycoprotein	CYP Substrate	CYP Inhibitor	CYP Inducer	UGT1A1
Cobicistat	Inhibitor	3A4	3A4, 2D6	...	...
Ritonavir	Substrate, inhibitor	3A4, 2D6	3A4, 2D6 (lesser extent)	1A2, 2C8, 2C9, 2C19	Inducer

Note: When HIV PIs are co-administered with PK boosters (i.e., cobicistat or ritonavir), the pharmacologic properties of both agents should be considered when assessing potential drug interactions.

Please refer to the full prescribing information and the DHHS guidelines for additional information on drug-drug interactions and any dose adjustment recommendations.

Risk Evaluation

As of April 27, 2015

Comments

Sentinel event advisories

- **Darunavir/cobicistat**: Post-marketing cases of liver injury have been reported with darunavir co-administered with ritonavir. A causal relationship with darunavir co-administered with ritonavir has not been established.
- **Atazanavir/cobicistat**: Nephrolithiasis and/or cholelithiasis have been reported in patients receiving atazanavir therapy resulting in hospitalization. Temporary interruption or discontinuation of therapy may be considered.
- **Cobicistat:** None

Look-alike/sound-alike error potentials

NME Drug Name	Lexi-Comp	First DataBank	ISMP	Clinical Judgment
Cobicistat-darunavir 150mg-800mg	None	None	None	Cobicistat-atazanavir
Prezcobix	Prezista	None	None	Protonix Procysbi Vectibix

Atazanavir-cobicistat 300mg-150mg	None	None	None	Atazanavir-ritonavir Atenolol-chlorthalidone Azilsartan-chlorthalidone Cobicistat-darunavir
Evotaz	None	None	None	Evista Evoxac Reyataz
Cobicistat 150mg tab	None	None	None	Orlistat Capastat Vorinostat Colestid
Tybost	None	None	None	Tyvaso Tysabri

Sources: Based on clinical judgment and an evaluation of LASA information from three data sources (Lexi-Comp, First Databank, and ISMP Confused Drug Name List)

Other Considerations[8]

The DHHS Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents were most recently updated in April 2015. The DHHS Panel positions the following Protease Inhibitor-based regimens as "**recommended**" regimens for antiretroviral-naïve patients:

- Darunavir 800mg and ritonavir 100mg once daily plus tenofovir 300mg/emtricitabine 200mg once daily (A1)

The DHHS Panel positions the following Protease Inhibitor based regimens as "**alternative**" regimens for antiretroviral-naïve patients (arranged in alphabetical order):

- Atazanavir 300mg/cobicistat 150mg once daily plus tenofovir 300mg/emtricitabine 200mg once daily for patients with pre-treatment estimated CrCl ≥70 mL/min (BI)
- Atazanavir 300mg/ritonavir 100mg once daily plus tenofovir 300mg/emtricitabine 200mg once daily (BI)
- Darunavir/cobicistat or daruanvir/ritonavir plus abacavir 600mg/lamiduvine 300mg once daily – only for pts who are HLAB*5701 negative (BIII and BII, respectively).
- Darunavir 800mg/cobicistat 150mg once daily plus tenofovir 300mg/emtricitabine 200mg – once daily for patients with pre-treatment estimated CrCl ≥70 mL/min (BII)

In antiretroviral-experienced patients, the Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents recommends a new ARV regimen of at least two, and preferably three, drugs with activity against drug-resistant viral strains. In the presence of certain drug resistance mutations, darunavir 600mg with ritonavir 100mg must be given twice daily in order to achieve high enough drug concentrations. For more details, please refer to guidelines.

Dosing and Administration[1-3]

In treatment-naïve and treatment-experienced patients without darunavir or atazanavir resistance-associated substitutions

- Darunavir/cobicistat 800mg/150mg orally once daily with food in combination with other antiretrovirals
- Atazanavir/cobicistat 300mg/150mg orally once daily with food in combination with other antiretrovirals
- Cobicistat 150mg orally once daily with food co-administered with either atazanavir 300mg orally once daily or darunavir 800mg orally once daily in combination with other antiretrovirals

Please note that treatment history and resistance testing should guide HIV regimen selection for treatment-experienced patients.

Special Populations (Adults)[1-3]

	Comments
Elderly	Clinical trials have not included sufficient number of subjects aged 65 and over. Caution should be used in the administration of atazanavir/cobicistat, darunavir/cobicistat or cobicistat in elderly as they are more likely to have decreased baseline renal function.

Pregnancy	**Darunavir/cobicistat:** Pregnancy Category C**;** Reproduction studies have only been performed in animals. Weigh potential risks and benefits to infant and mother before use. **Atazanavir/cobicistat**: Pregnancy Category B; Reproduction studies have only been performed in animals. Weigh potential risks and benefits to infant and mother before use. **Cobicistat:** Pregnancy Category B; Reproduction studies have only been performed in animals. Weigh potential risks and benefits to infant and mother before use.
Lactation	The CDC recommends that HIV-infected mothers not breastfeed their infant children to avoid risking postnatal transmission and the potential for serious adverse reactions in nursing infants.
Renal Impairment	**Darunavir/cobicistat:** There were no clinically relevant differences in pharmacokinetics observed in severe renal impairment and healthy subjects. No dose adjustments are required. **Atazanavir/cobicistat:** In end-stage renal disease managed with hemodialysis, atazanavir/cobicistat is not recommended. **Cobicistat:** No dosage adjustment is required for patients with renal impairment including those with severe renal impairment.
Hepatic Impairment	• **Darunavir/cobicistat**: Steady-state pharmacokinetic parameters for darunavir were similar in normal hepatic function and mild (Child-Pugh A) to moderate (Child-Pugh B) hepatic impairment. The effect of severe hepatic impairment has not been evaluated; thus, it is not recommended in patients with severe hepatic impairment. • **Atazanavir/cobicistat**: Not recommended for use in patients with hepatic impairment. • **Cobicistat:** No dosage adjustment is required for patients with mild to moderate hepatic impairment. The effect of severe hepatic impairment has not been studied.
Pharmacogenetics/genomics	• No data identified

Projected Place in Therapy

- The VHA Office of Public Health HIV Registry Reports indicates there were 26,784 HIV infected veterans in VHA care in 2013.[9]
- **Darunavir/cobicistat** is approved for use in combination with other antiretrovirals for treatment-naïve and treatment-experienced HIV-1 infections without darunavir resistance-associated substitutions. DHHS guidelines recommend darunavir/cobicistat co-administered with tenofovir/emtricitabine as an alternative regimen in treatment-naïve patients.
- **Atazanavir/cobicistat** is approved for use in combination with other antiretrovirals for treatment-naïve and treatment-experienced HIV-1 infections. DHHS guidelines recommend atazanavir/cobicistat co-administered with tenofovir/emtricitabine as an alternative regimen in treatment-naïve patients.
- **Cobicistat** is approved for use in treatment-naïve and treatment-experienced HIV-1 infections as a pharmacokinetic enhancer in combination with either atazanavir or darunavir in combination with other antiretrovirals. DHHS guidelines positon cobicistat administered with atazanavir or darunavir as an alternative regimen for treatment-naïve patients. Of note, elvitegravir/cobicistat/tenofovir/emtricitabine is a DHHS recommended regimen in treatment-naïve patients.

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Appendix A: GRADEing the Evidence

Designations of Quality

Quality of evidence designation	Description
High	Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes (2 consistent, higher-quality randomized controlled trials or multiple, consistent observational studies with no significant methodological flaws showing large effects).
Moderate	Evidence is sufficient to determine effects on health outcomes, but the number, quality, size, or consistency of included studies; generalizability to routine practice; or indirect nature of the evidence on health outcomes (1 higher-quality trial with > 100 participants; 2 higher-quality trials with some inconsistency; 2 consistent, lower-quality trials; or multiple, consistent observational studies with no significant methodological flaws showing at least moderate effects) limits the strength of the evidence.
Low	Evidence is insufficient to assess effects on health outcomes because of limited number or power of studies, large and unexplained inconsistency between higher-quality studies, important flaws in study design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes.

Please refer to Qaseem A, et al. The development of clinical practice guidelines and guidance statements of the American College of Physicians: Summary of Methods. Ann Intern Med 2010;153:194-199.