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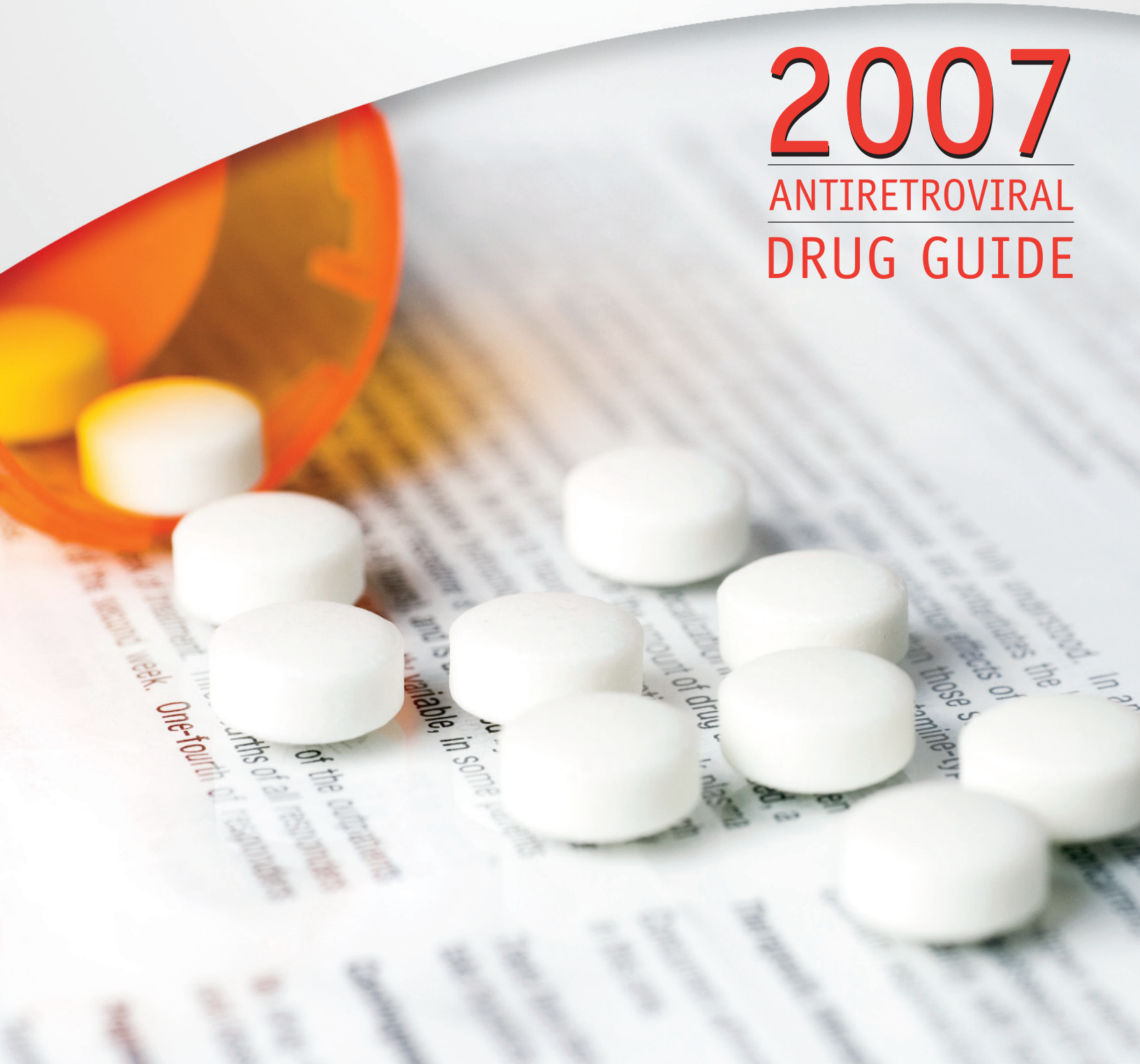
IAPAC

MONTHLY

2007 ANTIRETROVIRAL DRUG GUIDE



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IAPAC MONTHLY

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EMTRIVA®

	Brand Name	Generic Name	Format
	Emtriva®	emtricitabine (FTC)	■ 200 mg capsule ■ 10 mg/mL oral solution

Recommended Dosage		Dose Adjustments
Adult/Adolescent 1 x 200 mg capsule QD	*Pediatric* <3 months: Not approved ≥3 months: 6 mg/kg QD; maximum 240 mg QD Children >33 kg and able to swallow capsules: Adult dose	No dose adjustments necessary

Dosing in Renal Insufficiency and Hemodialysis

Creatinine Clearance	*Dose*
≥50 mL/min	200 mg q24h
30-49 mL/min	200 mg q48h
15-29 mL/min	200 mg q72h
<15 mL/min	200 mg q96h

Note(s)

No food restrictions

Pregnancy			
No evidence of risk in humans	Gilead Sciences	(800) 445-3235	www.emtriva.com

Black Box Warning

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of NRTIs alone or in combination with other ARV drugs.

Adverse Effects (≥3%)

Body as a Whole: abdominal pain, asthenia, headache

CNS: abnormal dreams, depressive disorders, dizziness, insomnia, neuropathy/peripheral neuritis, paresthesias

GI: diarrhea, dyspepsia, nausea, vomiting

Musculoskeletal: arthralgia, myalgia

Respiratory: increased cough, rhinitis

Skin: *rash,* skin discoloration (hyperpigmentation on the palms and/or soles)

Managing ARV Drug Resistance

Resistance to emtricitabine, as with resistance to lamivudine, is most frequently associated with the selection of a mutation at codon 184, although in one study no such mutation was detectable in the majority of individuals experiencing viral recurrence on a regimen containing emtricitabine.

To avoid long-term treatment failure resulting from resistance, emtricitabine should be used only in regimens that are expected to be fully suppressive of viral replication.

Implications of emtricitabine resistance for treatment with other ARV drugs
HIV isolates with resistance to emtricitabine by virtue of a mutation at codon 184 have been shown to be cross-resistant to lamivudine, but retained sensitivity to abacavir, didanosine, stavudine, tenofovir, and zidovudine.

Implications of resistance to other ARV drugs for treatment with emtricitabine
HIV strains harboring mutations conferring reduced susceptibility to stavudine and zidovudine (at codons 41, 67, 70, 210, 215, or 219) or didanosine (codon 74) have been found to remain sensitive to emtricitabine.

EPIVIR®

	Brand Name	Generic Name	Format
	Epivir®	lamivudine (3TC)	■ 150, 300 mg tablets ■ 10 mg/mL oral solution

Recommended Dosage		Dose Adjustments
Adult/Adolescent 1 x 300 mg tablet QD or 2 x 150 mg tablets QD or 1 x 150 mg tablet BID	*Pediatric* Infants, age <30 days: 2 mg/kg BID Pediatrics, age 1 month-12 years: 4 mg/kg BID; maximum 150 mg BID Adolescents, wt <50 kg: 4 mg/kg BID; maximum 150 mg BID Adolescents, wt ≥50 kg: Adult dose	No dose adjustments necessary

Dosing in Renal Insufficiency and Hemodialysis

Creatinine Clearance	Dose
≥50 mL/min	150 mg BID or 300 mg QD
30-49 mL/min	150 mg QD
15-29 mL/min	150 mg first dose, then 100 mg QD
5-14 mL/min	150 mg first dose, then 50 mg QD
<5 mL/min	insufficient data, consider 150 mg first dose, then 25 mg QD

Note(s)

No food restrictions

May cause pancreatitis in children; monitor appropriately for symptoms

Pregnancy	Manufacturer	Contact	Website
Risk cannot be ruled out	GlaxoSmithKline	(800) 825-5249	www.treatHIV.com

Black Box Warning

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of NRTIs, alone or in combination with other ARV drugs. Lamivudine tablets and oral solution (used to treat HIV infection) contain a higher dose of 3TC than Epivir-HBV tablets and oral solution (used to treat chronic hepatitis B). Patients with HIV infection should receive only dosage and formulations appropriate for treatment of HIV. Severe acute exacerbations of HBV infection have been reported in HBV/HIV-coinfected patients upon discontinuation of 3TC-containing products. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months after discontinuation of 3TC in patients with HIV/HBV coinfection. If appropriate, initiation of anti-HBV therapy may be warranted.

Adverse Effects (≥1%)

CNS: neuropathy, insomnia, sleep disorders, dizziness, depression, headache, fatigue, fever, chills

GI: nausea, diarrhea, vomiting, anorexia, abdominal pain, cramps, dyspepsia, hepatomegaly with steatosis, increased LFTs (ALT, amylase)

Hematologic: anemia, neutropenia, thrombocytopenia

Metabolic: lactic acidosis

Musculoskeletal: myalgia, arthralgia, malaise, pain

Respiratory: nasal symptoms, cough

Skin: rash

Managing ARV Drug Resistance

Resistance to lamivudine is most frequently associated with the selection of a single mutation at codon 184. Selection of this mutation may occur within weeks of initiating therapy that is not fully suppressive. Failure of combination regimens containing lamivudine may be associated with viral resistance to lamivudine without detectable resistance to other nucleoside analogue or protease inhibitor components. To avoid long-term treatment failure resulting from resistance, lamivudine should be used only in regimens that are expected to be fully suppressive of viral replication.

Implications of lamivudine resistance for treatment with other ARV drugs
Laboratory strains of HIV resistant to lamivudine by virtue of a mutation at codon 184 may show resistance to didanosine, but some clinical isolates with this mutation have been found to retain susceptibility to didanosine. Mutation at codon 184 may reverse resistance associated with thymidine analogues and tenofovir. Phenotypic resistance testing may be useful in this situation.

Implications of resistance to other ARV drugs for treatment with lamivudine
Mutation at codon 184, which establishes resistance to lamivudine, is found in a significant proportion of isolates selected by didanosine. Resistance testing may be helpful in assessing the utility of lamivudine following failure of a didanosine-containing regimen.

	Brand Name	Generic Name	Format
	Retrovir®	zidovudine (ZDV, AZT)	■ 100 mg capsule ■ 300 mg tablet ■ 10 mg/mL IV solution ■ 10 mg/mL oral solution

Recommended Dosage		Dose Adjustments
Adult 1 x 300 mg tablet BID or 2 x 100 mg capsules TID	*Pediatric* 6 weeks - 12 years: 160 mg/m^2 q8h; maximum 200 mg q8h (syrup, capsules, or tablets) Adolescents: Adult dose	No dose adjustments necessary

Dosing in Renal Insufficiency and Hemodialysis

Creatinine Clearance	Dose
<15 mL/min	100 mg TID
HD	100 mg TID

Note(s)

No food restrictions

Anemia may require dose interruption

Pregnancy	Manufacturer	Contact	Website
Risk cannot be ruled out	GlaxoSmithKline	(888) 825-5249	www.treatHIV.com

Black Box Warning

Zidovudine can be associated with hematologic toxicities, including granulocytopenia and severe anemia, including among advanced HIV patients. Prolonged ZDV use has been associated with symptomatic myopathy. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of NRTIs, alone or in combination with other ARV drugs.

Adverse Effects (≥1%)

Body as a Whole: fever, dyspnea, malaise, weakness, myalgia, myopathy

CNS: headache, insomnia, dizziness, paresthesias, mild confusion, anxiety, restlessness, agitation

GI: nausea, diarrhea, vomiting, anorexia, GI pain

Hematologic: bone marrow depression, granulocytopenia, anemia

Respiratory: cough, wheezing

Skin: rash, itching, diaphoresis

Managing ARV Drug Resistance

Resistance to zidovudine is associated with the selection of 1 or more of several resistance mutations, in particular at reverse transcriptase codons 41, 67, 70, 210, 215, and 219.

Implications of zidovudine resistance for treatment with other ARV drugs

The addition of lamivudine or didanosine may maintain selective pressure for zidovudine-sensitive variants. In clinical trials, individuals treated with zidovudine monotherapy for many months experienced suppression of viral load lasting months to years following the addition of lamivudine and indinavir, suggesting that resistance to zidovudine may take time to emerge or may be reversible with the addition of lamivudine.

High-level resistance to zidovudine is associated with some degree of resistance to stavudine and tenofovir as well.

Implications of resistance to other ARV drugs for treatment with zidovudine

Although HIV resistant to didanosine or lamivudine may retain susceptibility to zidovudine, treatment with stavudine may select mutations associated with zidovudine resistance. Zidovudine should be considered in choosing therapy for individuals experiencing viral recurrence on prior regimens, but resistance testing may be helpful in assessing the utility of zidovudine in the individual situation.

VIDEX®

	Brand Name	Generic Name	Format
	Videx® EC Videx®	didanosine (ddI)	■ 125, 200, 250, 400 mg enteric-coated capsules ■ 25, 50, 100, 150, 200 mg buffered tablets ■ 100, 167, 250 mg buffered powder for oral solution

Recommended Dosage			Dose Adjustments
Adult/Adolescent: ≥60 kg 1 x 400 mg capsule QD or 4 x 100 mg tablets QD or 1 x 200 mg tablet BID	*Adult/Adolescent: <60 kg* 1 x 250 mg capsule QD or 1 x 250 mg tablet QD or 1 x 125 mg tablet BID	*Pediatric* Age <90 days: 50 mg/m2 body surface area q12h (pediatric powder) Age 90 days-12 years: 120 mg/m2 body surface area BID (powder or tablets) Adolescents: Adult dose	■ TDF: ddI 250 mg QD or ddI 200 mg QD; TDF 300 mg QD; for body weight <60 kg ddI 200 mg QD; TDF 300 mg QD

Dosing in Renal Insufficiency and Hemodialysis

No dose adjustments necessary

Note(s)

Must be taken on an empty stomach

Should not be taken with alcohol

Pregnancy	Manufacturer	Contact	Website
No evidence of risk in humans	Bristol-Myers Squibb	(800) 272-4878	www.bms.com

Black Box Warning

Fatal and nonfatal pancreatitis have occurred with ddI alone or in combination with other antiretroviral drugs. ddI should be withheld if pancreatitis is suspected, and discontinued if pancreatitis is confirmed. Fatal lactic acidosis has been reported among pregnant women who received a combination of ddI and d4T with other ARV combinations. Thus a combination of ddI and d4T combination should only be used during pregnancy if the potential benefit clearly outweighs the potential risks. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of NRTIs, alone or in combination with other ARV drugs.

Adverse Effects (≥1%)

CNS: headache, dizziness, nervousness, insomnia, peripheral neuropathy, lethargy, poor coordination, seizures

CV: palpitations, thrombophlebitis, arrhythmia, vasodilation

GI: abdominal pain, nausea, vomiting, diarrhea, constipation, stomatitis, dry mouth, pancreatitis, increased liver enzymes

Hematologic: increased WBC, neutrophil, lymphocyte, and platelet counts, increased Hgb, thrombocytopenia, ecchymosis, hemorrhage, petechiae

Metabolic: hypocalcaemia, hypokalemia, hypomagnesemia, hyperuricemia (asymptomatic), hypertriglyceridemia

Musculoskeletal: muscle atrophy, myalgia, arthritis, decreased strength

Respiratory: asthma, cough, dyspnea, epistaxis, rhinitis, rhinorrhea, hypoventilation, pharyngitis, rhonchi or rales, sinusitis, congestion

Skin: rash, impetigo, eczema, pruritis, sweating, erythema

Special Senses: retinal depigmentation, photophobia, blurred vision, optic neuritis, diplopia, blindness

Managing ARV Drug Resistance

Resistance to didanosine is associated with the selection of 1 or more of several resistance mutations.

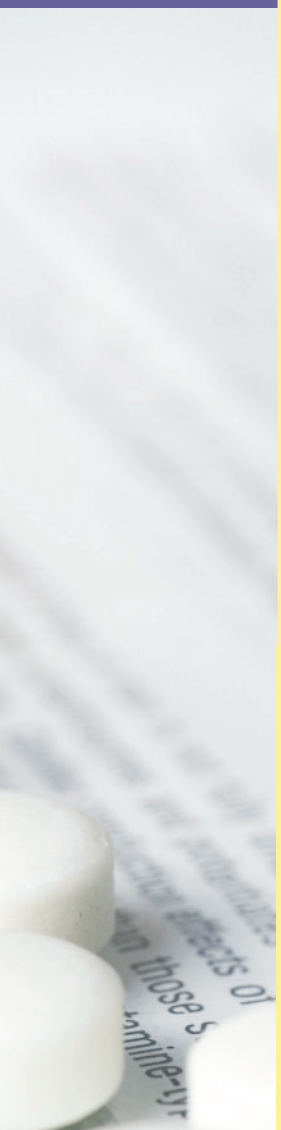
Implications of didanosine resistance for treatment with other ARV drugs

- Mutations at codon 184, which establish resistance to lamivudine, are found in a significant proportion of isolates selected by didanosine.
- The codon 151 mutation, associated with resistance to multiple nucleoside analogues, occurs infrequently but is most commonly observed in patients treated with zidovudine + didanosine or stavudine + didanosine.

Implications of resistance to other ARV drugs for treatment with didanosine

Didanosine should be considered in choosing therapy for individuals experiencing viral recurrence on prior regimens. Resistance testing may be helpful in assessing the utility of didanosine in the individual situation, although the results of genotype testing can sometimes be ambiguous. For example, laboratory strains of HIV resistant to lamivudine by virtue of a mutation at codon 184 may show resistance to didanosine, but some clinical isolates with this mutation have been found to retain susceptibility to didanosine. Phenotypic resistance testing may be useful in this situation.

VIREAD®



Brand Name	Generic Name	Format
Viread®	tenofovir (TDF)	300 mg tablet

Recommended Dosage

Adult/Adolescent
1 x 300 mg tablet QD

Pediatric
Not FDA approved in patients <18 years; under investigation

Dose Adjustments

- ATV: TDF 300 mg QD; ATV 300 mg QD + RTV 100 mg QD
- ddI: TDF 300 mg QD; ddI 250 mg QD (for body weight >60 kg) or ddI 200 mg QD (for body weight <60 kg)

Dosing in Renal Insufficiency and Hemodialysis

Experience in patients with creatinine clearance <60 mL/min is limited. Preliminary data suggest:

Creatinine Clearance	Dose
≥50 mL/min	300 mg QD
30-49 mL/min	300 mg q48h
10-29 mL/min	300 mg twice weekly
Hemodialysis	300 mg once weekly

Note(s)

No food restrictions

All patients with HIV should be tested for the presence of chronic HBV infection before initiating ART with TDF

Pregnancy	Manufacturer	Contact	Website
No evidence of risk in humans	Gilead Sciences	(800) 445-3235	www.viread.com

Black Box Warning

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of NRTIs, alone or in combination with other ARV drugs. Tenofovir is not indicated for the treatment of chronic HBV infection; safety and efficacy in patients with HIV/HBV coinfection have not been established. Severe acute exacerbations of hepatitis B have been reported in patients who discontinued TDF. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months after discontinuation of TDF in HIV/HBV-coinfected patients. If appropriate, initiation of anti-HBV therapy may be warranted after discontinuation of TDF.

Adverse Effects (≥1%)

Body as a Whole: asthenia

CNS: headache

GI: abdominal pain, diarrhea, flatulence, *nausea,* vomiting

Hematologic: neutropenia

Metabolic: increased creatine kinase, AST, ALT, serum amylase, triglycerides, serum glucose

Managing ARV Drug Resistance

Resistance to tenofovir is associated with the selection of 1 or more of several resistance mutations.

Implications of tenofovir resistance for treatment with other ARV drugs
The K65R mutation, associated with low-grade resistance to didanosine and abacavir, and moderate resistance to lamivudine, is selected by tenofovir in vitro but was found to occur infrequently in patients treated with tenofovir.

Implications of resistance to other ARV drugs for treatment with tenofovir
The presence of the lamivudine-associated M184V reverse transcriptase mutation does not reduce sensitivity to tenofovir. Single and some double thymidine analogue resistance mutations do not appear to confer tenofovir resistance. Tenofovir is also active against multinucleoside-resistant HIV expressing the Q151M mutation. However, in clinical trials, the presence of 3 or more thymidine analogue resistance mutations is associated with a decreased response to tenofovir, particularly if these mutations include M41L or L210W. The T69S insertion mutations, associated with resistance to multiple nucleoside analogues, are associated with resistance to tenofovir as well. Tenofovir resistance conferred by the T69S mutation or by multiple thymidine analogue resistance mutations appears to be multiplied if the M184V mutation is replaced by wild-type. The K65R mutation, which may be selected by prior nucleoside analogue therapy, is associated with a modest decrease in sensitivity to tenofovir.

Tenofovir should be considered in choosing therapy for individuals experiencing viral recurrence on prior regimens, but resistance testing may be helpful in assessing the utility of tenofovir in the individual situation.

ZERIT®

	Brand Name	Generic Name	Format
	Zerit®	stavudine (d4T)	■ 15, 20, 30, 40 mg capsules ■ 1 mg/mL for oral solution

Recommended Dosage

Adult/Adolescent: ≥60 kg

1 x 40 mg capsule BID

Adult/Adolescent: <60 kg

1 x 30 mg capsule BID

Pediatric

Birth - 13 days: 0.5 mg/kg q12h

Age >14 days, and wt <30 kg: 1 mg/kg q12h

Wt ≥30 kg: Adult dose

Dose Adjustments

No dose adjustments necessary

Dosing in Renal Insufficiency and Hemodialysis

Creatinine Clearance	Dose	
	Wt ≥ 60 kg	Wt <60 kg
≥50 mL/min	40 mg BID	30 mg BID
26-50 mL/min	20 mg BID	15 mg BID
10-25 mL/min	20 mg QD	15 mg QD
HD	20 mg QD	15 mg QD

Note(s)

No food restrictions

If peripheral neuropathy presents, discontinue d4T

Pregnancy	Manufacturer	Contact	Website
Risk cannot be ruled out	Bristol-Myers Squibb	(800) 272-4878	www.bms.com

Black Box Warning

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of NRTIs, alone or in combination with other ARV drugs. Fatal lactic acidosis has been reported among pregnant women who received combination of d4T and ddI with other ARV combinations. Thus a combination of d4T and ddI should only be used during pregnancy if the potential benefit clearly outweighs the potential risks. Fatal and non-fatal pancreatitis have occurred when d4T was part of a combination regimen with ddI, with or without hydroxyurea.

Adverse Effects (>1%)

Body as a Whole: headache, chills/fever, myalgia

CNS: peripheral neuropathy, parathesias

GI: anorexia, nausea, vomiting, diarrhea, cramping, pancreatitis, abdominal pain, elevated liver function tests, abdominal pain

Hematologic: anemia, neutropenia

Metabolic: lactic acidosis in pregnant women

Skin: rash

Managing ARV Drug Resistance

Resistance to stavudine is associated with the selection of 1 or more of several resistance mutations.

Implications of stavudine resistance for treatment with other ARV drugs

- Mutations at sites associated with zidovudine resistance (eg, codons 41 and 215) frequently occur on stavudine treatment.
- The codon 151 mutation, associated with resistance to multiple nucleoside analogues, occurs infrequently but is most commonly observed in patients treated with zidovudine + didanosine or stavudine + didanosine.

Implications of resistance to other ARV drugs for treatment with stavudine

Viral isolates with zidovudine resistance are likely to show resistance to stavudine, as are strains carrying multinucleoside-resistance mutations (including insertions following codon 69, or mutation at codon 151).

Resistance testing may be helpful in assessing the utility of stavudine in the individual situation, although the genotypic correlates of stavudine resistance are not clearly defined. For example, resistance to stavudine has been associated with a mutation at codon 75 in laboratory strains and some clinical isolates, but decreased virologic responses to stavudine frequently occur in the absence of this mutation.

ZIAGEN®

	Brand Name	Generic Name	Format
	Ziagen®	abacavir (ABC)	■ 300 mg tablet ■ 20 mg/mL oral solution

Recommended Dosage		Dose Adjustments
Adult/Adolescent 2 x 300 mg tablets QD or 1 x 300 mg tablet BID	*Pediatric* Age <3 months: Not FDA approved; under investigation Age 3 months - 16 years: 8 mg/kg BID; maximum 300 mg BID	No dose adjustments necessary

Dosing in Renal Insufficiency and Hemodialysis

No dose adjustments necessary

Note(s)

No food restrictions

Contraindicated if previous hypersensitivity (do not retry if previous allergic reaction)

Pregnancy	Manufacturer	Contact	Website
Risk cannot be ruled out	GlaxoSmithKline	(800) 825-5249	www.ziagen.com

Black Box Warning

Serious and sometimes fatal hypersensitivity reactions have been associated with ABC. This is a multi-organ clinical syndrome, characterized by two or more groups of the following signs or symptoms including: 1) fever, 2) rash, 3) GI symptoms (e.g., nausea, vomiting, diarrhea, or abdominal pain), 4) constitutional symptoms (including generalized malaise, fatigue, or achiness), and 5) respiratory symptoms (including dyspnea, cough, or pharyngitis). Abacavir should be discontinued as soon as hypersensitivity reaction is suspected. Any product containing Abacavir should be permanently discontinued if hypersensitivity cannot be ruled out, even when other diagnoses are possible, because more severe symptoms can occur within hours after restarting ABC and may include life-threatening hypotension and death. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of NRTIs, alone or in combination with other ARV drugs.

Adverse Effects (≥1%)

Body as a Whole: hypersensitivity reactions (including fever, skin rash, fatigue, nausea, vomiting, diarrhea, abdominal pain) malaise, lethargy, myalgia, arthralgia, paresthesia, edema, shortness of breath

CNS: insomnia, headache, fever

CV: hypotension (associated with hypersensitivity reaction)

GI: hepatomegaly with steatosis, nausea, vomiting, diarrhea, anorexia, pancreatitis increased GGT, increased LFTs

Skin: rash

Other: lactic acidosis, renal insufficiency

Managing ARV Drug Resistance

Resistance to abacavir is associated with the selection of 1 or more of several resistance mutations.

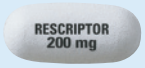
Implications of abacavir resistance for treatment with other ARV drugs

- Mutation at codon 184, which establishes resistance to lamivudine and may reduce sensitivity to didanosine, is found in a significant percentage of patients treated with abacavir.
- Mutation at codon 65, which is associated with decreased sensitivity to didanosine, may also be selected by abacavir.

Implications of resistance to other ARV drugs for abacavir treatment

- Individual mutations associated with resistance to zidovudine are not usually found to confer resistance to abacavir. However, the coexistence of more than 2 zidovudine resistance mutations is likely to confer resistance to abacavir.
- The codon 184 mutation, associated with resistance to lamivudine, does not by itself confer high-level resistance to abacavir.
- The codon 151 mutation, associated with resistance to multiple nucleoside analogues, is also associated with resistance to abacavir. This mutation occurs infrequently but is most frequently observed in patients treated with zidovudine + didanosine or stavudine + didanosine.

RESCRIPTOR®

	Brand Name	Generic Name	Format
	Rescriptor®	delavirdine (DLV)	100, 200 mg tablets

Recommended Dosage		Dose Adjustments
Adult/Adolescent 2 x 200 mg tablets TID or 4 x 100 mg tablets TID	*Pediatric* Birth - 16 years: Not FDA approved Adolescent, age ≥16 years: Adult dose	■ IDV: DLV 400 mg TID; IDV 600 mg Q8H ■ SQV: DLV 400 mg TID; SQV 800 mg TID

Dosing in Renal Insufficiency and Hemodialysis

No dose adjustments necessary

Note(s)

No food restrictions

Separate dosing with ddI or antacids by 1 hour

100 mg tablets may be dispersed in ≥3 oz water until uniform suspension is achieved

Pregnancy	Manufacturer	Contact	Website
Risk cannot be ruled out	Pfizer Inc	(888) 777-6637	www.pfizer.com

Adverse Effects (≥1%)

Body as a Whole: headache, fatigue, allergic reaction, chills, edema, arthralgia

CNS: abnormal coordination, agitation, amnesia, anxiety, confusion, dizziness

CV: chest pain, bradycardia, palpitations, postural hypotension, tachycardia

GI: nausea, vomiting, diarrhea, increased LFTs, abdominal cramps, anorexia, aphthous stomatitis

Hematologic: neutropenia

Respiratory: bronchitis, cough, dyspnea

Skin: rash, pruritus

Managing ARV Drug Resistance

Because virus resistant to all available NNRTIs is rapidly selected during failure of an NNRTI-containing regimen, it is important to assess patient motivation and discuss possible side effects and strategies for their management before treatment with delavirdine is initiated.

Resistance to delavirdine is associated with the selection of 1 or more of several resistance mutations. The commonly selected delavirdine resistance mutations frequently confer resistance to nevirapine and efavirenz as well.

Implications of delavirdine resistance for treatment with other ARV drugs

Resistance mutations selected by delavirdine are usually associated with resistance to nevirapine and efavirenz.

Delavirdine may select a mutation (P236L) associated with increased sensitivity to nevirapine. The clinical consequences of this phenomenon are unknown.

Implications of resistance to other ARV drugs for delavirdine treatment

Resistance to efavirenz or to nevirapine is frequently associated with resistance to delavirdine.

Brand Name	Generic Name	Format
Sustiva®	efavirenz (EFV) ■ 600 mg tablet ■ 600 mg tablet ■ 200 mg capsule	■ 50, 100, 200 mg capsules ■ 600 mg tablet

Recommended Dosage

Adult/Adolescent

1 x 600 mg tablet QD
or
3 x 200 mg capsules QD

Pediatric

Birth - 3 years: Unknown
Age <3 months: Not FDA approved
15 to <20 kg: 250 mg QD
20 to <25 kg: 300 mg QD
25 to <32.5 kg: 350 mg QD
32.5 to <40 kg: 400 mg QD
≥40 kg: Adult dose

Dose Adjustments

- ATV: EFV 600 mg QD; ATV 300 mg QD + RTV 100 mg QD
- FPV: EFV 600 mg QD; FPV 700 mg BID + RTV 100 mg BID *or* EFV 600 mg QD; FPV 1,400 mg QD + RTV 300 mg QD*
- IDV: EFV 600 mg QD; IDV 800-1,000 mg BID + RTV 100-200 mg BID
- LPV/r: EFV 600 mg QD; LPV/r 400/100 mg BID† *or* 600/150 mg BID‡
- SQV: Dose adjustment not established; consider EFV 600 mg QD; SQV 1,000 mg BID + RTV 200 mg BID
- TPV: Dose adjustment not established

* FPV QD dosing not recommended for PI-experienced patients
† ARV-naïve patients ‡ ARV-experienced patients

Dosing in Renal Insufficiency and Hemodialysis

No dose adjustments necessary

Note(s)

Take on an empty stomach; preferably at bedtime to minimize CNS effects

Barrier contraception should always be used in combination with other methods of contraception (eg, oral, other hormonal contraceptives)

Pregnancy	Manufacturer	Contact	Website
Risk cannot be ruled out	Bristol-Myers Squibb	(800) 334-4486	www.sustiva.com

Adverse Effects (≥1%)

CNS: dizziness, headache, hypoesthesia, impaired concentration, insomnia, abnormal dreams, somnolence, depression, nervousness

CV: hypercholesterolemia

GI: nausea, vomiting, diarrhea, dyspepsia, abdominal pain, flatulence, anorexia, increased liver function tests (ALT, AST)

Respiratory: cough

Skin: rash (erythematous rash, pruritis, maculopapular rash, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis), increased sweating

Urogenital: renal calculus, hematuria

Managing ARV Drug Resistance

Because virus resistant to all available NNRTIs is rapidly selected during failure of an NNRTI-containing regimen, it is important to assess patient motivation and discuss possible side effects and strategies for their management before treatment with efavirenz is initiated.

Resistance to efavirenz is associated with the selection of 1 or more of several resistance mutations. The commonly selected efavirenz resistance mutations confer resistance to delavirdine and nevirapine as well.

Implications of efavirenz resistance for treatment with other ARV drugs
Resistance mutations selected by efavirenz are usually associated with resistance to delavirdine and nevirapine.

Implications of resistance to other ARV drugs for efavirenz treatment
Resistance to delavirdine and nevirapine is usually associated with resistance to efavirenz.

VIRAMUNE®

	Brand Name	Generic Name	Format
	Viramune®	nevirapine (NVP)	■ 200 mg tablet ■ 50 mg/5 mL oral suspension

Recommended Dosage

Adult/Adolescent

Lead-in:
1 x 200 mg tablet QD for first 14 days

1 x 200 mg tablet BID

Pediatric

Birth - 2 months: 5 mg/kg for the first 14 days, then 120 mg/m^2 BID for 14 days, then 200 mg/m^2 BID; or 120 mg/m2 QD for the first 14 days, then 120 mg/m^2 BID for 14 days, then 200 mg/m^2 BID

2 months - adolescence: 120 mg/m2 QD for the first 14 days, then 120-200 mg/m^2 BID (maximum dose, 200 mg BID) or 7 mg/kg QD for 14 days, then 7 mg/kg BID; maximum 400 mg per day, if <8 years; 4 mg/kg QD for 14 days, then 4 mg/kg BID (maximum 400 mg per day) if ≥8 years

Adolescent: Adult dose

Dose Adjustments

- ATV: Dose adjustment not established; consider NVP 200 mg BID; ATV 300 mg QD + RTV 100 mg QD
- FPV: Dose adjustment not established; consider NVP 200 mg BID; FPV 700 mg BID + RTV 100 mg BID *or* NVP 200 mg BID; FPV 1,400 mg QD + RTV 300 mg QD*
- IDV: Consider NVP 200 mg BID; IDV 800-1,000 mg BID + RTV 100-200 mg BID
- LPV/r: NVP 200 mg BID; LPV/r 400/100 mg BID† *or* 600/150 mg BID‡
- SQV: Dose adjustment not established; consider NVP 200 mg BID; SQV 400 mg BID + RTV 400 mg BID

* FPV QD dosing not recommended for PI-experienced patients
† ARV-naïve patients ‡ ARV-experienced patients

Dosing in Renal Insufficiency and Hemodialysis

No dose adjustments necessary

Note(s)

No food restrictions

Baseline assessment of all patients should be performed during first 18 weeks; including LFTs and HBV/HCV infection status; continue to monitor closely

Pregnancy	Manufacturer	Contact	Website
Risk cannot be ruled out	Boehringer Ingelheim	(800) 274-8651	www.viramune.com

Black Box Warning

Severe, life threatening, and in some cases fatal hepatotoxicity, including fulminant and cholestatic hepatitis, hepatic necrosis, and hepatic failure, has been reported. Patients may present with non-specific prodromes of hepatitis and progress to hepatic failure. Women with CD4 counts >250 cells/mm^3, including pregnant women receiving chronic treatment for HIV infection are at considerably higher risk of hepatotoxicities. Severe, life threatening, and even fatal skin reactions, including Stevens-Johnson syndrome, toxic epidermal necrolysis, and hypersensitivity reactions characterized by rash, constitutional findings, and organ dysfunction have occurred with NVP treatment. Patients should be monitored intensively during the first 18 weeks of NVP therapy to detect potentially life-threatening hepatotoxicity or skin reactions. A 14-day lead-in period with NVP 200 mg QD must be followed strictly. Nevirapine should not be restarted after severe hepatic, skin, or hypersensitivity reactions.

Adverse Effects (≥1%)

Body as a Whole: fever, paresthesia, myalgia

CNS: headache

GI: nausea, diarrhea, abdominal pain, hepatitis, increased liver function tests

Hematologic: anemia, neutropenia

Skin: rash, Stevens-Johnson syndrome

Managing ARV Drug Resistance

Resistance to nevirapine is associated with the selection of 1 or more of several resistance mutations.

Implications of nevirapine resistance for treatment with other ARV drugs
Resistance mutations selected by nevirapine are frequently associated with resistance to delavirdine and efavirenz.

Implications of resistance to other ARV drugs for nevirapine treatment
Resistance to efavirenz or to delavirdine is usually associated with resistance to nevirapine.

APTIVUS®

	Brand Name	Generic Name	Format
	Aptivus®	tipranavir (TPV)	250 mg capsule

Recommended Dosage		Dose Adjustments
Adult/Adolescent 2 x 250 mg capsules + 2 x 100 mg capsules RTV BID	*Pediatric* Not FDA approved; under investigation	■ PIs (except RTV): Not recommended

Dosing in Renal Insufficiency and Hemodialysis

No dose adjustments necessary

Note(s)

Should be taken with food

Should not be used as sole PI; must be RTV-boosted

If combined with ddI, take 2 hours before or after ddI

Pregnancy	Manufacturer	Contact	Website
Risk cannot be ruled out	Boehringer Ingelheim	(800) 274-8651	www.aptivus.com

Black Box Warning

Tipranavir co-adminstered with RTV 200 mg has been associated with reports of both fatal and non-fatal intracranial hemorrhage, as well as with reports of clinical hepatitis and hepatic decompensation including some fatalities. Extra vigilance is warranted in patients with chronic HBV or HCV coinfection, as these patients have an increased risk of hepatotoxicity.

Adverse Effects (≥2%)

Body as a Whole: Fatigue

CNS: Depression, fever, headache

GI: Abdominal pain, diarrhea, nausea, vomiting

Respiratory: Bronchitis

Skin: Rash

Managing ARV Drug Resistance

Resistance to tipranavir is associated with the selection of 1 or more of several resistance mutations.

Implications of tipranavir resistance for treatment with other ARV drugs
In vitro studies of tipranavir + ritonavir show the emergence of a number of protease mutations. The resistance profile in human subjects has not been characterized fully. Results from studies of tipranavir in antiretroviral-naive patients (now under way) are needed to identify tipranavir resistance in initial therapy and to assess its implications for subsequent treatment. In patients with multiple preexisting mutations associated with resistance to protease inhibitors, emergent protease mutations included amino acid substitutions 10V/I/S, 13V, 33F/I/V, 82L/T, and 84V.

Implications of resistance to other ARV drugs for tipranavir treatment
Resistance mutations selected by other protease inhibitors can contribute to tipranavir resistance. Mutations at protease codons 10, 13, 20, 33, 35, 36, 43, 46, 47, 54, 58, 69, 74, 82, 83, and 84 are associated with decreased virologic response to tipranavir. In addition, the total number of primary protease mutations is associated with diminished response to tipranavir.

Phenotypic analysis has demonstrated that virologic response to tipranavir/ritonavir is most likely if the baseline tipranavir fold change in IC50 value (compared with reference tipranavir susceptibility) is ≤ 3-fold.

Regimens containing tipranavir + ritonavir and enfuvirtide may be effective as subsequent regimens in individuals without prior enfuvirtide experience, and appear to be more effective than regimens containing tipranavir + ritonavir without enfuvirtide. Genotypic or phenotypic testing may be useful in predicting the likelihood of response to tipranavir following failure of regimens containing other antiretrovirals.

CRIXIVAN®

	Brand Name	Generic Name	Format
	Crixivan®	indinavir (IDV)	200, 333, 400 mg capsules

Recommended Dosage

Adult/Adolescent

1 x 400 mg capsule + 1 x 100 mg capsule RTV BID

or

1 x 400 mg capsule + 2 x 100 mg capsules RTV BID

or

2 x 400 mg capsules TID

Pediatric:

Birth - 4 years: Not FDA approved in patients <18 years; should not be given to neonates

Age 4 - 15 years: 500 mg/m^2 q8h

Adolescent: Adult dose

Dose Adjustments

- DLV: IDV 600 mg q8h; DLV 400 mg TID
- DRV: Dose adjustment not established
- EFV: IDV 800-1,000 mg BID + RTV 100-200 mg BID; EFV 600 mg QD
- LPV/r: IDV 600-800 mg BID; LPV/r 400/100 mg BID
- NFV: IDV 1,200 mg BID; NFV 1,250 mg BID
- NVP: Consider IDV 800-1,000 mg BID + RTV 100-200 mg BID; NVP 200 mg BID
- TPV: Not recommended

Dosing in Renal Insufficiency and Hemodialysis

No dose adjustments necessary

Note(s)

When boosted with RTV, should be taken with food, as well as water (40 oz fluid/day) to avoid kidney stones

If unboosted (rare), must be taken on an empty stomach

IDV must be stored with desiccant to keep capsules dry

Buffered ddI tablets and IDV should be taken 1 hour apart

Pregnancy	Manufacturer	Contact	Website
Risk cannot be ruled out	Merck & Co.	(800) 850-3430	www.crixivan.com

Adverse Effects (≥1%)

CNS: fatigue, headache, insomnia, dizziness, somnolence, nervousness, agitation, anxiety, paresthesia, peripheral neuropathy, tremor, vertigo

CV: palpitations

Hematologic: anemia, splenomegaly, lymphadenopathy

GI: abdominal pain, abnormal LFTs, anorexia, cholecystitis, cholestasis, constipation, diarrhea, dry mouth, dyspepsia, flatulence, hepatitis, nausea, stomatitis, vomiting

Skin: body odor, rash, pruritus, dry skin, seborrhea, skin ulceration, sweating, urticaria

Other: myalgia, allergic reaction, bronchitis, cough, rhinitis, taste alterations, visual disturbances, hyperglycemia, diabetes, kidney stones

Managing ARV Drug Resistance

Resistance to indinavir is associated with the selection of 1 or more of several resistance mutations.

Implications of indinavir resistance for treatment with other ARV drugs

Resistance mutations selected by indinavir frequently confer or contribute to resistance against other protease inhibitors. Different mutations are associated with cross-resistance to different drugs. For example, M46I is associated with cross-resistance to ritonavir, nelfinavir, and amprenavir (but not to saquinavir); V82A,F,T,S alone is associated with cross-resistance to ritonavir, but in combination with other mutations also confers resistance to nelfinavir, amprenavir, and saquinavir; and I84V contributes to resistance against to all available protease inhibitors. Although no single one of these mutations is associated with full resistance to lopinavir or tipranavir, each contributes partial resistance, and the presence of several mutations together can confer resistance.

Response to ritonavir is unlikely in the setting of resistance to indinavir.

Genotypic or phenotypic testing may be useful in predicting the likelihood of response to other protease inhibitors following failure of regimens containing indinavir.

Implications of resistance to other ARV drugs for indinavir treatment

Response to indinavir is unlikely in the setting of resistance ritonavir.

Response to indinavir may be diminished by resistance to saquinavir.

Genotypic or phenotypic resistance testing may be useful in predicting the likelihood of response to indinavir following failure of regimens containing other protease inhibitors.

INVIRASE®

	Brand Name	Generic Name	Format
	Invirase®	saquinavir (SQV)	■ 200 mg capsule ■ 500 mg tablet

Recommended Dosage

Adult/Adolescent

2 x 500 mg tablets + 1 x 100 mg capsule RTV BID

or

5 x 200 mg capsules + 2 x 100 mg capsules RTV BID

Pediatric

Age <16 years: Not FDA approved; should not be used as a single PI

Age ≥16 years: Adult dose

Dose Adjustments

- ATV: Dose adjustment not established; consider SQV 1,600-2,000 mg QD + ATV 300 mg QD + RTV 100 mg QD
- DLV: SQV 800 mg TID; DLV 400 mg TID
- DRV: Not recommended
- EFV: Dose adjustment not established; consider SQV 1,000 mg BID + RTV 200 mg BID; EFV 600 mg QD
- FPV: Dose adjustment not established; consider SQV 1,000 mg BID + RTV 100-200 mg BID; FPV 700 mg BID
- LPV/r: SQV 1,000 mg BID; LPV/r 400/100 mg BID
- NVP: Dose adjustment not established; consider SQV 400 mg BID + RTV 400 mg BID; NVP 200 mg BID
- TPV: Not recommended

Dosing in Renal Insufficiency and Hemodialysis

No dose adjustments necessary

Note(s)

Must be taken within 2 hours of meal

Should not be used as a sole PI; must be RTV-boosted

Pregnancy	Manufacturer	Contact	Website
No evidence of risk in humans	Roche Laboratories	(800) 282-7780	www.invirase.com

Black Box Warning

Saquinavir may be used only if it is combined with RTV.

Adverse Effects (≥1%)

Body as a Whole: myalgia, allergic reaction

CNS: headache, paresthesia, numbness, dizziness, peripheral neuropathy, ataxia, confusion, convulsions, hyperflexia, hypoflexia, tremor, agitation, amnesia, anxiety, depression, excessive dreaming, hallucinations, euphoria, irritability, lethargy, somnolence

CV: chest pain, hypertension, hypotension, syncope

Endocrine: dehydration, hyperglycemia, diabetes, weight changes

Hematologic: anemia, splenomegaly, thrombocytopenia, pancytopenia

GI: nausea, diarrhea, abdominal discomfort, dyspepsia, mucosal damage, change in appetite, dry mouth

Skin: rash, pruritus, acne, erythema, seborrhea, hair changes, photosensitivity, skin ulceration, dry skin

Other: myalgia, allergic reaction, bronchitis, cough, rhinitis, taste alterations, visual disturbances, hyperglycemia, diabetes, kidney stones

Managing ARV Drug Resistance

Resistance to saquinavir is associated with the selection of 1 or more of several resistance mutations.

Implications of saquinavir resistance for treatment with other ARV drugs

Resistance mutations (G48V, L90M) selected by saquinavir frequently confer or contribute to resistance against other protease inhibitors. In one study, participants with protease resistance mutations after treatment with saquinavir hard-gel capsules were less likely to respond to treatment with indinavir than were patients without such mutations. Genotypic or phenotypic testing may be useful in predicting the likelihood of response to other protease inhibitors following failure of regimens containing saquinavir.

Implications of resistance to other ARV drugs for saquinavir treatment

Following failure of a nelfinavir-containing regimen, patients may still respond to regimens containing saquinavir boosted with ritonavir.

Following failure of an indinavir-containing regimen, sustained response to regimens containing saquinavir was observed in only a minority of patients.

Genotypic or phenotypic testing may be useful in predicting the likelihood of response to saquinavir following failure of regimens containing other antiretrovirals.

KALETRA®

	Brand Name	Generic Name	Format
	Kaletra®	lopinavir/ritonavir (LPV/r)	■ 200 mg LPV/50 mg RTV tablet ■ 80 mg LPV/20 mg RTV oral solution

Recommended Dosage

Adult/Adolescent

4 X 200 mg LPV/50 mg RTV tablet QD
or
2 x 200 mg LPV/50 mg RTV tablet BID

Pediatric

7 - 10 kg: Tablets are not recommended; use oral solution

>10 to <15 kg: Tablets are not recommended; use oral solution

15 to 20 kg: 2 tablets BID (100/25 mg formulation)
or
1 tablet BID (200/50 mg formulation)

>20 to 25 kg: 2 tablets BID
or
1 tablet BID: (200/50 mg formulation)

>25 to 30 kg: 3 tablets BID (100/25 mg formulation)

>30 to 35 kg: 3 tablets BID (100/25 mg formulation)

>35 to 40 kg: 4 tablets BID: (100/25 mg formulation)
or
2 tablets BID

>40kg: 4 tablets BID (100/25 mg formulation)
or
2 tablets BID: (200/50 mg formulation)

Dose Adjustments

- DRV: Not recommended
- EFV: LPV/r 400/100 mg BID† *or* 600/150 mg BID‡; EFV 600 mg QD
- FPV: Not recommended
- IDV: LPV/r 400/100 mg BID; IDV 600-800 mg BID
- NVP: LPV/r 400/100 mg BID† *or* 600/150 mg BID‡; NVP 200 mg BID
- SQV: LPV/r 400/100 mg BID; SQV 1,000 mg BID
- TPV: Not recommended

† For ARV-naïve patients
‡ For ARV-experienced patients

Dosing in Renal Insufficiency and Hemodialysis

No dose adjustments necessary

Note(s)

No food restriction

If co-administered with ddI, ddI should be taken 1 hour before or 2 hours after LPV/r

LPV/r oral solution contains 42% alcohol

Pregnancy	Manufacturer	Contact	Website
Risk cannot be ruled out	Abbott Laboratories	(800) 222-6885	www.kaletra.com

Black Box Warning

Co-administration of RTV with certain non-sedating antihistamines, sedative hypnotics, antiarrhythmics, or ergot alkaloids may result in potentially serious or life-threatening adverse events due to possible effects of RTV on hepatic metabolism of certain drugs.

Adverse Effects (≥1%)

Body as a Whole: asthenia, pain

CNS: headache, insomnia

GI: abdominal pain, abnormal stools, diarrhea, nausea, vomiting

Skin: rash

Managing ARV Drug Resistance

Resistance to lopinavir is associated with the selection of several resistance mutations.

Implications of lopinavir resistance for treatment with other ARV drugs
Resistance to lopinavir is seldom identified in the setting of viral rebound on lopinavir-containing initial regimens, and the implications of lopinavir resistance for treatment with other protease inhibitors are unknown. Genotypic or phenotypic analysis may be useful in predicting the response to protease inhibitors following failure of regimens containing lopinavir/ritonavir.

Implications of resistance to other ARV drugs for lopinavir treatment
While no single mutation has been found to confer high-level resistance to lopinavir, resistance mutations selected by other protease inhibitors can contribute to resistance. If 5 or more protease resistance mutations are present at baseline, the probability of lopinavir/ritonavir treatment failure increases with each additional mutation.

Regimens containing lopinavir/ritonavir and an NNRTI may be effective as subsequent regimens in individuals without prior NNRTI experience. Following failure of other protease inhibitors, the effectiveness of lopinavir/ritonavir used without an NNRTI, or in NNRTI-experienced individuals, is unclear. Genotypic or phenotypic testing may be useful in predicting the likelihood of response to lopinavir/ritonavir following failure of regimens containing other antiretrovirals.

	Brand Name	Generic Name	Format
	Lexiva®	fosamprenavir (FPV)	■ 700 mg tablet ■ 50 mg/mL oral suspension

Recommended Dosage

Adult/Adolescent: Treatment-naïve

2 x 700 mg tablets BID
or
2 x 700 mg tablets + 2 x 100 mg capsules RTV QD
or
1 x 700 mg tablet + 1 x 100 mg capsule RTV BID

Pediatric

Age <2 years: Not FDA approved; under investigation

Age 2 - 5 years and treatment-naïve: 30 mg/kg BID (oral suspension), not to exceed 1,400 mg BID

Age ≥6 years, single PI: 30 mg/kg BID (oral suspension), not to exceed 1,400 mg BID

Wt >47 kg: may give adult dose, using tablet formulation of FPV.

Age ≥6 years, boosted PI: FPV 18 mg/kg (oral suspension) BID + ritonavir 3 mg/kg BID, not to exceed FPV 700 mg BID + ritonavir 100 mg BID

Wt >39 kg: may give adult dose, using tablet formulation of FPV

Dose Adjustments

- EFV: FPV 700 mg BID + RTV 100 mg BID; EFV 600 mg QD *or* FPV 1,400 mg QD + RTV 300 mg QD*; EFV 600 mg QD
- LPV/r: Not recommended
- NVP: Dose adjustment not established; consider FPV 700 mg BID + RTV 100 mg BID; NVP 200 mg BID *or* FPV 1,400 mg QD + RTV 300 mg QD*; NVP 200 mg BID
- SQV: Dose adjustment not established; consider FPV 700 mg BID + RTV 100-200 mg BID; SQV 1,000 mg BID
- TPV: Not recommended

* FPV QD dosing not recommended for PI-experienced patients

Dosing in Renal Insufficiency and Hemodialysis

No dose adjustments necessary

Note(s)

No food restriction

Separate dosing with buffered ddI tablets or antacids by 1 hour

Pregnancy	Manufacturer	Contact	Website
Risk cannot be ruled out	GlaxoSmithKline	(800) 825-5249	www.lexiva.com

Adverse Effects (≥1%)

CNS: oral/perioral parathesia, peripheral parathesia, depression, mood disorders

GI: nausea, vomiting, diarrhea, taste disorders, increased triglycerides, hyperglycemia

Skin: rash, Stevens-Johnson syndrome

Managing ARV Drug Resistance

Resistance to fosamprenavir is associated with the selection of 1 or more of several resistance mutations.

Implications of fosamprenavir resistance for treatment with other ARV drugs

Mutations selected by fosamprenavir are also characteristic of amprenavir resistance, and include I50V, I54L/M, V32I, I47V, and M46I. These mutations do not appear to confer significant cross-resistance to other protease inhibitors. It appears that resistance to fosamprenavir may develop more readily during treatment with unboosted fosamprenavir than during treatment containing ritonavir-boosted fosamprenavir.

Results from clinical studies are needed to elucidate fosamprenavir resistance and its implications for subsequent therapy. Genotypic or phenotypic testing may be useful in predicting the likelihood of response to other protease inhibitors following failure of regimens containing fosamprenavir.

Implications of resistance to other ARV drugs for fosamprenavir treatment

Few data are available regarding the efficacy of fosamprenavir in individuals with HIV resistant to other protease inhibitors.

Genotypic or phenotypic testing may be useful in predicting the likelihood of response to fosamprenavir following failure of regimens containing other antiretrovirals, but further clinical studies are needed to clarify this question.

NORVIR®

	Brand Name	Generic Name	Format
	Norvir®	ritonavir (RTV)	■ 100 mg capsule ■ 600 mg/7.5 mL oral solution

Recommended Dosage

Adult/Adolescent

1 to 2 x 100 mg capsule(s) BID as a boosting agent

Pediatric

Age <1 month: Not FDA approved

Age 1 month - 12 years: 350-400 mg/m2 BID; maximum 600 mg BID

Adolescent: Adult dosing

Dosing in Renal Insufficiency and Hemodialysis

No dose adjustments necessary

Note(s)

Administration with food improves tolerability, but is not required

Rarely used as a single PI due to toxicity

Soft elastic capsule (and liquid formulation) can be stored at room temperature for up to 4 weeks

Separate dosing of ddI and RTV by 2.5 hours

Pregnancy	Manufacturer	Contact	Website
No evidence of risk in humans	Abbott Laboratories	(800) 222-6885	www.norvir.com

Black Box Warning

Co-administration of RTV with certain non-sedating antihistamines, sedative hypnotics, antiarrhythmics, or ergot alkaloids may result in potentially serious or life-threatening adverse events due to possible effects of RTV on hepatic metabolism of certain drugs.

Adverse Effects (≥1%)

Body as a Whole: myalgia, allergic reaction, bronchitis, cough, rhinitis, taste alterations, visual disturbances, dysuria, hyperglycemia, diabetes

CNS: asthenia, fatigue, headache, fever, malaise, circumoral or peripheral paresthesia, insomnia, dizziness, somnolence, abnormal thinking, amnesia, agitation, anxiety, confusion, convulsions, aphasia, ataxia, diplopia, emotional lability, euphoria, hallucinations, decreased libido, nervousness, neuralgia, neuropathy, peripheral neuropathy, paralysis, tremor, vertigo

CV: palpitations, vasodilation, hypotension, postural hypotension, syncope, tachycardia

Hematologic: anemia, thrombocytopenia, lymphadenopathy

GI: nausea, diarrhea, vomiting, abdominal pain, dyspepsia, stomatitis, anorexia, dry mouth, constipation, flatulence, cholecystitis, cholestasis, abnormal LFTs, hepatitis

Skin: rash, sweating, acne, contact dermatitis, pruritus, urticaria, skin ulceration, dry skin

Managing ARV Drug Resistance

Resistance to ritonavir is associated with the selection of 1 or more of several resistance mutations.

Implications of ritonavir resistance for treatment with other ARV drugs

Resistance mutations selected by ritonavir frequently confer or contribute to resistance against other protease inhibitors. Different mutations are associated with cross-resistance to different drugs. For example, M46I is associated with cross-resistance to indinavir, nelfinavir, and fosamprenavir (but not to saquinavir); V82A,F,T,S alone is associated with cross-resistance to indinavir, but in combination with other mutations also confers resistance to nelfinavir, fosamprenavir, and saquinavir; and I84V contributes to resistance against all available protease inhibitors. Although no single one of these mutations is associated with full resistance to lopinavir, each contributes partial resistance, and the presence of several mutations together can confer resistance.

Response to indinavir is unlikely in the setting of resistance to ritonavir.

Genotypic or phenotypic testing may be useful in predicting the likelihood of response to other protease inhibitors following failure of a regimen containing ritonavir.

Implications of resistance to other ARV drugs for ritonavir treatment

Response to ritonavir is unlikely in the setting of resistance to indinavir.

Following failure of a regimen containing a single protease inhibitor or NNRTI, patients may respond to regimens containing the combination of low-dose ritonavir and another protease inhibitor (a "boosted" protease inhibitor).

Genotypic or phenotypic testing may be useful in predicting the likelihood of response to ritonavir following failure of regimens containing other protease inhibitors.

PREZISTA™

	Brand Name	Generic Name	Format
	Prezista™	darunavir (DRV)	300 mg tablet

Recommended Dosage

Adult
2 x 300 mg tablet + 1 x 100 mg capsule RTV BID

Pediatric
Not FDA approved; under investigation

Dose Adjustments

- ATV: 600 mg DRV + 100 mg RTV BID; ATV 300 mg QD
- EFV: Use with caution
- IDV: Dose adjustment not established
- LPV/r: Not recommended
- NVP: Dose adjustment not established
- SQV: Not recommended

Dosing in Renal Insufficiency and Hemodialysis

N/A

Note(s)

Should be taken with food

Should not be used as sole PI; must be RTV-boosted

Pregnancy	Manufacturer	Contact	Website
No evidence of risk in humans	Tibotec	(877) 732-2488	www.tibotec-hiv.com

Black Box Warning

N/A

Adverse Effects (≥2%)

CNS: Headache

GI: Abdominal pain, constipation, diarrhea

Managing ARV Drug Resistance

Resistance to darunavir is associated with the selection of 1 or more of several resistance mutations.

Implications of darunavir resistance for treatment with other ARV drugs
In vitro studies of darunavir + ritonavir show the emergence of a number of protease mutations; however, the resistance profile of darunavir in human subjects has not been characterized fully. Results from studies of darunavir in antiretroviral-naive patients (now under way) are needed to identify darunavir resistance in initial therapy and to assess its implications for subsequent treatment. In patients with multiple preexisting mutations associated with resistance to protease inhibitors, emergent protease mutations included V32I, L33F, I47V, I54L, G73S, and L89V. In in vitro studies, viral isolates resistant to darunavir also were resistant to all other available protease inhibitors with the exception of tipranavir; some viruses remained susceptible to tipranavir. Clinical correlations for these observations are not available.

Implications of resistance to other ARV drugs for darunavir treatment
Resistance mutations selected by other protease inhibitors can contribute to darunavir resistance. Although no single mutation has been found to confer high-level resistance to darunavir, resistance mutations selected by other protease inhibitors can contribute to darunavir resistance. A number of protease mutations, including V11I, V32I, L33F, I47V, I50V, I54L/M, G73S, L76V, I84V, and L89V, are associated with decreased virologic response to darunavir. In addition, the total number of primary protease mutations is associated with diminished response to darunavir. If 7 or more protease resistance mutations are present at baseline, the probability of darunavir + ritonavir treatment failure increases significantly.

Phenotypic analysis has demonstrated that virologic response to darunavir + ritonavir is most likely if the baseline darunavir fold change in the half maximal inhibitory concentration (IC50) value (compared with reference darunavir susceptibility) is less than 10. In several analyses, the phenotypic fold change to darunavir has been the best predictor of virologic response to darunavir-containing regimens. The phenotypic clinical cutoff has not been defined.

Regimens containing darunavir + ritonavir and enfuvirtide may be effective as subsequent regimens in individuals without prior enfuvirtide experience, and appear to be more effective than regimens containing darunavir + ritonavir without enfuvirtide. Genotypic or phenotypic testing may be useful in predicting the likelihood of response to darunavir following failure of regimens containing other antiretrovirals.

REYATAZ®

	Brand Name	Generic Name	Format
	Reyataz®	atazanavir (ATV)	100, 150, 200 mg capsules

Recommended Dosage		Dose Adjustments
Adult/Adolescent *Treatment-naïve:* 2 x 200 mg capsules QD *Treatment-experienced:* 2 x 150 mg capsules + 1 x 100 mg RTV capsule QD	*Pediatric* Birth - 3 months: Not FDA approved; should not be administered Age <16 years: Not FDA approved; under investigation Age ≥16 years: Adult dose	■ DRV: ATV 300 mg QD; DRV 600 mg BID + RTV 100 mg BID ■ EFV: ATV 300 mg + RTV 100 mg QD; EFV 600 mg QD ■ NVP: Dose adjustment not established; consider ATV 300 mg + RTV 100 mg QD; NVP 200 mg BID

Dosing in Renal Insufficiency and Hemodialysis

No dose adjustments necessary

Note(s)

Must be taken with food

When co-administered with buffered ddI or antacids, ATV should be taken with food 2 hours before or 1 hour after; when co-administered with ddI enteric-coated capsules, they should be taken at different times

Pregnancy	Manufacturer	Contact	Website
No evidence of risk in humans	Bristol-Myers Squibb	(800) 272-4878	www.reyataz.com

Adverse Effects (≥3%)

Body as a Whole: back pain, fatigue, fever, headache

CNS: depression, dizziness, insomnia, peripheral neurologic symptoms

GI: abdominal pain, diarrhea, jaundice/scleral icterus, nausea, vomiting

Metabolic and Nutritional System: lipodystrophy

Musculoskeletal System: arthralgia

Respiratory System: increased cough

Skin: rash

Managing ARV Drug Resistance

Resistance to atazanavir is associated with the selection of 1 or more of several resistance mutations.

Implications of atazanavir resistance for treatment with other ARV drugs
Resistance to atazanavir has been associated with various known protease inhibitor mutations as well as with the novel I50L substitution. Some atazanavir resistance mutations have been associated, in vitro, with decreased susceptibility to other protease inhibitors, while the I50L mutation has been associated with increased susceptibility to other protease inhibitors. Results from clinical studies are needed to elucidate atazanavir resistance and its implications for subsequent therapy. Genotypic or phenotypic testing may be useful in predicting the likelihood of response to other protease inhibitors following failure of regimens containing atazanavir.

Implications of resistance to other ARV drugs for atazanavir treatment
Resistance mutations selected by other protease inhibitors may confer or contribute to resistance to atazanavir. Substitutions at a number of specific sites have been associated with decreased in vitro susceptibility to atazanavir. Although no single mutation was found to confer high-level resistance to atazanavir, the accumulation of 5 or more of these key mutations predicted reduced susceptibility to atazanavir. The clinical significance of these findings is under study.

Genotypic or phenotypic testing may be useful in predicting the likelihood of response to atazanavir following failure of regimens containing other antiretrovirals.

VIRACEPT®

	Brand Name	Generic Name	Format
	Viracept®	nelfinavir (NFV)	■ 250, 625 mg tablets ■ 50 mg/g oral powder

Recommended Dosage		Dose Adjustments
Adult/Adolescent 2 x 625 mg tablets BID or 5 x 250 mg tablets BID or 3 x 250 mg tablets TID	*Pediatric* Age <2 years: Not FDA approved; serum drug levels variable Age 2 - 13 years: 45-55 mg/kg BID or 25 - 35 mg/kg TID Adolescent: Adult dose	■ IDV: NFV 1,250 mg BID; IDV 1,200 mg BID

Dosing in Renal Insufficiency and Hemodialysis

No dose adjustments necessary

Note(s)

Must be taken with food containing fat

Boosting with RTV is not recommended

Pregnancy	Manufacturer	Contact	Website
No evidence of risk in humans	Pfizer Inc	(800) 777-6637	www.viracept.com

Adverse Effects (≥1%)

Body as a Whole: allergic reactions, back pain, fever, malaise, pain, asthenia, myalgia, arthralgia

CNS: headache, anxiety, depression, dizziness, insomnia, seizures

GI: abdominal pain, diarrhea, nausea, flatulence, anorexia, dyspepsia, GI bleeding, hepatitis, vomiting, pancreatitis, increased LFTs

Hematologic: anemia, leukopenia, thrombocytopenia

Respiratory: dyspnea, pharyngitis, rhinitis

Skin: pruritus, rash, pruritis, sweating, urticaria

Managing ARV Drug Resistance

Resistance to nelfinavir is associated with the selection of 1 or more of several resistance mutations.

Implications of nelfinavir resistance for treatment with other ARV drugs

Resistance mutations selected by nelfinavir may or may not confer or contribute to resistance against other protease inhibitors. The commonly selected D30N mutation does not appear to be associated with resistance to other drugs, while the L90M mutation, which is less commonly selected by nelfinavir, confers or contributes to resistance to all other protease inhibitors.

Genotypic or phenotypic testing may be useful in predicting the likelihood of response to other protease inhibitors following failure of regimens containing nelfinavir.

Implications of resistance to other ARV drugs for nelfinavir treatment

The likelihood of sustained response to nelfinavir is diminished in the setting of resistance to other protease inhibitors.

Genotypic or phenotypic resistance testing may be useful in predicting the likelihood of response to nelfinavir following failure of regimens containing other protease inhibitors.

FUZEON®

	Brand Name	Generic Name	Format
	Fuzeon®	enfuvirtide (ENF)	108 mg vial of lyophilized ENF powder [reconstituted with 1.1 mL of sterile water, giving 1.2 mL of solution]

Recommended Dosage		Dose Adjustments
Adult/Adolescent 90 mg (1 mL) subcutaneous injection BID	*Pediatric* Age <6 years: Not FDA approved Age 6 - 16 years: 2 mg/kg SQ BID; maximum dose 90 mg SQ BID Age >16 years: Adult dose	No dose adjustments necessary

Dosing in Renal Insufficiency and Hemodialysis

No dose adjustments necessary

Note(s)

Local injection site reactions occurred in 98% of patients in Phase III trials

Reconstituted solution must be kept refrigerated and used within 24 hours

Pregnancy	Manufacturer	Contact	Website
No evidence of risk in humans	Roche Laboratories	(877) 438-9366	www.fuzeon.com

Adverse Effects (≥2%)

CNS: peripheral neuropathy, taste disturbance

Eye Disorder: conjunctivitis

General: anorexia, decreased appetite, asthenia, influenza-like illness, decreased weight

GI: abdominal pain upper, constipation, pancreatitis

Hematologic: lymphadenopathy

Infections: influenza, herpes simplex, sinusitis, skin papilloma

Injection Site Reaction: generally mild to moderate pain/discomfort, induration, erythema, nodules and cysts. Fewer than or equal to 1% of patients experienced hypersensitivity reaction.

Musculoskeletal, Connective Tissue, and Bone Disorders: mylagia

Psychiatric Disorders: anxiety, depression, insomnia

Respiratory: cough

Skin: pruritus nos

Managing ARV Drug Resistance

Resistance to enfuvirtide may result from one or more of several mutations in gp41. The incidence and significance of specific enfuvirtide mutations is being studied in ongoing trials.

Implications of enfuvirtide resistance for treatment with other ARV drugs
Enfuvirtide is currently the only agent in the class of fusion inhibitor, and it has unique resistance mutations. Enfuvirtide-associated mutations do not affect sensitivity to other antiretrovirals (those in the NRTI, NNRTI, PI, coreceptor antagonist, or integrase inhibitor classes).

Implications of resistance to other ARV drugs for treatment with enfuvirtide
Resistance to other currently available antiretroviral agents is not associated with resistance to enfuvirtide

	Brand Name	Generic Name	Format
	Selzentry™	maraviroc (MRV)	■ 150, 300 mg tablets

Recommended Dosage		Dose Adjustments	
Adult/Adolescent 1 x 150 mg tablet BID	*Pediatric:* Not FDA approved, should not be used	■ DLV: MRV 150 mg BID ■ EFV: MRV 600 mg BID ■ ENF: MRV 300 mg BID ■ NVP: MRV 300 mg BID	■ TPV: MRV 300 mg BID ■ All other PIs: 150 mg BID ■ All NRTIs: 300 mg BID

Dosing in Renal Insufficiency and Hemodialysis

N/A

Note(s)

No food restriction

Tropism testing (and treatment history) must guide the use of MRV; its use is not recommended in patients with dual/mixed or CXCR4-tropic HIV-1

Pregnancy	Manufacturer	Contact	Website
No evidence of risk in humans	Pfizer Inc.	(800) 879-3477	www.selzentry.com

Black Box Warning

Hepatotoxicity has been reported with MRV use. Evidence of a systemic allergic reaction (e.g., pruritic rash, eosinophilia, or elevated IgE) prior to the development of hepatotoxicity may occur. Patients with signs or symptoms of hepatitis or allergic reaction following use of MRV should be evaluated immediately.

Adverse Effects (≥1%)

Body as a Whole: fever

CNS: dizziness, headache

GI: abdominal pain, diarrhea, flatulence, nausea

Respiratory: cough, upper respiratory tract infection

Skin: rash

Managing ARV Drug Resistance

Common Mutations
Currently under clinical review.

Selzentry should be used with caution in patients at increased risk for cardiovascular problems

Resistance to maraviroc is associated with one or more of several mutations in the V3 loop of gp120; however, these mutations do not appear to be consistent among various patients, and their role in causing resistance is not clear. Phenotypic analyses in maraviroc recipients with virologic failure show a plateau effect in viral inhibition whereby increasing concentrations of maraviroc do not result in a corresponding percentage increase in inhibition of HIV replication. The significance of these findings and the mechanisms of maraviroc resistance have not been well defined; further investigations are under way.

Virologic failure of regimens containing maraviroc may be caused not only by resistance but also (and perhaps more frequently) by emergence of non-CCR5-tropic virus or by changes in viral tropism; see "Special Considerations" below.

Implications of maraviroc resistance for treatment with other ARV drugs
It is unclear whether resistance mutations selected by maraviroc will confer resistance to other CCR5 antagonists now in development. Maraviroc mutations do not affect sensitivity to other classes of antiretroviral agents (nucleoside analogues, nonnucleoside reverse transcriptase inhibitors, protease inhibitors, fusion inhibitor, integrase inhibitors).

Further studies are needed to characterize maraviroc resistance and to assess its implications for subsequent treatment.

Implications of resistance to other ARV drugs for treatment with maraviroc
In an in vitro study, resistance to the investigational CCR5 antagonist vicriviroc appears to convey cross-resistance to maraviroc. Signature mutations that predict resistance to maraviroc have not been identified.

Resistance to antiretroviral drugs from other classes is not associated with resistance to maraviroc.

ATRIPLA™

	Brand Name	Format	Manufacturer
	Atripla™	600 mg EFV co-formulated with 200 mg FTC + 300 mg TDF tablet	Bristol-Myers Squibb and Gilead Sciences

Recommended Dosage		Food	Pregnancy
Adult/Adolescent 1 x 600/200/300 mg tablet QD	*Pediatric* No pediatric labeling	Take on an empty stomach, preferably at bed time to minimize CNS side effects	Risk cannot be ruled out

COMBIVIR®

	Brand Name	Format	Manufacturer
	Combivir®	150 mg 3TC co-formulated with 300 mg ZDV tablet	GlaxoSmithKline

Recommended Dosage		Food	Pregnancy
Adult/Adolescent 1 x 300/150 mg tablet BID	*Pediatric* No pediatric labeling	No food restrictions	Risk cannot be ruled out

EPZICOM®

	Brand Name	Format	Manufacturer
	Epzicom®	600 mg ABC co-formulated with 300 mg 3TC tablet	GlaxoSmithKline

Recommended Dosage		Food	Pregnancy
Adult/Adolescent 1 x 600/300 mg tablet QD	*Pediatric* No pediatric labeling	No food restrictions	Risk cannot be ruled out

TRIZIVIR®

	Brand Name	Format	Manufacturer
	Trizivir®	300 mg ABC co-formulated with 150 mg 3TC + 300 mg ZDV tablet	GlaxoSmithKline

Recommended Dosage		Food	Pregnancy
Adult/Adolescent 1 x 300/150/300 mg tablet BID	*Pediatric* No pediatric labeling	No food restrictions	Risk cannot be ruled out

TRUVADA®

	Brand Name	Format	Manufacturer
	Truvada®	200 mg FTC co-formulated with 300 mg TDF tablet	Gilead Sciences

Recommended Dosage		Food	Pregnancy
Adult/Adolescent 1 x 200/300 mg tablet QD	*Pediatric* No pediatric labeling	No food restrictions	No evidence of risk in humans

Emtriva® (emtricitabine, FTC)	**Potential interactions:** ***(may require close monitoring, alteration of drug dosage, or timing of administration)***	**Antiretrovirals (NRTIs):** stavudine, tenofovir, zidovudine **Antiretrovirals (PIs):** indinavir **Antivirals:** famciclovir
	Contraindications:	**See emtricitabine package insert**
Epivir® (lamivudine, 3TC)	**Potential interactions:** ***(may require close monitoring, alteration of drug dosage, or timing of administration)***	**Analgesics:** methadone **Antibiotics:** cotrimoxazole (TMP/SMX) **Antiretrovirals (NNRTIs):** efavirenz **Antiretrovirals (NRTIs):** abacavir, entecavir, stavudine, tenofovir, zidovudine **Antiretrovirals (PIs):** atazanavir, fosamprenavir, indinavir, nelfinavir, tipranavir **Antivirals:** adefovir dipivoxil, ribavirin
	Contraindications:	**See lamivudine package insert**
Retrovir® (zidovudine, ZDV)	**Potential interactions:** ***(may require close monitoring, alteration of drug dosage, or timing of administration)***	**Analgesics:** buprenorphine, l-alpha-acetylmethadol, methadone **Antibiotics:** clarithromycin, rifabutin, rifampin **Antiepileptics:** phenytoin, valproic acid **Antifungals:** fluconazole **Antigout:** probenecid **Antiparasitics:** atovaquone **Antiretrovirals (NNRTIs):** delavirdine, efavirenz, nevirapine **Antiretrovirals (NRTIs):** abacavir, didanosine, emtricitabine, lamivudine, stavudine **Antiretrovirals (PIs):** atazanavir, fosamprenavir, indinavir, lopinavir, nelfinavir, ritonavir, tipranavir **Antivirals:** ganciclovir, ribavirin **Opioid blockers:** naltrexone
	Contraindications:	**See zidovudine package insert**
Videx® (didanosine, ddI)	**Potential interactions:** ***(may require close monitoring, alteration of drug dosage, or timing of administration)***	**Analgesics:** methadone **Antibiotics:** ciprofloxacin, dapsone, rifabutin, sulfamethoxazole, trimethoprim **Antifungals:** itraconazole, ketoconazole **Antigout:** allopurinol **Antiretrovirals (NNRTIs):** delavirdine, efavirenz, nevirapine **Antiretrovirals (NRTIs):** stavudine, tenofovir, zidovudine **Antiretrovirals (PIs):** atazanavir, fosamprenavir, indinavir, lopinavir, nelfinavir, ritonavir, tipranavir **Antivirals:** cidofovir, ganciclovir, ribavirin **Gastrointestinal agents:** loperamide, metoclopramide, ranitidine
	Contraindications:	**See didanosine package insert**
Viread® (tenofovir, TDF)	**Potential interactions:** ***(may require close monitoring, alteration of drug dosage, or timing of administration)***	**Analgesics:** methadone **Antibiotics:** rifampin **Antigout:** probenecid **Antiretrovirals (NNRTIs):** efavirenz, nevirapine **Antiretrovirals (NRTIs):** abacavir, didanosine, emtricitabine, entecavir, lamivudine, stavudine **Antiretrovirals (PIs):** atazanavir, darunavir, fosamprenavir, indinavir, lopinavir, saquinavir, tipranavir **Antivirals:** adefovir dipivoxil, ribavirin **Steroids:** ethinylestradiol/norethindrone acetate
	Contraindications:	**See tenofovir package insert**
Zerit® (stavudine, d4T)	**Potential interactions:** ***(may require close monitoring, alteration of drug dosage, or timing of administration)***	**Analgesics:** methadone **Antibiotics:** clarithromycin, rifabutin **Antifungals:** fluconazole **Antiretrovirals (NRTIs):** didanosine, emtricitabine, lamivudine, tenofovir, zidovudine **Antiretrovirals (PIs):** atazanavir, indinavir, nelfinavir, tipranavir **Antivirals:** ganciclovir, ribavirin
	Contraindications:	**See stavudine package insert**
Ziagen® (abacavir, ABC)	**Potential interactions:** ***(may require close monitoring, alteration of drug dosage, or timing of administration)***	**Alcohol:** ethanol, wine, liquor, beer **Analgesics:** methadone **Antiretrovirals (NRTIs):** lamivudine, tenofovir, zidovudine **Antiretrovirals (PIs):** fosamprenavir, tipranavir **Immunosuppressants:** mycophenolate
	Contraindications:	**See abacavir package insert**

NNRTI DRUG INTERACTIONS

Rescriptor® (delavirdine, DLV)

Contraindications:	**Antibacterials:** rifabutin, rifampicin **Anticonvulsants:** carbamazepine, phenobarbital (phenobarbitone), phenytoin **Antihistamines:** astemizole, terfenadine **Antimigraine agents:** dihydroergotamine, ergometrine (ergonovine), ergotamine **Antiprotozoals:** halofantrine, lumefantrine **Antipsychotics/neuroleptics:** pimozide **Anxiolytics/hypnotics/sedatives:** alprazolam, midazolam, triazolam **Gastrointestinal agents:** cisapride **Herbals/nutraceuticals:** St John's Wort **Lipid-lowering agents:** lovastatin, simvastatin
Potential interactions: ***(may require close monitoring, alteration of drug dosage, or timing of administration)***	**Analgesics:** alfentanyl, buprenorphine, dextropropoxyphene, fentanyl, methadone, pethidine (meperidine), tramadol **Antiarrhythmics:** amiodarone, bepridil, disopyramide, flecainide, lidocaine (lignocaine), mexiletine, propafenone, quinidine **Antibacterials:** clarithromycin, dapsone, rifapentine **Anticonvulsants:** clonazepam, ethosuximide **Antidepressants:** buproprion, citalopram, doxepin, fluoxetine, mirtazapine, nefazodone, sertraline **Antifungals:** itraconazole, ketoconazole, voriconazole **Antihistamines:** fexofenadine, loratadine **Antineoplastics:** cyclophosphamide, paclitaxel, vinblastine, vincristine **Anti-platelet and anticoagulants:** warfarin **Antiprotozoals:** artemisinins, quinine **Antipsychotics/neuroleptics:** chlorpromazine, olanzapine **Antiretrovirals (NNRTIs):** efavirenz, nevirapine **Antiretrovirals (NRTIs):** didanosine **Antiretrovirals (PIs):** atazanavir, fosamprenavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, tipranavir **Antivirals:** adefovir **Anxiolytics/hypnotics/sedatives:** clorazepate, diazepam, estazolam, flurazepam, zolpidem **Beta blockers:** carvedilol **Calcium channel antagonists:** amlodipine, diltiazem, nicardipine, nifedipine, nisoldipine, verapamil **Erectile dysfunctional agents:** apomorphine, sildenafil, tadalafil, vardenafil **Gastrointestinal agents:** antacids, cimetidine, dronabinol, famotidine, ranitidine **General anesthetics:** ketamine **Herbals/nutraceuticals:** echinacea, garlic, milk thistle **Illicit/recreational:** MDMA (Ecstasy), methamphetamine **Immunosuppressants:** ciclosporin, sirolimus, tacrolimus **Lipid-lowering agents:** atorvastatin, fluvastatin **Oral anti-diabetics:** glipizide, tolbutamide **Steroids:** budesonide, dexamethasone, fluticasone, prednisolone, progesterone/progestogen, stanazolol, testosterone

Sustiva® (efavirenz, EFV)

Contraindications:	**Antiarrhythmics:** bepridil **Antifungals:** voriconazole **Antihistamines:** astemizole, terfenadine **Antimigraine agents:** dihydroergotamine, ergometrine (ergonovine), ergotamine **Antiprotozoals:** amodia, quinine **Antipsychotics/neuroleptics:** pimozide **Anxiolytics/hypnotics/sedatives:** midazolam, triazolam **Gastrointestinal agents:** cisapride **Herbals/nutraceuticals:** St John's Wort
Potential interactions: ***(may require close monitoring, alteration of drug dosage, or timing of administration)***	**Analgesics:** alfentanyl, buprenorphine, fentanyl, methadone, tramadol **Antiarrhythmics:** amiodarone, disopyramide, flecainide, lidocaine (lignocaine), mexiletine, propafenone, quinidine **Antibacterials:** clarithromycin, rifabutin, rifampicin, rifapentine **Anticonvulsants:** carbamazepine, clonazepam, ethosuximide, phenobarbital (phenobarbitone), phenytoin **Antidepressants:** buproprion, citalopram, mirtazapine, nefazodone, sertraline **Antifungals:** caspofungin, itraconazole, ketoconazole **Antihistamines:** fexofenadine, loratadine **Antineoplastics:** cyclophosphamide, paclitaxel, vinblastine, vincristine **Anti-platelet and anticoagulants:** warfarin **Antiprotozoals:** artemisinins, halofantrine, lumefantrine, quinine **Antipsychotics/neuroleptics:** olanzapine **Antiretrovirals (NNRTIs):** delavirdine, nevirapine **Antiretrovirals (PIs):** atazanavir, fosamprenavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, tipranavir **Anxiolytics/hypnotics/sedatives:** alprazolam, clorazepate, diazepam, estazolam, flurazepam, zolpidem **Beta blockers:** carvedilol **Calcium channel antagonists:** amlodipine, diltiazem, nicardipine, nifedipine, nisoldipine, verapamil **Erectile dysfunctional agents:** apomorphine, sildenafil, tadalafil, vardenafil **Gastrointestinal agents:** cimetidine, dronabino **General anesthetics:** ketamine **Herbals/nutraceuticals:** echinacea, garlic, milk thistle **Immunosuppressants:** ciclosporin, sirolimus, tacrolimus **Lipid-lowering agents:** atorvastatin, fluvastatin, lovastatin, pravastatin, simvastatin **Oral anti-diabetics:** glipizide, tolbutamide **Steroids:** dexamethasone, ethinylestradiol, prednisolone, progesterone/progestogen, stanazolol, testosterone

Viramune® (nevirapine, NVP)

Contraindications:	**Antibacterials:** rifampicin **Antifungals:** ketoconazole **Herbals/nutraceuticals:** St John's Wort
Potential interactions: ***(may require close monitoring, alteration of drug dosage, or timing of administration)***	**Analgesics:** alfentanyl, buprenorphine, fentanyl, methadone **Antiarrhythmics:** amiodarone, bepridil, disopyramide, flecainide, lidocaine (lignocaine), mexiletine, propafenone, quinidine **Antibacterials:** arithromycin, clarithromycin, rifabutin, rifapentine **Anticonvulsants:** carbamazepine, clonazepam, ethosuximide, phenobarbital (phenobarbitone), phenytoin, valproate **Antidepressants:** buproprion, citalopram, mirtazapine, nefazodone, sertraline **Antifungals:** caspofungin, fluconazole, itraconazole, miconazole, voriconazole **Antihistamines:** astemizole, fexofenadine, terfenadine **Antimigraine agents:** dihydroergotamine, ergometrine (ergonovine), ergotamine **Antineoplastics:** cyclophosphamide, paclitaxel, vinblastine, vincristine **Anti-platelet and anticoagulants:** warfarin **Antiprotozoals:** artemisinins, halofantrine, lumefantrine, quinine **Antipsychotics/neuroleptics:** olanzapine, pimozide **Antiretrovirals (NNRTIs):** delavirdine, efavirenz **Antiretrovirals (PIs):** atazanavir, fosamprenavir, indinavir, lopinavir, nelfinavir, saquinavir, tipranavir **Anxiolytics/hypnotics/sedatives:** alprazolam, clorazepate, diazepam, estazolam, flurazepam, midazolam, triazolam, zolpidem **Beta blockers:** carvedilol **Calcium channel antagonists:** amlodipine, diltiazem, nicardipine, nifedipine, nisoldipine, verapamil **Erectile dysfunctional agents:** apomorphine, sildenafil, tadalafil, vardenafil **Gastrointestinal agents:** cisapride, dronabinol **General anesthetics:** ketamine **Herbals/nutraceuticals:** echinacea, garlic, milk thistle **Immunosuppressants:** ciclosporin, sirolimus, tacrolimus **Lipid-lowering agents:** atorvastatin, fluvastatin, lovastatin, simvastatin **Oral anti-diabetics:** glipizide, rosiglitazone, tolbutamide **Steroids:** dexamethasone, ethinylestradiol, prednisolone, progesterone/progestogen, stanazolol, testosterone

PI DRUG INTERACTIONS

Aptivus® (tipranavir, TPV)

Contraindications:	**Antiarrhythmics:** amiodarone, bepridil, flecainide, propafenone, quinidine **Antibacterials:** rifampicin **Antihistamines:** astemizole, terfenadine **Antimigraine agents:** dihydroergotamine, ergonovine, ergotamine **Antiprotozoals:** halofantrine, lumefantrine **Antipsychotics/neuroleptics:** pimozide **Anxiolytics/hypnotics/sedatives:** midazolam, triazolam **Gastrointestinal agents:** cisapride **Herbals/nutraceuticals:** St John's Wort **Lipid-lowering agents:** lovastatin, simvastatin
Potential interactions: ***(may require close monitoring, alteration of drug dosage, or timing of administration)***	**Analgesics:** alfentanyl, buprenorphine, dextropropoxyphene, diamorphine, fentanyl, methadone, morphine, pethidine (meperidine), piroxicam, tramadol **Antiarrhythmics:** disopyramide, lidocaine (lignocaine), mexiletine **Antibacterials:** clarithromycin, dapsone, erythromycin, metronidazole, rifabutin, rifapentine, trimethoprim/sulfamethoxazole **Anticonvulsants:** carbamazepine, clonazepam, ethosuximide, phenobarbital, phenytoin, valproate **Antidepressants:** amitriptyline, bupropion, citalopram, desipramine, doxepin, fluoxetine, mirtazapine, nefazodone, nortriptyline, paroxetine, sertraline **Antifungals:** caspofungin, fluconazole, itraconazole, ketoconazole, miconazole, voriconazole **Antihistamines:** fexofenadine, loratadine **Antineoplastics:** cyclophosphamide, paclitaxel, vinblastine, vincristine **Anti-platelet and anticoagulants:** warfarin **Antiprotozoals:** artemisinins, atovaquone, quinine, sulfadoxine/pyrimethamine, artemisinins, mefloquine **Antipsychotics/neuroleptics:** chlorpromazine, clozapine, olanzapine, haloperidol **Antiretrovirals (NNRTIs):** delavirdine, efavirenz, nevirapine **Antiretrovirals (NRTIs):** abacavir, didanosine, zidovudine, tenofovir **Antiretrovirals (PIs):** atazanavir, fosamprenavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir **Anxiolytics/hypnotics/sedatives:** alprazolam, clorazepate, diazepam, estazolam, zolpidem **Beta blockers:** atenolol, bisoprolol, carvedilol, metoprolol, propramolol **Bronchodilators:** theophylline **Calcium channel antagonists:** amlodipine, diltiazem, nicardipine, nifedipine, nisoldipine, verapamil **Erectile dysfunctional agents:** apomorphine, sildenafil, tadalafil **Gastrointestinal agents:** antacids, cimetidine, dronabinol, famotidine, lansoprazole, loperamide, omeprazole, ondansetron, ranitidine **Herbals/nutraceuticals:** echinacea, garlic, milk thistle **Illicit/recreational:** gamma-hydroxybutyrate, MDMA ("Ecstasy"), methamphetamine **Immunosuppressants:** ciclosporin, sirolimus, tacrolimus **Lipid-lowering agents:** atorvastatin **Oral anti-diabetics:** glipizide, tolbutamide **Steroids:** budesonide, dexamethasone, ethinylestradiol, fluticasone, prednisolone, progesterone/progestogen, stanazolol, testosterone

Crixivan® (indinavir, IDV)

Contraindications:	**Antiarrhythmics:** amiodarone, flecainide **Antibacterials:** rifampicin **Antihistamines:** astemizole, terfenadine **Antimigraine agents:** dihydroergotamine, ergometrine (ergonovine), ergotamine **Antiprotozoals:** halofantrine, lumefantrine **Antipsychotics/neuroleptics:** pimozide **Antiretrovirals (PIs):** atazanavir **Anxiolytics/hypnotics/sedatives:** alprazolam, midazolam, triazolam **Erectile dysfunctional agents:** vardenafil **Gastrointestinal agents:** cisapride **Herbals/nutraceuticals:** St John's Wort **Lipid-lowering agents:** lovastatin, simvastatin
Potential interactions: ***(may require close monitoring, alteration of drug dosage, or timing of administration)***	**Analgesics:** alfentanyl, buprenorphine, dextropropoxyphene, diamorphine, fentanyl, methadone, morphine, pethidine (meperidine), piroxicam, tramadol **Antiarrhythmics:** bepridil, disopyramide, lidocaine (lignocaine), mexiletine, propafenone, quinidine **Antibacterials:** rifabutin, rifapentine **Anticonvulsants:** carbamazepine, clonazepam, ethosuximide, phenobarbital (phenobarbitone), phenytoin **Antidepressants:** amitriptyline, buproprion, citalopram, desipramine, doxepin, fluoxetine, mirtazapine, nefazodone, nortriptyline, paroxetine, sertraline **Antifungals:** itraconazole, ketoconazole, voriconazole **Antihistamines:** fexofenadine, loratadine **Antineoplastics:** cyclophosphamide, paclitaxel, vinblastine, vincristine **Anti-platelet and anticoagulants:** warfarin **Antiprotozoals:** artemisinins, mefloquine, mefloxquine, quinine **Antipsychotics/neuroleptics:** chlorpromazine, olanzapine, clozapine, haloperidol **Antiretrovirals (NNRTIs):** delavirdine, efavirenz, nevirapine **Antiretrovirals (NRTIs):** didanosine, tenofovir **Antiretrovirals (PIs):** darunavir, lopinavir, nelfinavir, ritonavir, saquinavir, tipranavir **Anxiolytics/hypnotics/sedatives:** clorazepate, diazepam, estazolam, flurazepam, zolpidem **Beta blockers:** carvedilol **Calcium channel antagonists:** amlodipine, diltiazem, nicardipine, nifedipine, nisoldipine, verapamil **Erectile dysfunctional agents:** apomorphine, sildenafil, tadalafil **Gastrointestinal agents:** antacids, dronabinol, famotidine, omeprazole **Herbals/nutraceuticals:** echinacea, garlic **Illicit/recreational:** gamma-hydroxybutyrate (GHB), MDMA (Ecstasy), methamphetamine **Immunosuppressants:** ciclosporin, sirolimus, tacrolimus **Lipid-lowering agents:** atorvastatin **Oral anti-diabetics:** glipizide, tolbutamide **Steroids:** budesonide, dexamethasone, ethinylestradiol, fluticasone, prednisolone, progesterone/progestogen, stanazolol, testosterone

Invirase® (saquinavir, SQV)

Contraindications:	**Antiarrhythmics:** amiodarone, bepridil, flecainide, propafenone, quinidine **Antibacterials:** rifampicin **Antihistamines:** astemizole, terfenadine **Antimigraine agents:** dihydroergotamine, ergometrine (ergonovine), ergotamine **Antiprotozoals:** halofantrine, lumefantrine **Antipsychotics/neuroleptics:** pimozide **Antiretrovirals (PIs):** darunavir **Anxiolytics/hypnotics/sedatives:** midazolam, triazolam **Gastrointestinal agents:** cisapride **Herbals/nutraceuticals:** St John's Wort **Lipid-lowering agents:** lovastatin, simvastatin
Potential interactions: ***(may require close monitoring, alteration of drug dosage, or timing of administration)***	**Analgesics:** alfentanyl, buprenorphine, dextropropoxyphene, diamorphine, fentanyl, methadone, morphine, pethidine (meperidine), piroxicam, tramadol **Antiarrhythmics:** disopyramide, lidocaine (lignocaine), mexiletine **Antibacterials:** dapsone, rifabutin, rifapentine **Anticonvulsants:** carbamazepine, clonazepam, ethosuximide, phenobarbital (phenobarbitone), phenytoin **Antidepressants:** amitriptyline, buproprion, citalopram, desipramine, doxepin, fluoxetine, mirtazapine, nefazodone, nortriptyline, paroxetine, sertraline **Antifungals:** voriconazole **Antihistamines:** fexofenadine, loratadine **Antineoplastics:** cyclophosphamide, paclitaxel, vinblastine, vincristine **Anti-platelet and anticoagulants:** warfarin **Antiprotozoals:** artemisinins, mefloquine, quinine **Antipsychotics/neuroleptics:** chlorpromazine, olanzapine, clozapine, haloperidol **Antiretrovirals (NNRTIs):** delavirdine, efavirenz, nevirapine **Antiretrovirals (NRTIs):** didanosine **Antiretrovirals (PIs):** atazanavir, fosamprenavir, indinavir, lopinavir, ritonavir, tipranavir **Antivirals:** adefovir **Anxiolytics/hypnotics/sedatives:** alprazolam, clorazepate, diazepam, estazolam, flurazepam, zolpidem **Beta blockers:** carvedilol **Calcium channel antagonists:** amlodipine, diltiazem, nicardipine, nifedipine, nisoldipine, verapamil **Erectile dysfunctional agents:** apomorphine, sildenafil, tadalafil, vardenafil **Gastrointestinal agents:** dronabinol, loperamide, omeprazole **Herbals/nutraceuticals:** echinacea, garlic, milk thistle **Illicit/recreational:** gamma-hydroxybutyrate (GHB), marijuana, MDMA (Ecstasy), methamphetamine **Immunosuppressants:** ciclosporin, sirolimus, tacrolimus **Lipid-lowering agents:** atorvastatin, pravastatin **Oral anti-diabetics:** glipizide, tolbutamide **Steroids:** budesonide, dexamethasone, ethinylestradiol, fluticasone, prednisolone, progesterone/progestogen, stanazolol, testosterone

Kaletra® (lopinavir/ritonavir, LPV/r)

Contraindications:	**Antiarrhythmics:** amiodarone, flecainide **Antibacterials:** rifampicin **Antifungals:** voriconazole **Antihistamines:** astemizole, terfenadine **Antimigraine agents:** dihydroergotamine, ergometrine (ergonovine), ergotamine **Antiprotozoals:** halofantrine, lumefantrine **Antiretrovirals (PIs):** darunavir **Antipsychotics/neuroleptics:** pimozide **Anxiolytics/hypnotics/sedatives:** midazolam, triazolam **Gastrointestinal agents:** cisapride **Herbals/nutraceuticals:** St John's Wort **Lipid-lowering agents:** lovastatin, simvastatin
Potential interactions: ***(may require close monitoring, alteration of drug dosage, or timing of administration)***	**Analgesics:** alfentanyl, buprenorphine, dextropropoxyphene, diamorphine, fentanyl, methadone, morphine, pethidine (meperidine), piroxicam, tramadol **Antiarrhythmics:** bepridil, disopyramide, lidocaine (lignocaine), mexiletine, propafenone, quinidine **Antibacterials:** clarithromycin, erythromycin, metronidazole, rifabutin, rifapentine **Anticonvulsants:** carbamazepine, clonazepam, ethosuximide, lamotrigine, phenobarbital (phenobarbitone), phenytoin, valproate **Antidepressants:** amitriptyline, buproprion, citalopram, desipramine, doxepin, fluoxetine, mirtazapine, nefazodone, nortriptyline, paroxetine, sertraline **Antifungals:** caspofungin, itraconazole, ketoconazole, miconazole **Antihistamines:** fexofenadine, loratadine **Antineoplastics:** cyclophosphamide, paclitaxel, vinblastine, vincristine **Anti-emetics:** dronabinol **Anti-platelet and anticoagulants:** warfarin **Antiprotozoals:** Atovaquone, quinine, artemisinins, mefloquine **Antipsychotics/neuroleptics:** chlorpromazine, olanzapine, clozapine, haloperidol **Antiretrovirals (NNRTIs):** delavirdine, efavirenz, nevirapine **Antiretrovirals (NRTIs):** abacavir, didanosine, tenofovir **Antiretrovirals (PIs):** atazanavir, fosamprenavir, indinavir, nelfinavir, ritonavir, saquinavir, tipranavir **Anxiolytics/hypnotics/sedatives:** alprazolam, clorazepate, diazepam, estazolam, flurazepam, zolpidem **Beta blockers:** atenolol, bisoprolol, carvedilol, metoprolol, propranolol **Bronchodilators:** theophylline **Calcium channel antagonists:** amlodipine, diltiazem, nicardipine, nifedipine, nisoldipine, verapamil **Erectile dysfunctional agents:** apomorphine, sildenafil, tadalafil, vardenafil **Gastrointestinal agents:** dronabinol, loperamide **Herbals/nutraceuticals:** echinacea, garlic, milk thistle **Illicit/recreational:** gamma-hydroxybutyrate (GHB), marijuana, MDMA (Ecstasy), methamphetamine **Immunosuppressants:** ciclosporin, sirolimus, tacrolimus **Lipid-lowering agents:** atorvastatin, rosuvastatin **Oral anti-diabetics:** glipizide, tolbutamide **Steroids:** budesonide, dexamethasone, ethinylestradiol, fluticasone, prednisolone, progesterone/progestogen, stanazolol, testosterone

PI DRUG INTERACTIONS

Lexiva® (fosamprenavir, FPV)

Contraindications:	**Antiarrhythmics:** flecainide, propafenone **Antimycobacterials:** rifampin **Antiretrovirals (NNRTI):** delavirdine **Ergot derivatives:** dihydroergotamine, ergonovine, ergotamine, ethylergonovine **Gastrointestinal agents:** cisapride **Herbal/nutraceuticals:** St. John's Wort **Lipid-lowering agents:** lovastatin, simvastatin **Neuroleptics:** pimozide **Sedatives/hypnotics:** midazolam, triazolam
Potential interactions: ***(may require close monitoring, alteration of drug dosage, or timing of administration)***	**Analgesics:** methadone **Antiarrhythmics:** amiodarone, bepridil, lidocaine, quinidine **Anticoagulants:** warfarin **Antidepressants:** amitriptyline, imipramine, trazodone **Antifungals:** itraconazole, ketoconazole **Antibacterials:** rifabutin **Antiretrovirals (NNRTIs):** efavirenz, nevirapine **Antiretrovirals (NRTIs):** didanosine, tenofovir **Antiretrovirals (PIs):** atazanavir, indinavir, lopinavir, ritonavir, saquinavir **Benzodiazepines:** alprazolam, clorazepate, diazepam, flurazepam **Calcium channel antagonists:** amlopidine, diltiazem, felodipine, isradipine, nicardipine, nifedipine, nimodipine, nisoldipine, verapamil **Corticosteroids:** dexamethasone **Erectile dysfunction agents:** sildenafil, vardenafil **Gastrointestinal agents:** cimetidine, esomeprazole, famotidine, lansoprazole, nizatidine, omeprazole, pantoprazole, rabeprazole, ranitidine **Immunosuppressants:** cyclosporine, tacrolimus, rapamycin **Lipid-lowering agents:** atorvastatin **Oral contraceptives:** ethinyl estradiol/norethindrone **Steroids:** fluticasone

Norvir® (ritonavir, RTV)

Contraindications:	**Analgesics:** piroxicam **Antiarrhythmics:** amiodarone, bepridil, flecainide, propafenone, quinidine **Antifungals:** voriconazole **Antihistamines:** astemizole, terfenadine **Antimigraine agents:** dihydroergotamine, ergometrine (ergonovine), ergotamine **Antiprotozoals:** halofantrine, lumefantrine **Antipsychotics/neuroleptics:** pimozide **Anxiolytics/hypnotics/sedatives:** midazolam, triazolam **Gastrointestinal agents:** cisapride **Herbals/nutraceuticals:** St John's Wort **Lipid-lowering agents:** lovastatin, simvastatin
Potential interactions: ***(may require close monitoring, alteration of drug dosage, or timing of administration)***	**Analgesics:** alfentanyl, buprenorphine, dextropropoxyphene, diamorphine, fentanyl, ibuprofen, methadone, morphine, pethidine (meperidine), tramadol **Antiarrhythmics:** disopyramide, lidocaine (lignocaine), mexiletine **Antibacterials:** azithromycin, clarithromycin, clindamycin, erythromycin, metronidazole, rifabutin, rifampicin, rifapentine **Anticonvulsants:** carbamazepine, clonazepam, ethosuximide, lamotrigine, phenobarbital (phenobarbitone), phenytoin, valproate **Antidepressants:** amitriptyline, buproprion, citalopram, desipramine, doxepin, fluoxetine, mirtazapine, nefazodone, nortriptyline, paroxetine, sertraline **Antifungals:** caspofungin, itraconazole, ketoconazole, miconazole **Antihistamines:** fexofenadine, loratadine **Antineoplastics:** cyclophosphamide, paclitaxel, vinblastine, vincristine **Anti-emetics:** dronabinol **Anti-platelet and anticoagulants:** warfarin **Antiprotozoals:** atovaquone, chloroquine, pentamidine, proguanil, pyrimethamine, quinine, sulfadoxine/pyrimethamine, artemisinins, mefloquine **Antipsychotics/neuroleptics:** chlorpromazine, clozapine, haloperidol, olanzapine, perphenazine, risperidone, thioridazine **Antiretrovirals (NNRTIs):** delavirdine, efavirenz **Antiretrovirals (NRTIs):** didanosine, tenofovir **Antiretrovirals (PIs):** atazanavir, darunavir, fosamprenavir, indinavir, lopinavir, nelfinavir, saquinavir, tipranavir **Anxiolytics/hypnotics/sedatives:** alprazolam, clorazepate, diazepam, estazolam, flurazepam, zolpidem **Beta blockers:** atenolol, bisoprolol, carvedilol, metoprolol, propranolol **Bronchodilators:** theophylline **Calcium channel antagonists:** amlodipine, diltiazem, nicardipine, nifedipine, nisoldipine, verapamil **Erectile dysfunctional agents:** apomorphine, sildenafil, tadalafil, vardenafil **Gastrointestinal agents:** dronabinol, lansoprazole, loperamide, prochiorperazine **Herbals/nutraceuticals:** echinacea, garlic, milk thistle **Illicit/recreational:** gamma-hydroxybutyrate (GHB), marijuana, MDMA (Ecstasy), methamphetamine **Immunosuppressants:** ciclosporin, sirolimus, tacrolimus **Lipid-lowering agents:** atorvastatin, rosurastatin **Oral anti-diabetics:** glipizide, tolbutamide **Steroids:** budesonide, dexamethasone, ethinylestradiol, fluticasone, prednisolone, progesterone/progestogen, stanazolol, testosterone

Prezista™ (darunavir, DRV)	**Contraindications:**	**Antiarrhythmics:** amiodarone, bepridil, flecainide, lidocaine, propafenone, quinidine **Antibacterials:** rifampicin **Anticonvulsants:** carbamazepine, phenobarbital, phenytoin **Antihistamines:** astemizole, terfenadine **Antimigraines:** ergotamine & ergot derivatives **Antiprotozoals:** halofantrine, lumefantrine **Antipsychotics/Neuroleptics:** pimozide **Antiretrovirals (PIs):** lopinavir, saquinavir **Anxiolytics/Hypnotics/Sedatives:** midazolam, triazolam **Gastrointestinal Agents:** cisapride **Herbals/Nutraceuticals:** St John's Wort **Lipid Lowering Agents:** lovastatin, simvastatin
	Potential interactions: ***(may require close monitoring, alteration of drug dosage, or timing of administration)***	**Antiarrhythmics:** disopyramide, mexiletine **Antibacterials:** azithromycin, clarithromycin, erythromycin, metronidazole, rifabutin, rifapentine **Anticonvulsants:** clonazepam, ethosuximide **Antidepressants:** amitriptyline, bupropion, citalopram, desipramine, doxepin, fluoxetine, mirtazapine, nefazodone, nortriptyline, paroxetine, sertraline **Antifungals:** caspofungin, itraconazole, ketoconazole, miconazole, voriconazole **Antihistamines:** fexofenadine, loratadine **Antineoplastics:** cyclophosphamide, paclitaxel, vinblastine, vincristine **Antiplatelet and Anticoagulant:** warfarin **Antiprotozoals:** artemisinis, atovaquone, mefloquine, pyrimethamine, artemiginins, mefloquine
Reyataz® (atazanavir, ATV)	**Contraindications:**	**Antiarrhythmics:** bepridil, flecainide, quinidine, propafenone **Antibacterials:** rifampicin **Antihistamines:** astemizole, terfenadine **Antimigraine agents:** dihydroergotamine, ergometrine (ergonovine), ergotamine **Antiprotozoals:** halofantrine, lumefantrine **Antipsychotics/neuroleptics:** pimozide **Anxiolytics/hypnotics/sedatives:** midazolam, triazolam **Antiretrovirals (PIs):** indinavir **Gastrointestinal agents:** cisapride, lansoprazole, omeprazole **Herbals/nutraceuticals:** St John's Wort **Lipid-lowering agents:** lovastatin, simvastatin
	Potential interactions: ***(may require close monitoring, alteration of drug dosage, or timing of administration)***	**Analgesics:** alfentanyl, buprenorphine, dextropropoxyphene, diamorphine, fentanyl, methadone, morphine, pethidine (meperidine), piroxicam, tramadol **Antiarrhythmics:** disopyamide, lidocaine (lignocaine), mexiletine **Antibacterials:** rifabutin, rifapentine, clarithromcin, metronidazole **Anticonvulsants:** carbamazepine, clonazepam, ethosuximide, phenobarbital (phenobarbitone), phenytoin, valproate, lamotrigne **Antidepressants:** buproprion, citalopram, doxepin, mirtazapine, nefazodone, sertraline **Antifungals:** voriconazole, caspofungin, itraconazole, ketoconazole, miconazole **Antihistamines:** loratadine, fexofenadrine **Antineoplastics:** cyclophosphamide, paclitaxel, vinblastine, vincristine **Anti-emetics:** dronabinol **Anti-platelet and anticoagulants:** warfarin **Antiprotozoals:** artemisinins, atoraquone, mefloquine, quinine **Antipsychotics/neuroleptics:** chlorpromazine, olanzapine, clozapine, haloperidol **Antiretrovirals (NNRTIs):** delavirdine, efavirenz, nevirapine **Antiretrovirals (NRTIs):** didanosine, tenofovir **Antiretrovirals (PIs):** amprenavir, indinavir, lopinavir, ritonavir, tipranavir, nelfinavir, saquinavir **Anxiolytics/hypnotics/sedatives:** alprazolam, clorazepate, diazepam, estazolam, flurazepam, zolpidem **Beta blockers:** carvedilol, atenolol, bisoprolol, metoprolol, propranolol **Bronchodilators:** theophylline **Calcium channel antagonists:** amlodipine, diltiazem, nicardipine, nifedipine, nisoldipine, verapamil **Erectile dysfunctional agents:** apomorphine, sildenafil, tadalafil, vardenafil **Gastrointestinal agents:** dronabinol, antacids, cimetidine, famotidine, loperamide, ranitidine **Herbals/nutraceuticals:** echinacea, garlic, milk thistle **Illicit/recreational:** gamma-hydroxybutyrate (GHB), MDMA (Ecstasy), methamphetamine, marijuana **Immunosuppressants:** ciclosporin, sirolimus, tacrolimus **Lipid-lowering agents:** atorvastatin, rosurastatin **Oral anti-diabetics:** glipizide, tolbutamide **Steroids:** budesonide, dexamethasone, ethinylestradiol, fluticasone, prednisolone, progesterone/progestogen, stanazolol, testosterone

PI DRUG INTERACTIONS

Viracept® (nelfinavir, NFV)

Contraindications:	**Antiarrhythmics:** amiodarone, quinidine **Antibacterials:** rifampicin **Antihistamines:** astemizole, terfenadine **Antimigraine agents:** dihydroergotamine, ergometrine (ergonovine), ergotamine **Antiprotozoals:** halofantrine, lumefantrine **Antipsychotics/neuroleptics:** pimozide **Anxiolytics/hypnotics/sedatives:** midazolam, triazolam **Gastrointestinal agents:** cisapride, lansoprazole, omeprazole **Herbals/nutraceuticals:** St John's Wort **Lipid-lowering agents:** lovastatin, simvastatin
Potential interactions: ***(may require close monitoring, alteration of drug dosage, or timing of administration)***	**Analgesics:** alfentanyl, buprenorphine, dextropropoxyphene, diamorphine, fentanyl, methadone, morphine, pethidine (meperidine), piroxicam, tramadol **Antiarrhythmics:** bepridil, disopyamide, flecainide, lidocaine (lignocaine), mexiletine, propafenone **Antibacterials:** rifabutin, rifapentine **Anticonvulsants:** carbamazepine, clonazepam, ethosuximide, phenobarbital (phenobarbitone), phenytoin, valproate **Antidepressants:** buproprion, citalopram, doxepin, mirtazapine, nefazodone, sertraline **Antifungals:** voriconazole **Antihistamines:** loratadine **Antineoplastics:** cyclophosphamide, paclitaxel, vinblastine, vincristine **Anti-emetics:** dronabinol **Anti-platelet and anticoagulant:** warfarin **Antiprotozoals:** quinine, artemisinins, mefloquine **Antipsychotics/neuroleptics:** chlorpromazine, olanzapine. clozapine, haloperidol **Antiretrovirals (NNRTIs):** delavirdine, efavirenz, nevirapine **Antiretrovirals (NRTIs):** didanosine, tenofovir **Antiretrovirals (PIs):** atazanavir, darunavir, indinavir, lopinavir, ritonavir, tipranavir **Anxiolytics/hypnotics/sedatives:** alprazolam, clorazepate, diazepam, estazolam, flurazepam, zolpidem **Beta blockers:** carvedilol **Calcium channel antagonists:** amlodipine, diltiazem, nicardipine, nifedipine, nisoldipine, verapamil **Erectile dysfunctional agents:** apomorphine, sildenafil, tadalafil, vardenafil **Gastrointestinal agents:** dronabinol **Herbals/nutraceuticals:** echinacea, garlic, milk thistle **Illicit/recreational:** gamma-hydroxybutyrate (GHB), MDMA (Ecstasy), methamphetamine **Immunosuppressants:** ciclosporin, sirolimus, tacrolimus **Lipid-lowering agents:** atorvastatin **Oral anti-diabetic:** glipizide, tolbutamide **Steroids:** budesonide, dexamethasone, ethinylestradiol, fluticasone, prednisolone, progesterone/progestogen, stanazolol, testosterone

FUSION INHIBITOR DRUG INTERACTIONS

Fuzeon® (enfuvirtide, ENF)

Contraindications:	**Antibiotics:** rifampin **Antiretrovirals (PIs):** ritonavir, saquinavir
Potential interactions: ***(may require close monitoring, alteration of drug dosage, or timing of administration)***	**See enfuvirtide package insert**

CCR5 ANTAGONIST DRUG INTERACTIONS

Selzentry™ (maraviroc, MRV)

Contraindications:	**Antibacterials:** rifampicin + efavirenz **Herbals/nutraceuticals:** St John's Wort
Potential interactions: ***(may require close monitoring, alteration of drug dosage, or timing of administration)***	**Antibacterials:** clarithromycin, rifabutin + pi, rifampicin **Anticonvulsants:** clonazepam, phenobarbital, phenytoin **Antidepressants:** nefazodone **Antifungals:** itraconazole, ketoconazole **Antiretrovirals (NNRTIs):** delavirdine, efavirenz, efavirenz + atazanivir/r, efavirenz + darunavir/r, efavirenz + lopinavir/r, efavirenz + saquinavir/r **Antiretrovirals (PIs):** atazanavir, atazanavir/r, darunavir/r, indinavir, nelfinavir, ritonavir, saquinavir, saquinavir/r

ATRIPLA™

℞ ONLY

(efavirenz 600 mg/emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg) Tablets

Brief Summary of Prescribing Information, 07/06. For complete prescribing information, please consult official package circular.

WARNING

LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY WITH STEATOSIS, INCLUDING FATAL CASES, HAVE BEEN REPORTED WITH THE USE OF NUCLEOSIDE ANALOGS ALONE OR IN COMBINATION WITH OTHER ANTIRETROVIRALS (SEE WARNINGS).

ATRIPLA IS NOT INDICATED FOR THE TREATMENT OF CHRONIC HEPATITIS B VIRUS (HBV) INFECTION AND THE SAFETY AND EFFICACY OF ATRIPLA HAVE NOT BEEN ESTABLISHED IN PATIENTS COINFECTED WITH HBV AND HIV. SEVERE ACUTE EXACERBATIONS OF HEPATITIS B HAVE BEEN REPORTED IN PATIENTS WHO HAVE DISCONTINUED EMTRIVA® OR VIREAD®. HEPATIC FUNCTION SHOULD BE MONITORED CLOSELY WITH BOTH CLINICAL AND LABORATORY FOLLOW-UP FOR AT LEAST SEVERAL MONTHS IN PATIENTS WHO DISCONTINUE ATRIPLA AND ARE COINFECTED WITH HIV AND HBV. IF APPROPRIATE, INITIATION OF ANTI-HEPATITIS B THERAPY MAY BE WARRANTED (SEE WARNINGS).

CONTRAINDICATIONS

ATRIPLA™ (efavirenz 600 mg/emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg) is contraindicated in patients with previously demonstrated hypersensitivity to any of the components of the product.

ATRIPLA should not be administered concurrently with astemizole, cisapride, midazolam, triazolam, or ergot derivatives because competition for CYP3A4 by efavirenz could result in inhibition of metabolism of these drugs and create the potential for serious and/or life-threatening adverse events (eg, cardiac arrhythmias, prolonged sedation, or respiratory depression). ATRIPLA should not be administered concurrently with voriconazole because efavirenz significantly decreases voriconazole plasma concentrations **(see CLINICAL PHARMACOLOGY** in Full Prescribing Information **and PRECAUTIONS, Drug Interactions)**.

WARNINGS

Lactic Acidosis/Severe Hepatomegaly with Steatosis

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs alone or in combination with other antiretrovirals. A majority of these cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors. Particular caution should be exercised when administering nucleoside analogs to any patient with known risk factors for liver disease; however, cases have also been reported in patients with no known risk factors. Treatment with ATRIPLA should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

Patients with HIV and HBV Coinfection

It is recommended that all patients with HIV be tested for the presence of HBV before initiating antiretroviral therapy. ATRIPLA is not indicated for the treatment of chronic HBV infection and the safety and efficacy of ATRIPLA have not been established in patients co-infected with HBV and HIV. Severe acute exacerbations of hepatitis B have been reported in patients after the discontinuation of EMTRIVA and VIREAD. Hepatic function should be closely monitored with both clinical and laboratory follow up for at least several months in patients who discontinue ATRIPLA and are coinfected with HIV and HBV. If appropriate, initiation of anti-hepatitis B therapy may be warranted.

ALERT: Find out about medicines that should NOT be taken with ATRIPLA. This statement is also included on the product's bottle labels **(see CONTRAINDICATIONS and PRECAUTIONS, Drug Interactions)**.

Coadministration with Related Drugs

Related drugs not for coadministration with ATRIPLA include EMTRIVA (emtricitabine), VIREAD (tenofovir DF), TRUVADA (emtricitabine/tenofovir DF), and SUSTIVA® (efavirenz), which contain the same active components as ATRIPLA. Due to similarities between emtricitabine and lamivudine, ATRIPLA should not be coadministered with drugs containing lamivudine, including COMBIVIR®, EPIVIR®, EPIVIR-HBV®, EPZICOM™, or TRIZIVIR®.

Drug Interactions (see CONTRAINDICATIONS, CLINICAL PHARMACOLOGY, Drug Interactions, in Full Prescribing Information **and PRECAUTIONS, Drug Interactions)**

Concomitant use of ATRIPLA and St. John's wort *(Hypericum perforatum)* or St. John's wort-containing products is not recommended. Coadministration of NNRTIs, including efavirenz, with St. John's wort is expected to substantially decrease NNRTI concentrations and may result in suboptimal levels of efavirenz and lead to loss of virologic response and possible resistance to efavirenz or to the class of NNRTIs.

Psychiatric Symptoms

Serious psychiatric adverse experiences have been reported in patients treated with efavirenz. In controlled trials of 1008 patients treated with regimens containing efavirenz for a mean of 2.1 years and 635 patients treated with control regimens for a mean of 1.5 years, the frequency of specific serious psychiatric events among patients who received efavirenz or control regimens, respectively, were: severe depression (2.4%, 0.9%), suicidal ideation (0.7%, 0.3%), nonfatal suicide attempts (0.5%, 0%), aggressive behavior (0.4%, 0.5%), paranoid reactions (0.4%, 0.3%), and manic reactions (0.2%, 0.3%). When psychiatric symptoms similar to those noted above were combined and evaluated as a group in a multifactorial analysis of data from Study AI266006 (006), treatment with efavirenz was associated with an increase in the occurrence of these selected psychiatric symptoms. Other factors associated with an increase in the occurrence of these psychiatric symptoms were history of injection drug use, psychiatric history, and receipt of psychiatric medication at study entry; similar associations were observed in both the efavirenz and control treatment groups. In Study 006, onset of new serious psychiatric symptoms occurred throughout the study for both efavirenz-treated and control-treated patients. One percent of efavirenz-treated patients discontinued or interrupted treatment because of one or more of these selected psychiatric symptoms. There have also been occasional postmarketing reports of death by suicide, delusions, and psychosis-like behavior, although a causal relationship to the use of efavirenz cannot be determined from these reports. Patients with serious psychiatric adverse experiences should seek immediate medical evaluation to assess the possibility that the symptoms may be related to the use of efavirenz, and if so, to determine whether the risks of continued therapy outweigh the benefits **(see ADVERSE REACTIONS)**.

Nervous System Symptoms

Fifty-three percent of patients receiving efavirenz in controlled trials reported central nervous system symptoms compared to 25% of patients receiving control regimens. These symptoms included dizziness (28.1%), insomnia (16.3%), impaired concentration (8.3%), somnolence (7.0%), abnormal dreams (6.2%), and hallucinations (1.2%). Other reported symptoms were euphoria, confusion, agitation, amnesia, stupor, abnormal thinking, and depersonalization. The majority of these symptoms were mild-moderate (50.7%); symptoms were severe in 2.0% of patients. Overall, 2.1% of patients discontinued therapy as a result. These symptoms usually begin during the first or second day of therapy and generally resolve after the first 2–4 weeks of therapy. After 4 weeks of therapy, the prevalence of nervous system symptoms of at least moderate severity ranged from 5% to 9% in patients treated with regimens containing efavirenz and from 3% to 5% in patients treated with a control regimen. Patients should be informed that these common symptoms were likely to improve with continued therapy and were not predictive of subsequent onset of the less frequent psychiatric symptoms **(see WARNINGS, Psychiatric Symptoms)**. Dosing at bedtime may improve the tolerability of these nervous system symptoms **(see ADVERSE REACTIONS, and DOSAGE AND ADMINISTRATION** in Full Prescribing Information**)**.

Analysis of long-term data from Study 006, (median follow-up 180 weeks, 102 weeks, and 76 weeks for patients treated with efavirenz + zidovudine + lamivudine, efavirenz + indinavir, and indinavir + zidovudine + lamivudine, respectively) showed that, beyond 24 weeks of therapy, the incidences of new-onset nervous system symptoms among efavirenz-treated patients were generally similar to those in the indinavir-containing control arm.

Patients receiving ATRIPLA (efavirenz 600 mg/emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg) should be alerted to the potential for additive central nervous system effects when ATRIPLA is used concomitantly with alcohol or psychoactive drugs.

Patients who experience central nervous system symptoms such as dizziness, impaired concentration, and/or drowsiness should avoid potentially hazardous tasks such as driving or operating machinery.

Renal Impairment

Emtricitabine and tenofovir are principally eliminated by the kidney, however efavirenz is not. Since ATRIPLA is a combination product and the dose of the individual components cannot be altered, patients with creatinine clearance <50 mL/min should not receive ATRIPLA.

Renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphatemia), has been reported in association with the use of tenofovir DF **(see ADVERSE REACTIONS, Post Marketing Experience)**. The majority of these cases occurred in patients with underlying systemic or renal disease, or in patients taking nephrotoxic agents; however, some cases occurred in patients without identified risk factors.

ATRIPLA (efavirenz 600 mg/emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg) should be avoided with concurrent or recent use of a nephrotoxic agent. Patients at risk for, or with a history of, renal dysfunction and patients receiving concomitant nephrotoxic agents should be carefully monitored for changes in serum creatinine and phosphorus.

Reproductive Risk Potential

Pregnancy Category D: Efavirenz may cause fetal harm when administered during the first trimester to a pregnant woman. Pregnancy should be avoided in women receiving ATRIPLA. Barrier contraception should always be used in combination with other methods of contraception (eg, oral or other hormonal contraceptives). Women of childbearing potential should undergo pregnancy testing before initiation of ATRIPLA. If this drug is used during the first trimester of pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential harm to the fetus.

There are no adequate and well-controlled studies of ATRIPLA in pregnant women. ATRIPLA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus, such as in pregnant women without other therapeutic options.

Antiretroviral Pregnancy Registry: To monitor fetal outcomes of pregnant women, an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients who become pregnant by calling (800) 258-4263.

Efavirenz: As of July 2005, the Antiretroviral Pregnancy Registry has received prospective reports of 282 pregnancies exposed to efavirenz-containing regimens, nearly all of which were first-trimester exposures (277 pregnancies). Birth defects occurred in 5 of 228 live births (first-trimester exposure) and 1 of 14 live births (second/third-trimester exposure). None of these prospectively reported defects were neural tube defects. However, there have been four retrospective reports of findings consistent with neural tube defects, including meningomyelocele. All mothers were exposed to efavirenz-containing regimens in the first trimester. Although a causal relationship of these events to the use of efavirenz has not been established, similar defects have been observed in preclinical studies of efavirenz.

Animal toxicology: Malformations have been observed in 3 of 20 fetuses/infants from efavirenz-treated cynomolgus monkeys (versus 0 of 20 concomitant controls) in a developmental toxicity study. The pregnant monkeys were dosed throughout pregnancy (postcoital days 20–150) with efavirenz 60 mg/kg daily, a dose which resulted in plasma drug concentrations similar to those in humans given 600 mg/day of efavirenz. Anencephaly and unilateral anophthalmia were observed in one fetus, microophthalmia was observed in another fetus, and cleft palate was observed in a third fetus. Efavirenz crosses the placenta in cynomolgus monkeys and produces fetal blood concentrations similar to maternal blood concentrations. Efavirenz has been shown to cross the placenta in rats and rabbits and produces fetal blood concentrations of efavirenz similar to maternal concentrations. An increase in fetal resorptions was observed in rats at efavirenz doses that produced peak plasma concentrations and AUC values in female rats equivalent to or lower than those achieved in humans given 600 mg once daily of efavirenz. Efavirenz produced no reproductive toxicities when given to pregnant rabbits at doses that produced peak plasma concentrations similar to and AUC values approximately half of those achieved in humans given 600 mg once daily of efavirenz.

PRECAUTIONS

Skin Rash

In controlled clinical trials, 26% (266/1008) of patients treated with 600 mg efavirenz experienced new-onset skin rash compared with 17% (111/635) of patients treated in control groups. Rash associated with blistering, moist desquamation, or ulceration occurred in 0.9% (9/1008) of patients treated with efavirenz. The incidence of Grade 4 rash (eg, erythema multiforme, Stevens-Johnson syndrome) in patients treated with efavirenz in all studies and expanded access was 0.1%. Rashes are usually mild-to-moderate maculopapular skin eruptions that occur within the first 2 weeks of initiating therapy with efavirenz (median time to onset of rash in adults was 11 days) and, in most patients continuing therapy with efavirenz, rash resolves within 1 month (median duration, 16 days). The discontinuation rate for rash in clinical trials was 1.7% (17/1008). ATRIPLA can be reinitiated in patients interrupting therapy because of rash. ATRIPLA should be discontinued in patients developing severe rash associated with blistering, desquamation, mucosal involvement, or fever. Appropriate antihistamines and/or corticosteroids may improve the tolerability and hasten the resolution of rash.

Experience with efavirenz in patients who discontinued other antiretroviral agents of the NNRTI class is limited. Nineteen patients who discontinued nevirapine because of rash have been treated with efavirenz. Nine of these patients developed mild-to-moderate rash while receiving therapy with efavirenz, and two of these patients discontinued because of rash.

Liver Enzymes

In patients with known or suspected history of hepatitis B or C infection and in patients treated with other medications associated with liver toxicity, monitoring of liver enzymes is recommended **(see WARNINGS, Patients with HIV and HBV Coinfection)**. In patients with persistent elevations of serum transaminases to greater than five times the upper limit of the normal range, the benefit of continued therapy with ATRIPLA needs to be weighed against the unknown risks of significant liver toxicity **(see ADVERSE REACTIONS, Laboratory Abnormalities)**.

Because of the extensive cytochrome P450 mediated metabolism of efavirenz and limited clinical experience in patients with hepatic impairment, caution should be exercised in administering ATRIPLA to these patients.

Bone Effects

In a 144-week study of treatment-naïve patients, decreases in bone mineral density (BMD) were seen at the lumbar spine and hip in both arms of the study. At Week 144, there was a significantly greater mean percentage decrease from baseline in BMD at the lumbar spine in patients receiving tenofovir DF + lamivudine + efavirenz compared with patients receiving stavudine + lamivudine + efavirenz. Changes in BMD at the hip were similar between the two treatment groups. In both groups, the majority of the reduction in BMD occurred in the first 24–48 weeks of the study and this reduction was sustained through 144 weeks. Twenty-eight percent of tenofovir DF treated patients vs. 21% of the comparator patients lost at least 5% of BMD at the spine or 7% of BMD at the hip. Clinically relevant fractures (excluding fingers and toes) were reported in 4 patients in the tenofovir DF group and 6 patients in the comparator group. Tenofovir DF was associated with significant increases in biochemical markers of bone metabolism (serum bone-specific alkaline phosphatase, serum osteocalcin, serum C-telopeptide, and urinary N-telopeptide), suggesting increased bone turnover. Serum parathyroid hormone levels and 1,25 vitamin D levels were also higher in patients receiving tenofovir DF. The effects of tenofovir DF associated changes in BMD and biochemical markers on long-term bone health and future fracture risk are unknown. For additional information, please consult the tenofovir DF prescribing information.

Bone monitoring should be considered for HIV infected patients who have a history of pathologic bone fracture or are at risk for osteopenia. Although the effect of supplementation with calcium and vitamin D was not studied, such supplementation may be beneficial for all patients. If bone abnormalities are suspected then appropriate consultation should be obtained.

Convulsions

Convulsions have been observed in patients receiving efavirenz, generally in the presence of known medical history of seizures. Caution must be taken in any patient with a history of seizures.

Patients who are receiving concomitant anticonvulsant medications primarily metabolized by the liver, such as phenytoin and phenobarbital, may require periodic monitoring of plasma levels **(see PRECAUTIONS, Drug Interactions)**.

Animal toxicology: Nonsustained convulsions were observed in 6 of 20 monkeys receiving efavirenz at doses yielding plasma AUC values 4- to 13-fold greater than those in humans given the recommended dose.

Fat Redistribution

Redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and "cushingoid appearance" have been observed in patients receiving antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including the components of ATRIPLA (efavirenz 600 mg/emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg). During the initial phase of combination antiretroviral treatment, patients whose immune system responds may develop an inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis jiroveci* pneumonia (PCP), or tuberculosis), which may necessitate further evaluation and treatment.

Information for Patients

A statement to patients and healthcare providers is included on the product's bottle labels: **ALERT: Find out about medicines that should NOT be taken with ATRIPLA.** A Patient Package Insert (PPI) for ATRIPLA is available for patient information.

ATRIPLA is not a cure for HIV infection and patients may continue to experience illnesses associated with HIV infection, including opportunistic infections. Patients should remain under the care of a physician when using ATRIPLA.

Patients should be advised that:

- the use of ATRIPLA (efavirenz 600 mg/emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg) has not been shown to reduce the risk of transmission of HIV to others through sexual contact or blood contamination,
- the long term effects of ATRIPLA are unknown,
- ATRIPLA Tablets are for oral ingestion only,
- it is important to take ATRIPLA on a regular dosing schedule to avoid missing doses,
- redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy and that the cause and long-term health effects of these conditions are not known.
- ATRIPLA should not be coadministered with SUSTIVA, EMTRIVA, VIREAD, or TRUVADA, or drugs containing lamivudine, including COMBIVIR, EPIVIR, EPIVIR-HBV, EPZICOM, or TRIZIVIR.

Patients should be advised to take ATRIPLA on an empty stomach.

Patients should be informed that central nervous system symptoms including dizziness, insomnia, impaired concentration, drowsiness, and abnormal dreams are commonly reported during the first weeks of therapy with efavirenz. Dosing at bedtime may improve the tolerability of these symptoms, and these symptoms are likely to improve with continued therapy. Patients should be alerted to the potential for additive central nervous system effects when ATRIPLA is used concomitantly with alcohol or psychoactive drugs. Patients should be instructed that if they experience these symptoms they should avoid potentially hazardous tasks such as driving or operating machinery **(see WARNINGS, Nervous System Symptoms, ADVERSE REACTIONS, and DOSAGE AND ADMINISTRATION** in Full Prescribing Information**)**. In clinical trials, patients who develop central nervous system symptoms were not more likely to subsequently develop psychiatric symptoms **(see WARNINGS, Psychiatric Symptoms)**.

Patients should also be informed that serious psychiatric symptoms including severe depression, suicide attempts, aggressive behavior, delusions, paranoia, and psychosis-like symptoms have also been reported in patients receiving efavirenz. Patients should be informed that if they experience severe psychiatric adverse experiences they should seek immediate medical evaluation to assess the possibility that the symptoms may be related to the use of ATRIPLA, and if so, to determine whether discontinuation of ATRIPLA may be required. Patients should also inform their physician of any history of mental illness or substance abuse **(see WARNINGS, Psychiatric Symptoms).**

Patients should be informed that another common side effect is rash. These rashes usually go away without any change in treatment. In a small number of patients, rash may be serious. Patients should be advised that they should contact their physician promptly if they develop a rash.

Women receiving ATRIPLA should be instructed to avoid pregnancy **(see WARNINGS, Reproductive Risk Potential)**. A reliable form of barrier contraception should always be used in combination with other methods of contraception, including oral or other hormonal contraception, because the effects of efavirenz on hormonal contraceptives are not fully characterized. Women should be advised to notify their physician if they become pregnant or plan to become pregnant while taking ATRIPLA. If this drug is used during the first trimester of pregnancy, or if the patient becomes pregnant while taking this drug, she should be apprised of the potential harm to the fetus.

ATRIPLA may interact with some drugs; therefore, patients should be advised to report to their doctor the use of any other prescription, nonprescription medication, or herbal products, particularly St. John's wort.

Animal Toxicology

Tenofovir and tenofovir DF administered in toxicology studies to rats, dogs and monkeys at exposures (based on AUCs) greater than or equal to 6-fold those observed in humans caused bone toxicity. In monkeys the bone toxicity was diagnosed as osteomalacia. Osteomalacia observed in monkeys appeared to be reversible upon dose reduction or discontinuation of tenofovir. In rats and dogs, the bone toxicity manifested as reduced bone mineral density. The mechanism(s) underlying bone toxicity is unknown.

Evidence of renal toxicity was noted in 4 animal species administered tenofovir and tenofovir DF. Increases in serum creatinine, BUN, glycosuria, proteinuria, phosphaturia and/or calciuria and decreases in serum phosphate were observed to varying degrees in these animals. These toxicities were noted at exposures (based on AUCs) 2–20 times higher than those observed in humans. The relationship of the renal abnormalities, particularly the phosphaturia, to the bone toxicity is not known.

Drug Interactions (see CONTRAINDICATIONS and CLINICAL PHARMACOLOGY, Drug Interactions in Full Prescribing Information**)**

Efavirenz: Efavirenz has been shown *in vivo* to induce CYP3A4. Other compounds that are substrates of CYP3A4 may have decreased plasma concentrations when coadministered with efavirenz. *In vitro* studies have demonstrated that efavirenz inhibits 2C9, 2C19, and 3A4 isozymes in the range of observed efavirenz plasma concentrations. Coadministration of efavirenz with drugs primarily metabolized by these isozymes may result in altered plasma concentrations of the coadministered drug. Therefore, appropriate dose adjustments may be necessary for these drugs.

Drugs which induce CYP3A4 activity (eg, phenobarbital, rifampin, rifabutin) would be expected to increase the clearance of efavirenz resulting in lowered plasma concentrations.

Emtricitabine and tenofovir disoproxil fumarate: Since emtricitabine and tenofovir are primarily eliminated by the kidneys, coadministration of ATRIPLA with drugs that reduce renal function or compete for active tubular secretion may increase serum concentrations of emtricitabine, tenofovir, and/or other renally eliminated drugs. Some examples include, but are not limited to, adefovir dipivoxil, cidofovir, acyclovir, valacyclovir, ganciclovir, and valganciclovir.

Coadministration of tenofovir DF and didanosine should be undertaken with caution and patients receiving this combination should be monitored closely for didanosine-associated adverse events. Didanosine should be discontinued in patients who develop didanosine-associated adverse events (for didanosine dosing adjustment recommendations, **see Table 2 in the PRECAUTIONS Section**).

Atazanavir and lopinavir/ritonavir have been shown to increase tenofovir concentrations. The mechanism of this interaction is unknown. Higher tenofovir concentrations could potentiate tenofovir-associated adverse events, including renal disorders. Patients receiving either atazanavir or lopinavir/ritonavir with tenofovir DF should be monitored for tenofovir-associated adverse events. ATRIPLA should be discontinued in patients who develop tenofovir-associated adverse events (for atazanavir dosing adjustment recommendations, **see Table 2 in the PRECAUTIONS Section**).

Other important drug interaction information for ATRIPLA (efavirenz 600 mg/emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg) is summarized in Table 1 and 2. The drug interactions described are based on studies conducted with efavirenz, emtricitabine or tenofovir DF as individual agents or are potential drug interactions; no drug interaction studies have been conducted using ATRIPLA. The tables include potentially significant interactions, but are not all inclusive.

Table 1 Drugs That Are Contraindicated or Not Recommended for Use With ATRIPLA

Drug Class: Drug Name	Clinical Comment
Antifungal: voriconazole	CONTRAINDICATED because efavirenz significantly decreases voriconazole plasma concentrations, and coadministration may decrease the therapeutic effectiveness of voriconazole. Also, voriconazole significantly increases efavirenz plasma concentrations, which may increase the risk of efavirenz-associated side effects. See Tables 1 and 2 in Full Prescribing Information.
Antihistamine: astemizole	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Antimigraine: ergot derivatives (dihydroergotamine, ergonovine, ergotamine, methylergonovine)	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as acute ergot toxicity characterized by peripheral vasospasm and ischemia of the extremities and other tissues.
Antiretrovirals: EMTRIVA, VIREAD, TRUVADA, SUSTIVA, COMBIVIR, EPIVIR, EPIVIR-HBV, EPZICOM, TRIZIVIR	Not for use with ATRIPLA because the active ingredients of EMTRIVA (emtricitabine), VIREAD (tenofovir DF), TRUVADA (emtricitabine/tenofovir DF) and SUSTIVA (efavirenz) are components of ATRIPLA. Lamivudine, which is similar to emtricitabine, is a component of COMBIVIR, EPIVIR, EPIVIR-HBV, EPZICOM, and TRIZIVIR.
Benzodiazepines: midazolam, triazolam	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as prolonged or increased sedation or respiratory depression.
GI motility agent: cisapride	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
St. John's wort *(Hypericum perforatum)*	NOT RECOMMENDED: Expected to substantially decrease plasma levels of efavirenz; has not been studied in combination with efavirenz.

Table 2 Established[1] and Other Potentially Significant[2] Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction

Concomitant Drug Class: Drug Name	Effect	Clinical Comment
Antiretroviral agents		
Protease inhibitor: Amprenavir	↓ amprenavir concentration	Efavirenz has the potential to decrease serum concentrations of amprenavir.
Protease inhibitor: Fosamprenavir calcium	↓ amprenavir concentration	Fosamprenavir (unboosted): Appropriate doses of fosamprenavir and ATRIPLA (efavirenz 600 mg/emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg) with respect to safety and efficacy have not been established. Fosamprenavir/ritonavir: An additional 100 mg/day (300 mg total) of ritonavir is recommended when ATRIPLA is administered with fosamprenavir/ritonavir once daily. No change in the ritonavir dose is required when ATRIPLA is administered with fosamprenavir plus ritonavir twice daily.
Protease inhibitor: Atazanavir	↓ atazanavir concentration ↑ tenofovir concentration	Plasma concentrations of atazanavir were decreased by both efavirenz and tenofovir DF. Sufficient data are not available to make a dosing recommendation for atazanavir or atazanavir/ritonavir with ATRIPLA. Therefore, co-administration of ATRIPLA and atazanavir is not recommended due to concerns regarding decreased atazanavir concentrations.
Protease inhibitor: Indinavir	↓ indinavir concentration	The optimal dose of indinavir, when given in combination with efavirenz, is not known. Increasing the indinavir dose to 1000 mg every 8 hours does not compensate for the increased indinavir metabolism due to efavirenz.
Protease inhibitor: Lopinavir/ritonavir	↓ lopinavir concentration ↑ tenofovir concentration	A dose increase of lopinavir/ritonavir to 600/150 mg (3 tablets) twice daily may be considered when used in combination with efavirenz in treatment-experienced patients where decreased susceptibility to lopinavir is clinically suspected (by treatment history or laboratory evidence). **Patients should be monitored for tenofovir-associated adverse events. ATRIPLA should be discontinued in patients who develop tenofovir-associated adverse events.**
Protease inhibitor: Ritonavir	↑ ritonavir concentration ↑ efavirenz concentration	When ritonavir 500 mg every 12 hours was coadministered with efavirenz 600 mg once daily, the combination was associated with a higher frequency of adverse clinical experiences (eg, dizziness, nausea, paresthesia) and laboratory abnormalities (elevated liver enzymes). Monitoring of liver enzymes is recommended when ATRIPLA is used in combination with ritonavir.
Protease inhibitor: Saquinavir	↓ saquinavir concentration	Should not be used as sole protease inhibitor in combination with ATRIPLA.
NRTI: Didanosine	↑ didanosine concentration	Higher didanosine concentrations could potentiate didanosine-associated adverse events, including pancreatitis, and neuropathy. **In adults weighing >60 kg, the didanosine dose should be reduced to 250 mg if coadministered with ATRIPLA. Data are not available to recommend a dose adjustment of didanosine for patients weighing <60 kg.** When coadministered, ATRIPLA and VIDEX® EC may be taken under fasted conditions or with a light meal (<400 kcal, 20% fat). Coadministration of didanosine buffered formulation with ATRIPLA should be under fasted conditions. **Coadministration of ATRIPLA and didanosine should be undertaken with caution and patients receiving this combination should be monitored closely for didanosine-associated adverse events. For additional information, please consult the Videx /Videx EC (didanosine) prescribing information.**
Other agents		
Anticoagulant: Warfarin	↑ or ↓ warfarin concentration	Plasma concentrations and effects potentially increased or decreased by efavirenz.
Anticonvulsants: Carbamazepine	↓ carbamazepine concentration ↓ efavirenz concentration	There are insufficient data to make a dose recommendation for ATRIPLA (efavirenz 600 mg/emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg). Alternative anticonvulsant treatment should be used.
Phenytoin Phenobarbital	↓ anticonvulsant concentration ↓ efavirenz concentration	Potential for reduction in anticonvulsant and/or efavirenz plasma levels; periodic monitoring of anticonvulsant plasma levels should be conducted.
Antidepressant: Sertraline	↓ sertraline concentration	Increases in sertraline dose should be guided by clinical response.
Antifungals: Itraconazole Ketoconazole	↓ antifungal concentration	Drug interaction studies with ATRIPLA and these imidazole and triazole antifungals have not been conducted. Efavirenz has the potential to decrease plasma concentrations of itraconazole and ketoconazole.
Anti-infective: Clarithromycin	↓ clarithromycin concentration ↑ 14-OH metabolite concentration	Clinical significance unknown. In uninfected volunteers, 46% developed rash while receiving efavirenz and clarithromycin. No dose adjustment of ATRIPLA is recommended when given with clarithromycin. Alternatives to clarithromycin, such as azithromycin, should be considered. Other macrolide antibiotics, such as erythromycin, have not been studied in combination with ATRIPLA.
Antimycobacterial: Rifabutin	↓ rifabutin concentration	Increase daily dose of rifabutin by 50%. Consider doubling the rifabutin dose in regimens where rifabutin is given 2 or 3 times a week.
Antimycobacterial: Rifampin	↓ efavirenz concentration	Clinical significance of reduced efavirenz concentrations is unknown.
HMG-CoA reductase inhibitors: Atorvastatin Pravastatin Simvastatin	↓ atorvastatin concentration ↓ pravastatin concentration ↓ simvastatin concentration	Plasma concentrations of atorvastatin, pravastatin, and simvastatin decreased with efavirenz. Consult the complete prescribing information for the HMG-CoA reductase inhibitor for guidance on individualizing the dose.
Narcotic analgesic: Methadone	↓ methadone concentration	Coadministration of efavirenz in HIV-infected individuals with a history of injection drug use resulted in decreased plasma levels of methadone and signs of opiate withdrawal. Methadone dose was increased by a mean of 22% to alleviate withdrawal symptoms. Patients should be monitored for signs of withdrawal and their methadone dose increased as required to alleviate withdrawal symptoms.
Oral contraceptive: Ethinyl estradiol	↑ ethinyl estradiol concentration	Clinical significance unknown. Because the potential interaction of efavirenz with oral contraceptives has not been fully characterized, a reliable method of barrier contraception should be used in addition to oral contraceptives.

1. See Tables 1–5 in Full Prescribing Information.
2. This table is not all inclusive.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Efavirenz: Long-term carcinogenicity studies in mice and rats were carried out with efavirenz. Mice were dosed with 0, 25, 75, 150, or 300 mg/kg/day for 2 years. Incidences of hepatocellular adenomas and carcinomas and pulmonary alveolar/bronchiolar adenomas were increased above background in females. No increases in tumor incidence above background were seen in males. In studies in which rats were administered efavirenz at doses of 0, 25, 50, or 100 mg/kg/day for 2 years, no increases in tumor incidence above background were observed. The systemic exposure (based on AUCs) in mice was approximately 1.7-fold that in humans receiving the 600-mg/day dose. The exposure in rats was lower than that in humans. The mechanism of the carcinogenic potential is unknown. However, in genetic toxicology assays, efavirenz showed no evidence of mutagenic or clastogenic activity in a battery of *in vitro* and *in vivo* studies. These included bacterial mutation assays in *S. typhimurium* and *E. coli*, mammalian mutation assays in Chinese hamster ovary cells, chromosome aberration assays in human peripheral blood lymphocytes or Chinese hamster ovary cells, and an *in vivo* mouse bone marrow micronucleus assay. Given the lack of genotoxic activity of efavirenz, the relevance to humans of neoplasms in efavirenz-treated mice is not known.

Efavirenz did not impair mating or fertility of male or female rats, and did not affect sperm of treated male rats. The reproductive performance of offspring born to female rats given efavirenz was not affected. As a result of the rapid clearance of efavirenz in rats, systemic drug exposures achieved in these studies were equivalent to or below those achieved in humans given therapeutic doses of efavirenz.

Emtricitabine: In long-term carcinogenicity studies of emtricitabine, no drug-related increases in tumor incidence were found in mice at doses up to 750 mg/kg/day (26 times the human systemic exposure at the therapeutic dose of 200 mg/day) or in rats at doses up to 600 mg/day (31 times the human systemic exposure at the therapeutic dose).

Emtricitabine was not genotoxic in the reverse mutation bacterial test (Ames test), mouse lymphoma or mouse micronucleus assays.

Emtricitabine did not affect fertility in male rats at approximately 140-fold or in male and female mice at approximately 60-fold higher exposures (AUC) than in humans given the recommended 200 mg daily dose. Fertility was normal in the offspring of mice exposed daily from before birth (in utero) through sexual maturity at daily exposures (AUC) of approximately 60-fold higher than human exposures at the recommended 200 mg daily dose.

Tenofovir disoproxil fumarate: Long-term oral carcinogenicity studies of tenofovir DF in mice and rats were carried out at exposures up to approximately 16 times (mice) and 5 times (rats) those observed in humans at the therapeutic dose for HIV infection. At the high dose in female mice, liver adenomas were increased at exposures 16 times that in humans. In rats, the study was negative for carcinogenic findings at exposures up to 5 times that observed in humans at the therapeutic dose.

Tenofovir DF was mutagenic in the *in vitro* mouse lymphoma assay and negative in an *in vitro* bacterial mutagenicity test (Ames test). In an *in vivo* mouse micronucleus assay, tenofovir DF was negative when administered to male mice.

There were no effects on fertility, mating performance or early embryonic development when tenofovir DF was administered to male rats at a dose equivalent to 10 times the human dose based on body surface area comparisons for 28 days prior to mating and to female rats for 15 days prior to mating through day seven of gestation. There was, however, an alteration of the estrous cycle in female rats.

Pregnancy

Pregnancy Category D
(see WARNINGS, Reproductive Risk Potential)

Nursing Mothers

The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breast-feed their infants to avoid risking postnatal transmission of HIV. Studies in rats have demonstrated that both efavirenz and tenofovir are secreted in milk. It is not known whether efavirenz, emtricitabine, or tenofovir is excreted in human milk. Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, **mothers should be instructed not to breast-feed if they are receiving ATRIPLA (efavirenz 600 mg/emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg).**

Pediatric Use

ATRIPLA is not recommended for patients less than 18 years of age because it is a fixed-dose combination tablet containing a component, tenofovir DF, for which safety and efficacy have not been established in this age group.

Geriatric Use

Clinical studies of efavirenz, emtricitabine, or tenofovir DF did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for the elderly patients should be cautious, keeping in mind the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS

For additional safety information about SUSTIVA (efavirenz), EMTRIVA (emtricitabine) or VIREAD (tenofovir DF) in combination with other antiretroviral agents, consult the Prescribing Information for these products.

In addition to the adverse events in study 934 (Table 3), the following adverse events were observed in clinical studies of efavirenz, emtricitabine, or tenofovir DF in combination with other antiretroviral agents.

Efavirenz: The most significant adverse events observed in patients treated with efavirenz are nervous system symptoms **(see WARNINGS, Nervous System Symptoms)**, psychiatric symptoms **(see WARNINGS, Psychiatric Symptoms)**, and rash **(see PRECAUTIONS, Skin Rash)**.

Selected clinical adverse experiences of moderate or severe intensity observed in ≥2% of efavirenz-treated patients in two controlled clinical trials included pain, impaired concentration, anorexia, dyspepsia, abdominal pain, anxiety, nervousness, and pruritus.

Pancreatitis has been reported, although a causal relationship with efavirenz has not been established. Asymptomatic increases in serum amylase levels were observed in a significantly higher number of patients treated with efavirenz 600 mg than in control patients.

Emtricitabine and Tenofovir disoproxil fumarate: Adverse events that occurred in at least 5% of patients receiving emtricitabine or tenofovir DF with other antiretroviral agents in clinical trials include anxiety, arthralgia, increased cough, dyspepsia, fever, myalgia, pain, abdominal pain, back pain, paresthesia, peripheral neuropathy (including peripheral neuritis and neuropathy), pneumonia, rhinitis and rash event (including rash, pruritus, maculopapular rash, urticaria, vesiculobullous rash, pustular rash and allergic reaction).

Skin discoloration has been reported with higher frequency among emtricitabine treated patients. Skin discoloration, manifested by hyperpigmentation on the palms and/or soles, was generally mild and asymptomatic. The mechanism and clinical significance are unknown.

In addition to the laboratory abnormalities described for Study 934 (Table 4), Grade 3/4 elevations of bilirubin (>2.5 x ULN), pancreatic amylase (>2.0 x ULN), serum glucose (<40 or >250 mg/dL), serum lipase (>2.0 x ULN), and urine glucose (≥3+) occurred in up to 3% of patients treated with emtricitabine or tenofovir DF with other antiretroviral agents in clinical trials.

Clinical Trials

Study 934 - Treatment Emergent Adverse Events: Study 934 was an open-label active-controlled study in which 511 antiretroviral-naïve patients received either emtricitabine + tenofovir DF administered in combination with efavirenz (N=257) or zidovudine/lamivudine administered in combination with efavirenz (N=254). Adverse events observed in this study, regardless of treatment relationship, are shown in Table 3.

Table 3 Selected Treatment-Emergent Adverse Events (Grades 2–4) Reported in ≥3% in Any Treatment Group in Study 934 (0–48 weeks)

	FTC + TDF + EFV (N=257)	AZT/3TC + EFV (N=254)
Gastrointestinal Disorder		
Diarrhea	7%	4%
Nausea	8%	6%
Vomiting	1%	4%
General Disorders and Administration Site Condition		
Fatigue	7%	6%
Infections and Infestations		
Sinusitis	4%	2%
Upper respiratory tract infections	3%	3%
Nasopharyngitis	3%	1%
Nervous System Disorders		
Somnolence	3%	2%
Headache	5%	4%
Dizziness	8%	7%
Psychiatric Disorders		
Depression	4%	7%
Insomnia	4%	5%
Abnormal dreams	4%	3%
Skin and Subcutaneous Tissue Disorders		
Rash	5%	4%

Laboratory Abnormalities: Laboratory abnormalities observed in this study were generally consistent with those seen in other studies (Table 4).

Table 4 Significant Laboratory Abnormalities Reported in ≥1% in Any Treatment Group in Study 934 (0–48 weeks)

	FTC + TDF + EFV (N=257)	AZT/3TC + EFV (N=254)
Any ≥ Grade 3 Laboratory Abnormality	25%	22%
Fasting Cholesterol (>240 mg/mL)	15%	17%
Creatine Kinase (M: >990 U/L) (F: >845 U/L)	7%	6%
Serum Amylase (>175 U/L)	7%	3%
Alkaline Phosphatase (>550 U/L)	1%	0%
AST (M: >180 U/L) (F: >170 U/L)	3%	2%
ALT (M: >215 U/L) (F: >170 U/L)	2%	2%
Hemoglobin (<8.0 mg/dL)	0%	3%
Hyperglycemia (>250 mg/dL)	1%	1%
Hematuria (>75 RBC/HPF)	2%	2%
Neutrophil (<750/mm^3)	3%	4%
Fasting Triglyceride (>750 mg/dL)	4%	2%

Lipids: In Study 934 at Week 48, the mean increase from baseline fasting triglyceride concentrations was 3 mg/dL for the tenofovir DF, emtricitabine and efavirenz group and 31 mg/dL for the zidovudine/lamivudine and efavirenz group. For fasting total, LDL, and HDL cholesterol concentrations, the mean increases from baseline were 21 mg/dL, 13 mg/dL, and 6 mg/dL, respectively, for the tenofovir DF group and 35 mg/dL, 20 mg/dL, and 9 mg/dL, respectively, for the zidovudine/lamivudine group.

Hepatic Events: In Study 934, 10 patients treated with efavirenz, emtricitabine, and tenofovir DF and 16 patients treated with efavirenz and fixed-dose zidovudine/lamivudine were hepatitis C antibody positive. Among these HCV coinfected patients, one patient (1/10) in the efavirenz, emtricitabine and tenofovir DF arm had elevations in ALT and AST to greater than five times ULN through 48 weeks. One patient (1/16) in the fixed-dose zidovudine/lamivudine arm had elevations in ALT to greater than five times ULN through 48 weeks. Nine patients treated with efavirenz, emtricitabine and tenofovir DF and 4 patients treated with efavirenz and fixed-dose zidovudine/lamivudine were hepatitis B surface antigen positive. None of these patients had treatment-emergent elevations in ALT and AST to greater than five times ULN through 48 weeks. No HBV and/or HCV coinfected patient discontinued from the study due to hepatobiliary disorders **(see PRECAUTIONS, Liver Enzymes).**

Post Marketing Experience

In addition to adverse events reported from clinical trials, the following events have been identified during post-approval use of efavirenz, emtricitabine, or tenofovir DF. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion because of a combination of their seriousness, frequency of reporting or potential causal connection.

Efavirenz:

CARDIAC DISORDERS: Palpitations, EAR AND LABYRINTH DISORDERS: Tinnitus, ENDOCRINE DISORDERS: Gynecomastia, EYE DISORDERS: Abnormal vision, GASTROINTESTINAL DISORDERS: Constipation, Malabsorption, GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS: Asthenia, HEPATOBILIARY DISORDERS: Hepatic enzyme increase, Hepatic failure, Hepatitis, IMMUNE SYSTEM DISORDERS: Allergic reactions, METABOLISM AND NUTRITION DISORDERS: Redistribution/accumulation of body fat **(see PRECAUTIONS, Fat Redistribution)**, Hypercholesterolemia, Hypertriglyceridemia, MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS: Arthralgia, Myalgia, Myopathy, NERVOUS SYSTEM DISORDERS: Abnormal coordination, Ataxia, Convulsions, Hypoesthesia, Paresthesia, Neuropathy, Tremor, PSYCHIATRIC DISORDERS: Aggressive reactions, Agitation, Delusions, Emotional lability, Mania, Neurosis, Paranoia, Psychosis, Suicide, RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS: Dyspnea, SKIN AND SUBCUTANEOUS TISSUE DISORDERS: Flushing, Erythema multiforme, Nail disorders, Photoallergic dermatitis, Skin discoloration, Stevens-Johnson syndrome

Emtricitabine: No additional events have been identified for inclusion in this section.

Tenofovir disoproxil fumarate:

IMMUNE SYSTEM DISORDERS: Allergic reaction, METABOLISM AND NUTRITION DISORDERS: Hypophosphatemia, Lactic acidosis, RESPIRATORY, THORACIC, AND MEDIASTINAL DISORDERS: Dyspnea, GASTROINTESTINAL DISORDERS: Abdominal pain, Increased amylase, Pancreatitis, HEPATOBILIARY DISORDERS: Increased liver enzymes, Hepatitis, RENAL AND URINARY DISORDERS: Renal insufficiency, Renal failure, Acute renal failure, Fanconi syndrome, Proximal tubulopathy, Proteinuria, Increased creatinine, Acute tubular necrosis, Nephrogenic diabetes insipidus, Polyuria, Nephritis

OVERDOSAGE

If overdose occurs, the patient should be monitored for evidence of toxicity, including monitoring of vital signs and observation of the patient's clinical status; standard supportive treatment should then be applied as necessary. Administration of activated charcoal may be used to aid removal of unabsorbed efavirenz. Hemodialysis can remove both emtricitabine and tenofovir DF (refer to detailed information below), but is unlikely to significantly remove efavirenz from the blood.

Efavirenz: Some patients accidentally taking 600 mg twice daily have reported increased nervous system symptoms. One patient experienced involuntary muscle contractions.

Emtricitabine: Limited clinical experience is available at doses higher than the therapeutic dose of emtricitabine. In one clinical pharmacology study single doses of emtricitabine 1200 mg were administered to 11 patients. No severe adverse reactions were reported.

Hemodialysis treatment removes approximately 30% of the emtricitabine dose over a 3-hour dialysis period starting within 1.5 hours of emtricitabine dosing (blood flow rate of 400 mL/min and a dialysate flow rate of 600 mL/min). It is not known whether emtricitabine can be removed by peritoneal dialysis.

Tenofovir disoproxil fumarate: Limited clinical experience at doses higher than the therapeutic dose of tenofovir DF 300 mg is available. In one study, 600 mg tenofovir DF was administered to 8 patients orally for 28 days, and no severe adverse reactions were reported. The effects of higher doses are not known.

Tenofovir is efficiently removed by hemodialysis with an extraction coefficient of approximately 54%. Following a single 300 mg dose of tenofovir DF, a 4-hour hemodialysis session removed approximately 10% of the administered tenofovir dose.

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Pill shown in "approved" is not actual size.

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