Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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Elvitegravir (EVG) *(Last updated April 16, 2019; last reviewed April 16, 2019)*

For additional information, see Drugs@FDA: [https://www.accessdata.fda.gov/scripts/cder/daf](https://www.accessdata.fda.gov/scripts/cder/daf)

### Formulations

**Tablet:** Discontinued by the manufacturer. Elvitegravir is only available in fixed-dose combination (FDC) tablets.

**Fixed-Dose Combination Tablets:**

- *Genvoya* Elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir alafenamide (TAF) 10 mg
- *Stribild* Elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir disoproxil fumarate (TDF) 300 mg

### Dosing Recommendations

#### [Genvoya] Elvitegravir/Cobicistat/Emtricitabine/TAF

**Child (Weighing <25 kg) Dose:**
- There are no data on the appropriate dose of elvitegravir in Genvoya for children weighing <25 kg.

**Child and Adolescent (Weighing ≥25 kg) and Adult Dose:**
- One tablet once daily *with food*

#### [Stribild] Elvitegravir/Cobicistat/Emtricitabine/TDF

**Child and Adolescent (Weighing <35 kg) Dose:**
- There are no data on the appropriate dose of elvitegravir in Stribild for children or adolescents weighing <35 kg.

**Adolescent (Weighing ≥35 kg and Sexual Maturity Rating [SMR] 4 or 5) and Adult Dose:**
- One tablet once daily *with food*

**Note:** Stribild and Genvoya are approved by the Food and Drug Administration for use in antiretroviral (ARV)-naive patients or to replace the current ARV regimen in patients who have been virologically suppressed (HIV RNA <50 copies/mL) 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 of Genvoya or Stribild.

### Selected Adverse Events

**Elvitegravir-Associated Adverse Events:**
- Diarrhea

**Stribild-Associated Adverse Events:**
- Nausea
- Diarrhea
- Fatigue
- Headache

**TDF-Specific Adverse Events:**
- Glomerular and proximal renal tubular dysfunction
- Decreased bone mineral density
- Flatulence

**Cobicistat-Specific Adverse Events:**
- Benign increases in serum creatinine levels (reductions in estimated glomerular filtration) due to inhibition of tubular secretion of creatinine.

**Genvoya-Associated Adverse Events:**
- Nausea
- Diarrhea
- Fatigue
- Headache

**TAF-Specific Adverse Events:**
- Increased levels of low-density lipoprotein cholesterol and total cholesterol.

**Cobicistat-Specific Adverse Events:**
- Benign increases in serum creatinine levels (reductions in estimated glomerular filtration) due to inhibition of tubular secretion of creatinine.
Special Instructions

- Administer both Genvoya and Stribild with food.

- Separate elvitegravir dosing from antacids and iron, calcium, aluminum, and/or magnesium-containing supplements and multivitamins by at least 4 hours.

- When using Stribild, which contains TDF, monitor estimated creatinine clearance (CrCl), urine glucose, and urine protein at baseline and every 3 months to 6 months while on therapy. In patients who are at risk of renal impairment, also monitor serum phosphate. Patients with an increase in serum creatinine levels >0.4 mg/dL should be closely monitored for renal safety.

- Screen patients for hepatitis B virus (HBV) infection before using emtricitabine, TDF, or TAF. Severe acute exacerbation of HBV can occur when emtricitabine, TDF, or TAF are discontinued; therefore, monitor hepatic function for several months after stopping therapy with emtricitabine, TDF, or TAF.

Metabolism/Elimination

- Elvitegravir is metabolized by cytochrome P450 (CYP) 3A4 and is a modest inducer of CYP2C9.

- Elvitegravir should only be used with the pharmacokinetic enhancer (boosting agent) cobicistat in Stribild or Genvoya. Refer to the TDF and TAF sections for further details.

- Stribild should not be initiated in patients with estimated CrCl <70 mL/min, and it should be discontinued in patients with estimated CrCl <50 mL/min. Emtricitabine and TDF require dose adjustments in these patients, and these adjustments cannot be achieved with an FDC tablet.

- Genvoya should not be initiated in patients with estimated CrCl <30 mL/min.

- Stribild and Genvoya should be not used in patients with severe hepatic impairment.
Drug Interactions (see also the Adult and Adolescent Antiretroviral Guidelines and the HIV Drug Interaction Checker)

- **Absorption:** Elvitegravir plasma concentrations are lower with concurrent administration of divalent cations because of the formation of complexes in the gastrointestinal tract and not because of changes in gastric pH. Because of this, **Stribild and Genvoya should be administered at least 4 hours before or after administering antacids and iron, calcium, aluminum, and/or magnesium-containing supplements and multivitamins.**

- **Metabolism:** Stribild and Genvoya contain elvitegravir and cobicistat. Elvitegravir is metabolized predominantly by cytochrome P450 (CYP) 3A4, secondarily by uridine diphosphate glucuronyl transferase 1A1/3, and by oxidative metabolism pathways. Elvitegravir is a moderate inducer of CYP2C9. Cobicistat is a strong inhibitor of CYP3A4 and a weak inhibitor of CYP2D6; in addition, cobicistat inhibits the adenosine triphosphate-dependent transporters BCRP and P-glycoprotein and the organic anion-transporting polypeptides OATP1B1 and OATP1B3. There is potential for multiple drug interactions when using both elvitegravir and cobicistat. **Neither Stribild nor Genvoya should be administered concurrently with products or regimens that contain ritonavir, due to the similar effects of cobicistat and ritonavir on CYP3A4 metabolism.**

- **Renal elimination:** Drugs that decrease renal function or compete for active tubular secretion could reduce clearance of tenofovir disoproxil fumarate (TDF) or emtricitabine. Concomitant use of nephrotoxic drugs should be avoided when using Stribild. **Cobicistat inhibits MATE1, which increases serum creatinine levels up to 0.4 mg/dL in adults. Significant increases in serum creatinine levels may represent renal toxicity and should be evaluated.**

Major Toxicities

- **More common:** Nausea, diarrhea, and flatulence.

- **Less common (more severe):** Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported in patients receiving nucleoside reverse transcriptase inhibitors, including TDF and emtricitabine. TDF caused bone toxicity (osteomalacia and reduced bone mineral density [BMD]) in animals when given in high doses. Decreases in BMD have been reported in both adults and children taking TDF; the clinical significance of these changes is not yet known. Evidence of renal toxicity has been observed in patients taking TDF, including a higher incidence of glycosuria, proteinuria, phosphaturia, and/or calciuria; increases in the levels of serum creatinine and blood urea nitrogen; and decreases in serum phosphate levels. Numerous case reports of renal tubular dysfunction have been reported in patients receiving TDF; patients at increased risk of renal dysfunction should be closely monitored if they are being treated with Stribild.

Resistance

The International Antiviral Society-USA (IAS-USA) maintains a list of updated resistance mutations and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation. There is phenotypic cross-resistance between elvitegravir and raltegravir.

Pediatric Use

Approval

Stribild (which contains elvitegravir, cobicistat, emtricitabine, and TDF) is approved by the Food and Drug Administration (FDA) for use in children and adolescents aged ≥12 years and weighing ≥35 kg. **However, the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV recommends limiting the use of Stribild in adolescents with sexual maturity ratings (SMRs) of 4 or 5 due to concerns about decreased BMD in pre-pubertal patients.**

Genvoya (which contains elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide [TAF]) is
approved by the FDA for use in children and adolescents weighing ≥25 kg with any SMR.5

**Efficacy in Clinical Trials**

A combination of elvitegravir/cobicistat/emtricitabine/TDF was found to be noninferior to a regimen of efavirenz/emtricitabine/TDF6 and noninferior to a regimen of atazanavir/ritonavir (ATV/r) plus emtricitabine/TDF in adults at 144 weeks of treatment.7 In two studies, 1,733 adults were randomly assigned to receive either elvitegravir/cobicistat/emtricitabine/TDF or elvitegravir/cobicistat/emtricitabine/TAF. After 48 weeks, those receiving elvitegravir/cobicistat/emtricitabine/TAF had significantly smaller mean serum creatinine increases (0.08 vs. 0.12 mg/dL; *P* < 0.0001), significantly less proteinuria (median percent change in protein -3% vs. +20%; *P* < 0.0001), and a significantly smaller decrease in BMD at the spine (mean percent change -1.30% vs. -2.86%; *P* < 0.0001) and hip (-0.66% vs. -2.95%; *P* < 0.0001).8

**Formulations**

Elvitegravir is an INSTI that is metabolized by CYP3A4. Elvitegravir must be used in the FDC products Stribild4 or Genvoya,5 both of which contain cobicistat (see below). Cobicistat itself does not have antiretroviral (ARV) activity, but it is a CYP3A4 inhibitor that acts as a pharmacokinetic (PK) enhancer, similar to ritonavir.9

Stribild is approved by the FDA as a complete antiretroviral therapy (ART) regimen for ARV-naive adults and adolescents with HIV aged ≥12 years and weighing ≥35 kg. It can also be used to replace the current ART regimen in those who have been virologically suppressed (HIV RNA <50 copies/mL) on a stable ART regimen for at least 6 months with no history of treatment failure and no known substitutions associated with resistance to the individual components of Stribild.4 Trials have shown that Stribild is noninferior to regimens of emtricitabine plus TDF plus ATV10,11 or emtricitabine plus TDF plus efavirenz.12,13 Cobicistat inhibits renal tubular secretion of creatinine, and serum creatinine will often increase soon after initiation of treatment with Stribild. Therefore, creatinine-based calculations of estimated glomerular filtration rate (GFR) will be altered, even though the actual GFR might be only minimally changed.14 People who experience a confirmed increase in serum creatinine levels >0.4 mg/dL from baseline should be closely monitored for renal toxicity; clinicians should monitor creatinine levels for further increases and perform a urinalysis to look for evidence of proteinuria or glycosuria.4 Careful periodic evaluation of renal function is warranted, because Stribild contains TDF, which has been associated with renal toxicity. This nephrotoxicity may be more pronounced in patients with pre-existing renal disease.4

Genvoya is approved for use in children weighing ≥25 kg. Genvoya is approved by the FDA as a complete ART regimen in children with HIV who are ARV-naive. It can also be used to replace the current ARV regimen in those who have been virologically suppressed (i.e., HIV RNA <50 copies/mL) on a stable ART regimen for at least 6 months with no history of treatment failure and no known substitutions associated with resistance to the individual components of Genvoya.5 Because Genvoya contains TAF instead of TDF, Genvoya is expected to have a lower risk of bone and renal toxicity than Stribild. Two studies of adults have shown that fewer cases of renal and bone toxicity occurred among patients who received Genvoya than among those who received Stribild. After 48 weeks of treatment, participants who were treated with Genvoya had significantly smaller increases in levels of serum creatinine, less proteinuria, and smaller decreases in BMD at the spine and hip than participants treated with Stribild.5 In children aged ≥6 years and weighing ≥25 kg who were treated with TAF-containing regimens, no clinically relevant changes were observed in BMD, levels of serum creatinine, and estimated GFR between baseline and 48 weeks of treatment.14

**Coadministration of Elvitegravir, Cobicistat, and Darunavir**

The combination of Stribild or Genvoya plus darunavir has the potential to provide a low pill burden regimen for treatment-experienced individuals. However, an unfavorable drug interaction between elvitegravir/cobicistat and darunavir is possible and the available data on the magnitude of the interaction are conflicting. There are also conflicting data on the efficacy of the combination in adults.16-22

The most rigorous drug interaction study, performed in HIV-seronegative adults, found 21% lower darunavir
trough concentrations and 52% lower elvitegravir trough concentrations with darunavir 800 mg plus elvitegravir/cobicistat 150 mg/150 mg once daily compared to administration of either darunavir/cobicistat 800/150 once daily or elvitegravir/cobicistat 150 mg/150 mg once daily alone.\textsuperscript{14} The actual trough values were 1,050 ng/mL for darunavir and 243 ng/mL for elvitegravir.

Despite the findings of the aforementioned drug interaction study in HIV-seronegative adults, the most rigorous efficacy evaluation found that among 89 treatment-experienced adults on five-tablet ARV regimens, 96.6% achieved virologic suppression (HIV RNA <50 copies/mL) 24 weeks after simplifying their regimens to a two-tablet regimen of Genvoya plus darunavir 800 mg once daily.\textsuperscript{20} Intensive PK sampling was performed in 15 of these patients (17%). Mean darunavir and elvitegravir troughs were 1,250 ng/mL and 464 ng/mL, respectively.

Given the uncertainty around the true magnitude of the drug interaction and absence of data in children, this combination should be used with caution in children.

**Use of Elvitegravir as Genvoya or Stribild in Children Weighing <25 kg**

Neither Genvoya nor Stribild is approved to treat children weighing <25 kg.\textsuperscript{4,5} An ongoing study is evaluating the use of Genvoya in children aged <6 years and weighing <25 kg.

**Use of Elvitegravir as Genvoya in Children Aged 6 Years to <12 Years**

Genvoya is approved by the FDA to treat children with any SMR who weigh ≥25 kg;\textsuperscript{5} this approval is based on 24 weeks of data from a study in 23 children.\textsuperscript{23} In this study, children who had been virologically suppressed (HIV RNA <50 copies/mL) for at least 6 months were switched from their current regimens to Genvoya. There were no study discontinuations due to medication toxicity, but at Week 24 the participants’ CD4 T lymphocyte (CD4) cell counts had decreased by median of 130 cells/mm\textsuperscript{3} (with a range of -472 cells/mm\textsuperscript{3} to 266 cells/mm\textsuperscript{3}), and CD4 percentages decreased by a median of 2.1% (with a range of -8.4% to 5.9%). After 48 weeks of follow-up, the CD4 cell count decline from baseline was -90 cells/mm\textsuperscript{3}. The mechanism for the reduction in CD4 cells is unclear, and this reduction has only been observed in this study. Plasma exposures of all four drugs were higher in these children than the plasma exposures seen in historical data from adults, but there was no association between plasma exposures of the four components of Genvoya and CD4 cell counts.\textsuperscript{24} Stribild is not approved by the FDA for use in children weighing <35 kg.

**Use of Elvitegravir as Stribild or Genvoya in Adolescents Aged 12 Years to 18 Years**

Studies of the adult dosage formulations of Stribild and Genvoya used in children with HIV aged ≥12 years and weighing ≥35 kg have demonstrated safety and efficacy similar to that seen in adults through 24 weeks and 48 weeks of study, respectively; these formulations are approved by the FDA for use in this age/weight group.\textsuperscript{4} Genvoya is preferred over Stribild when treating children with SMRs 1 to 3, as Genvoya carries a lower risk of renal and bone toxicity than Stribild.\textsuperscript{5}

**References**


5. Elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (Genvoya) [package insert]. Food and Drug Administration.


