

Elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (Genvoya®)

National Drug Monograph

March 2016

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

The purpose of VA PBM Services drug monographs is to provide a focused 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 Documents will be placed in the Archive section when the information is deemed to be no longer current.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^{1,2}

Description/Mechanism of Action

- Genvoya® is a fixed-dose combination of elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide. Elvitegravir is an integrase strand inhibitor (INSTI), cobicistat is a CYP3A inhibitor (used to increase elvitegravir levels), and emtricitabine and tenofovir are nucleoside analog reverse transcriptase inhibitors (NRTIs).
- The individual components elvitegravir, cobicistat, and emtricitabine have previously been approved by the FDA. Tenofovir alafenamide is a new molecular entity currently available only in this combination product. A similar fixed-dose combination containing elvitegravir, cobicistat, emtricitabine, and another salt form of tenofovir, tenofovir disoproxil fumarate, is currently available as Stribild®.
- Tenofovir alafenamide is a prodrug of tenofovir. Intracellularly, tenofovir is phosphorylated to the active moiety, tenofovir-diphosphate which is the same active moiety of tenofovir disoproxil fumarate. While intracellular tenofovir-diphosphate is responsible for antiviral activity, high plasma levels of tenofovir have been associated with renal and bone toxicity. Tenofovir alafenamide has been shown to be more stable in plasma with much higher intracellular levels of tenofovir-diphosphate. As a result, tenofovir alafenamide is dosed at 10mg compared to tenofovir disoproxil fumarate at 300mg. Lower dosing of tenofovir alafenamide has been shown to have >90% lower plasma exposure of tenofovir compared with tenofovir disoproxil fumarate which is believed to reduce the risk of associated toxicities.

Indication(s) under Review in this document (may include off label)

Elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide is indicated as a complete regimen for the treatment of human immunodeficiency virus (HIV)-1 infection in adults and pediatric patients 12 years of age and older with:

- No previous antiretroviral treatment history OR
- To replace the current antiretroviral regimen in those who are virologically-suppressed (HIV-1 RNA <50 copies/mL) on a stable antiretroviral regimen for at least 6 months with no history of treatment failure and no known substitutions associated with resistance to the individual components of this combination product.

Dosage Form(s) Under Review

Available as elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide 150mg/150mg/200mg/10 mg tablet

REMS

REMS No REMS Postmarketing Requirements

Pregnancy

Pregnancy Category B

See Special Populations for additional information

Executive Summary^{1,3-6}

Efficacy

- Approval of elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide was primarily based on four Phase 3 trials.
- Two identically designed, randomized, double-blind clinical trials in treatment-naïve HIV-1 infected patients found elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide to be non-inferior to elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate with 92% vs 90% of patients achieving plasma HIV RNA <50 copies/mL at 48 weeks.
- A randomized, open-label, switch study in virologically suppressed HIV-1

Updated March 2016

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	<p>infected patients also found elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide to be non-inferior to maintaining a tenofovir disoproxil fumarate containing regimen with 96% vs 93% of patients achieving plasma HIV RNA <50 copies/mL at 48 weeks.</p> <ul style="list-style-type: none"> An open-label study in renally impaired patients with eGFR of 30-69 mL/min also supported these results with 95% of virologically suppressed patients on elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide achieving HIV RNA <50 copies/mL at 24 weeks.
Safety	<ul style="list-style-type: none"> Common adverse events observed were nausea, diarrhea, headache, and fatigue. Boxed warnings exist for lactic acidosis and severe hepatomegaly with steatosis. Additionally, severe acute exacerbations of hepatitis B in HIV and hepatitis B co-infected patients who have discontinued products containing emtricitabine and/or tenofovir disoproxil fumarate have been reported and may occur with discontinuation of elvitegravir/cobicistat/emtricitabine/ tenofovir alafenamide. Renal and bone mineral density toxicities with elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide are expected to occur less often than with elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate due to lower plasma concentrations of tenofovir. In treatment-naïve patients, less proteinuria and small changes in bone mineral density changes occurred in patients taking elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide than in patients taking elvitegravir/cobicistat/emtricitabine/ tenofovir disoproxil fumarate.
Projected Place in Therapy	<ul style="list-style-type: none"> Elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide is a DHHS recommended regimen for antiretroviral-naïve patients.
Potential Impact	<ul style="list-style-type: none"> Elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide is available as a fixed-dose one tablet once daily regimen. It is FDA approved for the treatment of HIV-1 infection in treatment-naïve patients and to replace the current antiretroviral regimen in patients with HIV-1 RNA <50 copies/mL on a stable regimen for at least 6 months with no history of treatment failure and no known resistance to the components of the product. Because of the expected improved long-term safety of the tenofovir alafenamide containing product compared to the tenofovir disoproxil fumarate product, providers and or patients may choose to pro-actively replace existing elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate regimens with elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide.

Background

Purpose for review

Recent FDA approval: November 2015

Issues to be determined:

- ✓ Evidence of need
- ✓ Does elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide offer advantages over current VANF agents?
- ✓ What safety issues need to be considered?

Other therapeutic options

Formulary Alternatives for DHHS "Recommended" Regimens for Antiretroviral-Naïve Patients	Other Considerations
Abacavir/dolutegravir/ lamivudine	<ul style="list-style-type: none"> One pill once a day Only for HLA B*5701 negative patients
Elvitegravir/cobicistat/ emtricitabine/tenofovir disoproxil fumarate	<ul style="list-style-type: none"> One pill once a day Not recommended in patients with CrCl <70 mL/min
Dolutegravir plus emtricitabine/ tenofovir disoproxil fumarate	<ul style="list-style-type: none"> Not recommended in patients with CrCl <50 mL/min
Raltegravir plus emtricitabine/ tenofovir disoproxil fumarate	<ul style="list-style-type: none"> Raltegravir BID dosing Not recommended in patients

	with CrCl <50 mL/min
Darunavir, ritonavir plus emtricitabine /tenofovir disoproxil fumarate	<ul style="list-style-type: none"> Not recommended in patients with CrCl <50 mL/min

Efficacy (FDA Approved Indications)

Literature Search Summary

A literature search was performed on PubMed/Medline (1966 to January 2016) using the search terms elvitegravir, cobicistat, emtricitabine, tenofovir alafenamide and Genvoya. The search was limited to studies performed in humans and published in the English language. The FDA medical review and AMCP dossier were also searched for relevant clinical trials. Key Phase 3 trials were included.

Review of Efficacy^{1,3-5}

The FDA approval of elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide was primarily based on four Phase 3 trials reviewed below. In addition, one Phase 2 and one Phase 2/3 trial were also submitted for FDA review but will not be discussed in monograph.

Study	Trial Design	Population	Regimen/Duration	Primary Efficacy Endpoint Results
292-0104/ 292-0111 (Identically designed trials-pooled results)	Phase 3, randomized, double blind, multicenter, active control, non-inferiority	HIV-1 infected, treatment naïve adults	E/C/F/TAF (n=866) vs. E/C/F/TDF (n=867) Duration 96 wks	HIV-1 RNA <50 copies/mL at 48 wks: E/C/F/TAF 92% vs. E/C/F/TDF 90% (95% CI -0.7 to 4.7%)
292-0109	Phase 3, randomized, open label, switch study, multicenter, active control, non-inferiority	HIV-1 infected, virologically suppressed adults on ARV w/ TDF x 6 mo	Switch to E/C/F/TAF (n=959) vs. Maintain ARV (n=477) Duration 96 wks	HIV-1 RNA <50 copies/mL at 48 wks: E/C/F/TAF 96% vs. Maintain ARV 93% (95% CI -0.3 to 5.6%)
292-0112	Phase 3, open label multicenter, multi-cohort, uncontrolled	HIV-1 infected, adults w/ eGFR 30 – 69 ml/min	Cohort 1: Switch to E/C/F/TAF (n=242) Cohort 2: Treatment naïve (n=6) Duration 96 wks	HIV-1 RNA <50 copies/mL at 24 wks: Cohort 1: Switch to E/C/F/TAF 95% Cohort 2: Treatment naïve 5/6 pts

Overall quality of evidence: High (Refer to Appendix A); please note that all trials were funded by Gilead Sciences
E/C/F/TAF = elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide; E/C/F/TDF = elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate; ARV = antiretroviral; eGFR = estimated glomerular filtration rate

Study 292-0104/Study 292-0111

- Study 292-0104 and Study 292-0111 were both Phase 3, randomized, double blind, multicenter, active controlled trials to assess the safety and efficacy of initiating elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide compared to elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate in treatment naïve patients. The two trials were identically designed but differed in geographical locations of study sites.
- HIV-1 infected adults ≥18 years with no previous antiretroviral (ARV) therapy, HIV-1 RNA ≥1000 copies/mL, eGFR ≥50 mL/min, and no resistance to elvitegravir, emtricitabine, or tenofovir were included. Patients were excluded if they had a positive hepatitis B surface antigen, hepatitis C antibody, or new AIDS-defining illness within 30 days of screening.
- Patients were randomized 1:1 to receive elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide + placebo matching alternative treatment once daily or elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate + placebo matching alternative treatment once daily.

- The primary endpoint was the proportion of patients with HIV-1 RNA <50 copies/mL at 48 weeks in the intention-to-treat population.
- In both studies combined, a total of 1733 patients were included in the intention-to-treat population. Of those, 866 patients received elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide and 867 received elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate. Baseline characteristics were similar between groups with a mean age of 36 years, 85% male, 57% White, 25% Black, and 10% Asian. The mean baseline CD4+ count was 427 cells/mm³ and the mean baseline HIV-1 RNA was 4.5-log₁₀ copies/mL.
- At 48 weeks, 800 of 866 (92%) patients receiving elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide vs. 784 of 867 (90%) patients receiving elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate had HIV-1 RNA <50 copies/mL (95% CI -0.7 to 4.7%).
- Virologic failure with resistance occurred in 7 of 866 (0.8%) patients receiving elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide vs. 5 of 867 (0.6%) of patients receiving elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate. Resistance mutations developed were similar between groups.
- At 48 weeks, the mean CD4 count change from baseline was 230 cells/mL for elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide vs. 211 cells/mL for elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (95% CI 3 to 36 cells/mL; p=0.024).

Study 292-0109

- Study 292-0109 was a Phase 3 randomized, open label, multicenter, active control trial to assess safety and efficacy of switching to elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide from an ARV regimen containing tenofovir disoproxil fumarate in virologically suppressed patients.
- HIV-1 infected adults ≥18 years with HIV-1 RNA ≤50 copies/mL for ≥6 months, eGFR ≥50 mL/min, and taking an ARV regimen containing tenofovir disoproxil fumarate (elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate; efavirenz/emtricitabine/tenofovir disoproxil fumarate; or emtricitabine, tenofovir disoproxil fumarate, atazanavir boosted with cobicistat or ritonavir) for at least 6 months were included.
- Patients were randomized 2:1 to switch to elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide once daily or maintain their previous ARV regimen.
- The primary endpoint was the proportion of patients with HIV-1 RNA <50 copies/mL at 48 weeks in the intention-to-treat population.
- A total of 1196 patients were included in the intention-to-treat population. Of those, 799 received elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide and 397 received their prior ARV regimen. Baseline characteristics were similar between groups with the exception of ethnicity. More patients in the elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide group were of Hispanic ethnicity (26% vs. 17%). Overall participants had mean age of 41 years, with 89% male, 67% White, 19% Black and 77% non-Hispanic. The median baseline CD4+ count was 669 cells/μL.
- At 48 weeks, 764 of 799 (96%) patients receiving elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide vs. 369 of 399 (93%) patients maintaining their ARV regimen had HIV-1 RNA <50 copies/mL (95% CI -0.3 to 5.6%).
- Virologic failure occurred in 24 of 799 (3%) of patients receiving elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide vs. 8 of 397 (2%) of patients who stayed on their initial regimen.
- At 48 weeks, the mean CD4 count change from baseline was 33 cells/μL in patients receiving elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide vs. 26 cells/μL in patients who maintained their ARV regimen.

Study 292-0112

- Study 292-0112 was a Phase 3, open label, multicenter, multi-cohort, uncontrolled trial to assess safety and efficacy of elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide in patients with renal impairment.
- Cohort 1 included HIV-1 infected adults on successful ARV regimen with HIV RNA <50 copies/mL and eGFR (measured by the Cockcroft-Gault formula) between 30 and 69 mL/min for ≥3 months prior to enrollment. Cohort 2 included HIV-1 infected treatment naïve adults with HIV-1 RNA ≥1000 copies/mL and eGFR (measured by the Cockcroft-Gault formula) between 30 and 69 mL/min for ≥3 months prior to enrollment.
- Patients had their ARV regimen switched to or were initiated on elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide.
- The primary endpoint was the proportion of patients with HIV-1 RNA <50 copies/mL at 24 weeks in the intention-to-treat population.

- A total of 248 patients were enrolled. Of those, 242 were virologically suppressed and switched to elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide while 6 were treatment-naïve and were initiated on elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide. Patients switched to elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide were 79% male, 63% White, 18% Black, 14% Asian, and 13% Hispanic/Latino. When segregated by renal function, 80 patients had an eGFR ≥ 30 and < 50 mL/min while 162 had an eGFR ≥ 50 and < 70 mL/min. The mean baseline CD4+ count was 664 cells/mm³.
- At 24 weeks, 230/242 (95%) patients switched to elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide had HIV-1 RNA < 50 copies/mL. Five out of the 6 patients (83%) treatment-naïve patients started on elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide had HIV-1 RNA < 50 copies/mL at 24 weeks.
- Virologic failure occurred in 3 of 242 (1%) patients switched to elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide and 1 of 6 (17%) treatment-naïve patients started on elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide.

Potential Off-Label Use⁷

- Elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide for HIV-1 infected treatment-experienced patients
- HIV-1/hepatitis virus B (HBV) co-infected patients

Safety^{1,3-5}

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

Comments

Boxed Warning

- Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs.
- Elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide is not approved for the treatment of chronic HBV infection. Severe acute exacerbations of hepatitis B have been reported in patients who are co-infected with HIV-1 and HBV and have discontinued products containing emtricitabine and/or tenofovir disoproxil fumarate, and may occur with elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide. Hepatic function should be monitored closely in these patients. If appropriate, initiation of anti-hepatitis B therapy may be warranted.

Contraindications

Co-administration of elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide is contraindicated with drugs that:

- Are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious adverse events
- Strongly induce CYP3A, which may lead to lower exposure of one or more components and loss of efficacy of elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide and possible resistance.

Warnings/Precautions

- Do not use with drugs containing elvitegravir, cobicistat, emtricitabine, tenofovir disoproxil fumarate, lamivudine, ritonavir, or adefovir dipivoxil.
- Risk of adverse reactions or loss of virologic response due to drug interactions.
- Redistribution/accumulation of body fat.
- Immune reconstitution syndrome: May necessitate further evaluation and treatment.
- New onset or worsening renal impairment: Assess creatinine clearance, urine glucose, and urine protein before initiating therapy and monitor during therapy. Monitor serum phosphorus in patients with chronic kidney disease.
- Bone loss and mineralization defects: Consider monitoring BMD in patients with a history of pathologic fracture or other risk factors of osteoporosis or bone loss.

Safety Considerations

The primary safety assessment was based on the pooled results from Phase 3 Studies 292-0104 and 292-0111 in HIV-1 treatment-naïve patients. Additional results from Phase 3 trials 292-109 and 292-112 were combined for death, serious adverse reactions, discontinuations due to adverse reactions, and bone mineral density and renal effects. Of note, Studies 292-0104 and 292-0111 were not powered to determine whether renal failure and fracture rates were different between groups.

Bone Mineral Density Effects

- Dual-energy X-ray absorptiometry (DXA) was used to assess bone mineral density (BMD) in clinical trials. In treatment-naïve patients, a decline in mean BMD at the lumbar spine and total hip was seen in those treated with elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide and those treated with elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate. In virologically suppressed patients, those switched to elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide experienced an increase in lumbar spine and total hip mean BMD while patients maintaining tenofovir disoproxil fumarate regimens had a slight decrease in mean BMD. The long-term clinical significance of the changes in BMD observed is unknown.
- No fractures reported in trials were determined to be fragility fractures.

Mean % Change in BMD at 48 Weeks						
	Treatment-Naïve (Studies 292-104/292-111)			Virologically Suppressed (Study 292-109)		
	E/C/F/TAF	E/C/F/TDF	p-value	E/C/F/TAF	TDF Regimen	p-value
Lumbar spine BMD	-1.30%	-2.86%	<0.001	+1.86%	-0.11%	<0.001
Total hip BMD	-0.66%	-2.95%	<0.001	+1.95%	-0.14%	<0.001

Renal Laboratory Tests

- In treatment-naïve patients, median increase in serum creatinine in patients receiving elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide at 48 weeks was 0.08mg/dL compared to 0.11mg/dL in patients receiving elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate. The mean increase in serum creatinine was negligible for virologically suppressed patients switching to elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide except in those who switch from efavirenz/emtricitabine/tenofovir disoproxil fumarate where there was a mean increase of 0.11mg/dL at 48 weeks. Similarly, minimal changes in serum creatinine were seen in patients with renal impairment enrolled in Study 292-112.
- Proteinuria was measured by urine protein-to-creatinine ratio (UPCR). Treatment-naïve patients receiving elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide showed no change in UPCR while patients receiving elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate had a mean increase from 44mg/g to 55 mg/g. Virologically suppressed patients maintaining their ARV regimen showed minimal increases in mean UPCR while patients switched to elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide had a mean decrease from 61 mg/g to 46 mg/g. In patients with renal impairment, mean UPCR decreased from 161 mg/g to 93 mg/g.
- No cases of Fanconi syndrome were observed in patients treated with elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide.

Mean Change in Urine Protein-to-Creatinine Ratio (UPCR)					
	Treatment-Naïve (Studies 292-104/ 292-111)		Virologically Suppressed (Study 292-109)		Renal Impairment (Study 292-112)
	E/C/F/TAF	E/C/F/TDF	E/C/F/TAF	TDF Regimen	E/C/F/TAF
UPCR Baseline	44 mg/g	44 mg/g	61 mg/g	60 mg/g	161 mg/g
Follow up UPCR	44 mg/g	55 mg/g	46 mg/g	63 mg/g	93 mg/g

Lipid Changes

- Patients receiving elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide experienced greater increases in serum lipids compared to those receiving elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil

fumarate.

Mean Changes in Lipids in Treatment-Naïve (Studies 292-104/292-111)						
	E/C/F/TAF n=866			E/C/F/TDF N=867		
	N	Baseline mg/dL	Week 48 Change	N	Baseline mg/dL	Week 48 Change
Total Cholesterol (fasted)	757	162	+30	742	166	+13
HDL-cholesterol (fasted)	757	46	+7	742	45	+4
LDL-cholesterol (fasted)	753	104	+15	744	107	+3
Triglycerides (fasted)	757	113	+29	742	119	+10

Adverse Reactions

Common adverse reactions	<ul style="list-style-type: none"> Incidence $\geq 5\%$: Nausea (10%), diarrhea (7%), headache (6%), fatigue (5%)
Death/Serious adverse reactions	<ul style="list-style-type: none"> In the pooled clinical trial results, there were 10 total deaths, 6 which occurred in patients who received elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide. The causes of death were all considered unrelated to study drug. Serious adverse events occurred in 169 of 2185 (9%) of patients who received elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide vs. 97 of 1402 (7%) of those in control arms. In treatment-naïve patients, infection and infestation was the most common adverse event encountered with 36 of 866 (4%) in the elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide group and 22 of 867 (3%) in the elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate group affected.
Discontinuations due to adverse reactions	<ul style="list-style-type: none"> In the pooled clinical trials result, 1.5% of patients who received elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (vs. 1.6% in control arms).

Drug Interactions

Drug-Drug Interactions¹

- Elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide is a complete regimen for the treatment of HIV-1 and should not be administered with other ARV medications.
- Cobicistat is an inhibitor of CYP3A and CYP2D6 as well as p-glycoprotein (P-gp), BCRP, OATP1B1, and OATP1B3 transporters. Co-administration of elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide with drugs metabolized by CYP3A or CYP2D6 or which are substrates of these transporters may result increased plasma concentrations. Elvitegravir is a modest inducer of CYP2C9 and may decrease plasma concentrations of CYP2C9 substrates. Tenofovir alafenamide is a weak inhibitor of CYP3A *in vitro*.
- Elvitegravir and cobicistat are metabolized by CYP3A. Plasma concentrations of elvitegravir, cobicistat, and tenofovir alafenamide may decrease when administered with drugs that induce CYP3A. Additionally, co-administration of elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide with drugs that inhibit CYP3A may increase the plasma concentrations of cobicistat. Cobicistat is also metabolized to a minor extent by CYP2D6. Tenofovir alafenamide is a P-gp, BCRP, OATP1B1, and OATP1B3 substrate. Administration of drugs that induce P-gp activity may decrease the absorption of tenofovir alafenamide and decrease plasma concentrations.
- Since emtricitabine and tenofovir are primarily excreted by the kidneys via glomerular filtration and active tubular secretion, co-administration of elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide with drugs that may reduce renal function or compete with active tubular secretion may increase the risk of adverse events
 - Examples: Acyclovir, cidofovir, ganciclovir, valganciclovir, aminoglycosides, and high-dose or multiple NSAIDs.
- Co-administration of elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide is contraindicated with drugs that

are highly dependent on CYP3A for clearance.

- Examples: alfuzosin, carbamazepine, phenobarbital, phenytoin, rifampin, dihydroergotamine, ergotamine, methylergonovine, cisapride, St. John’s wort, lovastatin, simvastatin, pimozide, sildenafil (when dosed for pulmonary arterial hypertension), triazolam, midazolam PO
- Other drugs with established or potentially significant interactions that may require dose or regimen alteration are listed below. Please refer to the package insert for full details.
 - Examples: antacids, antiarrhythmics, clarithromycin, telithromycin), warfarin, ethosuximide, oxcarbazepine, selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), antifungals, colchicine, rifabutin, rifapentine, benzodiazepines, beta-blockers, calcium channel blockers, dexamethasone (systemic), fluticasone (inhaled/intranasal), bosentan, atorvastatin, norgestimate/ethinyl, estradiol, immunosuppressants, buprenorphine/naloxone, salmeterol, neuroleptics, phosphodiesterase-5 (PDE5) inhibitors, sedative hypnotics

Risk Evaluation

As of January 2016

	Comments				
Sentinel event advisories	<ul style="list-style-type: none"> ● None for elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide ● Sources: ISMP, FDA, TJC 				
Look-alike/sound-alike error potentials	NME Drug Name	Lexi-Comp	First DataBank	ISMP	Clinical Judgment
	Cobicistat-150mg/ Elvitegravir-150mg/ Emtricitabine- 200mg/ Tenofovir alafenamide10mg	None	None	None	Cobicistat-150mg/ Elvitegravir-150mg/ Emtricitabine- 200mg/ Tenofovir disoproxil fumarate 10mg
	Genvoya	None	None	None	Gianvi Januvia

Other Considerations⁶

The DHHS Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents were most recently updated in January 2016. The DHHS Panel positions the following five integrase strand transfer inhibitor (INSTI)-based regimens and one protease inhibitor (PI)-based regimen as “recommended” for antiretroviral-naïve patients (arranged in alphabetic order):

INSTI-Based Regimens

- Abacavir 600mg/dolutegravir 50mg/lamivudine 300mg once daily in patients who are HLA B*5701 negative (AI)
- Dolutegravir 50mg once daily plus tenofovir disoproxil fumarate 300mg/emtricitabine 200mg once daily (AI)
- Elvitegravir 150mg/cobicistat 150mg/elvitegravir 150mg/emtricitabine 200mg /tenofovir alafenamide once daily for patients with pre-ARV therapy CrCl ≥ 30 mL/min (AI)
- Elvitegravir 150mg/cobicistat 150mg/elvitegravir 150mg/emtricitabine 200mg /tenofovir disoproxil fumarate 300 mg once daily in patients with pre-ARV therapy CrCl ≥ 70 mL/min (AI)
- Raltegravir 400mg twice daily plus tenofovir disoproxil fumarate 300mg/emtricitabine 200mg once daily (AI)

PI-Based Regimens

- Darunavir 800mg/ritonavir 100mg plus tenofovir disoproxil fumarate 300mg/emtricitabine 200 mg once daily (AI)

The DHHS Panel provides recommendations for initial ARV regimen selection in patients with specific clinical considerations. For patients with chronic kidney disease (defined as eGFR < 60 mL/min), it is recommended to avoid tenofovir disoproxil fumarate due to the association with renal tubulopathy. For patients with osteoporosis, it is also recommended to avoid tenofovir disoproxil fumarate since it has been associated with greater decrease in bone mineral density along with urine phosphate wasting, and osteomalacia.

Dosing and Administration¹

Updated March 2016

Updated version may be found at www.pbm.va.gov or [PBM INTRANet](http://PBM.INTRANet)

- Prior to initiation of elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide, patients should be tested for hepatitis B infection.
- Recommended dosage in adults with body weight at least 35 kg (at least 77 lbs): One tablet taken orally once daily with food.

Special Populations (Adults)¹

	Comments
Elderly	<ul style="list-style-type: none"> • Clinical trials included 97 subjects (80 receiving elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide) aged 65 years and over. No differences in safety or efficacy have been observed between subjects aged 65 years and over.
Pregnancy	<ul style="list-style-type: none"> • Pregnancy Category B; There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
Lactation	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • No dosage adjustment of elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide is required in patients with estimated creatinine clearance ≥ 30 mL/min. • Elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide is not recommended in patients with estimated creatinine clearance below 30 mL/min because data in this population is insufficient.
Hepatic Impairment	<ul style="list-style-type: none"> • Elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide is not recommended in patients with severe hepatic impairment (Child-Pugh Class C).
Pharmacogenetics/genomics	<ul style="list-style-type: none"> • No data identified.

Projecte, Place in Therapy (this section may be edited prior to final approval of document and web posting)⁶⁻⁸

- The VHA Office of Public Health HIV Registry Reports indicates there were 27,405 HIV infected veterans in VHA care in 2014.
- Elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide is approved for the use in HIV-1 infected patients who are treatment-naïve or virologically suppressed HIV-1 infected patients on a stable ARV regimen for at least 6 months with no history of treatment failure and no known substitutions associated with resistance to the individual components. This fixed-dose combination allows for one tablet once daily regimen that may improve patient adherence with antiretroviral therapy.
- Elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide is considered to be a DHHS recommended regimen for antiretroviral-naïve patients. At this time, it is not suitable for patients with Hepatitis B co-infection. However, preliminary data indicate that elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide may be safely substituted for tenofovir disoproxil fumarate-based regimens in hepatitis B-infected patients who have suppression of HBV and HIV.
- Lower plasma levels of tenofovir may correlate with a lower incidence of renal and BMD toxicities compared to other antiretroviral regimens containing tenofovir disoproxil fumarate. Treatment-naïve patients on elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide had smaller decline in eGFR, less proteinuria, and smaller reductions in bone mineral density at the spine and the hip compared to patients on elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate. These studies did not have adequate power to assess between group differences in renal failure and fractures. Long term safety effects are yet to be determined.

References

1. Genvoya (package insert). Gilead Sciences, Inc. Foster City, CA; November 2015.
2. U.S. National Institutes of Health. ClinicalTrials.gov website.
<https://clinicaltrials.gov/ct2/results?term=tenofovir+alafenamide&pg=1>. Accessed February 17, 2016

Updated March 2016

Updated version may be found at www.pbm.va.gov or PBM INTRANet

3. Sax PE, Wohl D, Post F, et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate, coformulated with elvitegravir, cobicistat, and emtricitabine, for initial treatment of HIV-1 infection: two randomized, double-blind, phase 3, non-inferiority trials. *Lancet* 2015; 385: 2606-15.
4. Genvoya. Drugs@FDA. Food and Drug Administration Web site. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/207561Orig1s000MedR.pdf. Accessed January 4, 2016.
5. Genvoya. Drugs@FDA. Food and Drug Administration Web site. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/207561Orig1s000SumR.pdf. Accessed January 4, 2016.
6. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. Available at <http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf>. Accessed February 3, 2016.
7. J Gallant, J Brunetta, G Crofoot, et al. Efficacy and safety of switching to simpler single tablet regimen of elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (E/C/F/TAF) in HIV-1/hepatitis B co-infected adults in North America and Japan (NCT02071082): week 48 results. 8th International AIDS Society Conference on HIV Pathogenesis, Treatment, and Prevention. Vancouver, July 19-22, 2015. Abstract WELBPE13.
8. Office of Public Health HIV Infection Status of HIV Registry Patients 2013. <http://vaww.hiv.va.gov/data-reports/ccr2013/Demo-InCare-Jan14-HIVPARV-2013-All.asp>.

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Appendix A: GRADEing the Evidence

Designations of Quality

<u>Quality of evidence designation</u>	<u>Description</u>
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.