

AIDS DRUG ASSISTANCE PROGRAM (ADAP)

*Information for Healthcare Providers on
Use of ADAP Formulary Medication in Adults*



Bureau of HIV/AIDS
Florida Department of Health
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Tallahassee, FL 32399-1715

Dear Healthcare Provider:

This booklet was designed to be a supplement to guide healthcare professionals through prescribing and monitoring HIV patients taking antiretroviral therapy. **This booklet should not replace the approved treatment guidelines or the manufacturers' recommendations on how to use their products.** Guidelines concerned with the proper initiation of antiretroviral therapy in the treatment of HIV/AIDS are located in tables at the end of this booklet. These tables and other information were taken from www.aidsinfo.nih.gov. Guidelines relative to the use of antiretrovirals in pregnancy, pediatrics and post exposure prophylaxis also can be found at this website.

A few important tips to remember when managing HIV-infected patients:

- Select the appropriate therapy for the given situation being sure to use triple therapy for optimum effects.
- Continuously emphasize the importance of adherence to therapy to patients explaining the importance of taking medications to avoid the development of resistance; this not only includes taking the medication daily but to avoid factors that will affect absorption such as food intake.
- Always monitor for potential adverse effects.
- Use appropriate laboratory parameters (e.g. viral load, CD4 count, resistance testing) when making decisions concerning changes in therapy.
- Adjust dosages in patients with renal or hepatic dysfunction when necessary.
- Monitor the patient's complete therapy for potential drug interactions.
- Remind patients that antiretroviral therapy is not a cure for HIV infection or AIDS.
- Transmission of HIV from an infected to an uninfected person can still occur regardless of the level of viral load or CD4 lymphocyte count.

Although pharmacotherapy can manage HIV infection successfully, the field is ever changing. Stay abreast of the latest developments in this field.

Respectfully,

AIDS Drug Assistance Program
Bureau of HIV/AIDS
Florida Department of Health

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TABLE OF CONTENTS

<u>Drug</u>	<u>Page</u>
<u>Antiretroviral Agents</u>	
Nucleoside/tide Reverse Transcriptase Inhibitors (NRTIs and NtRTIs)	
Abacavir (Ziagen [®])	6
Didanosine (ddI, Videx [®] , Videx EC [®])	9
Lamivudine (Epivir [®] , 3TC)	13
Stavudine (d4T, Zerit [®])	15
Tenofovir (Viread [™])	18
Zalcitabine (ddC, Hivid [®])	20
Zidovudine (AZT [™] , Retrovir [®])	23
Emtricitabine (Emtriva [®])	26
Protease Inhibitors	
Amprenavir(Agenerase [®])	29
Fosamprenavir (Lexiva [®])	33
Indinavir (Crixivan [®])	36
Lopinavir/Ritonavir (Kaletra [®])	39
Nelfinavir (Viracept [®])	42
Ritonavir (Norvir [®])	45
Saquinavir (Fortovase [®] , Invirase [®])	49
Atazanavir (Reyataz [®])	53
Tipranavir (Aptivus [®])	56
Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)	
Delavirdine (Rescriptor [®])	59
Efavirenz (Sustiva [®])	62
Nevirapine (Viramune [®])	65
Fusion Inhibitor	
Fuzeon	69
Miscellaneous HIV Medications	
Hydroxyurea (Hydrea [®])	71
<u>Non-Antiretroviral Formulary Medications</u>	
Anti Diabetic Agents	
Glipizide (Glucotrol [®])	74
Glyburide (Micronase [®] , Diabeta [®] , Glynase [®])	76
Metformin (Glucophage [®])	78
Hyperlipidemic Agents	
Atorvastatin (Lipitor [®])	80
Gemfibrozil (Lopid [®])	82
Pravastatin (Pravachol [®]).	83

Rosuvastatin (Crestor [®])	85
AIDS Wasting Syndrome	
Megestrol Acetate (Megace [®])	87
Nandrolone (Deca- Durabolin [®]).	89
Oxandrolone (Oxandrin [®])	90
Testosterone Cypionate)	91
Testosterone Gel (AndroGel [®])	92
Dronabinol (Marinol [®]).	93
Vaccines	
Hepatitis A Vaccine Havrix [®])	94
Hepatitis B Vaccine (Engerix B [®])	95
Hepatitis A and Hepatitis B (TwinRx [®])	96
Pneumococcal Vaccine (Pneumovax [®])	97
Adjunct Therapy for Peripheral Neuropathy	
Amitriptyline (Elavil [®])	98
Nortriptyline (Pamelor [®]).	100
Gabapentin (Neurontin [®]).	102
Lamotrigine (Lamictal [®])	104
Additional Non-Antiretroviral Formulary Agents	
Diphenoxylate (Lomotil [®])	106
with atropine	
Prochlorperazine (Compazine [®])	107
Acyclovir (Zovirax [®])	108
Atovaquone (Mepron [®])	110
Azithromycin (Zithromax [®])	111
Clarithromycin (Biaxin [®])	113
Dapsone (generic)	115
Ethambutol (Myambutol [®])	116
Fluconazole (Diflucan [®])	118
Erythropoietin or Epoetin Alfa (Epogen [®])(Procrit [®])	120
Itraconazole (Sporanox [®])	122
Leucovorin Calcium	124
Miconazole (Monistat [®])	125
Filgrastim (Neupogen [®])	126
Pyrimethamine (Daraprim [®])	127
Rifabutin (Mycobutin [®])	128
Terconazole (Terazol [®])	130
Trimethoprim/Sulfamethoxazole (Bactrim [®])	131
Tables Concerning Antiretroviral Therapy (www.aidsinfo.nih.gov)	133

**NUCLEOSIDE/TIDE
REVERSE TRANSCRIPTASE
INHIBITORS
(NRTI)**

Abacavir (ABC) (Ziagen®)

Formulations

- Solution, oral (strawberry-banana flavor) 20mg/mL (Available in 240mL bottles)
 - The oral solution does not require reconstitution.
- Tablet 300mg (Available in bottles of 60 tablets or blister packs of 60 tablets)
Combination: Abacavir (300mg)/Lamivudine/Zidovudine (Trizivir®)
Abacavir (600mg)/Lamivudine(300mg) (Epzicom®)

Adult Dose & Administration

- Abacavir 300mg twice a day in combination with other antiretroviral agents.
- May be taken with or without food.
- Trizivir: 1 tablet twice a day.
- Epzicom: 1 tablet daily.

Dosage in impaired renal/hepatic function- (Metabolized by alcohol dehydrogenase and glucuronyl transferase with an 82% renal excretion of metabolites) No dosage adjustment necessary for renal or hepatic impairment. Epzicom® and Trizivir® should not be used in patients with creatinine clearance values less than 50ml/min.

Use in Pregnancy/Lactation

- Classified as FDA **pregnancy category C**.
- No studies have been performed with abacavir in pregnant women or neonates.
- Abacavir crosses the placenta and is excreted into the breast milk of lactating rats.

Adverse Effects

- Fatal **hypersensitivity reactions** have occurred (5% of adults). **Patients having fever, skin rash, fatigue, respiratory symptoms (eg. pharyngitis, dyspnea, or cough), and GI symptoms should discontinue therapy immediately.** Anaphylaxis, liver failure, renal failure, hypotension, and death have occurred in association with hypersensitivity reactions.
- Other adverse events include insomnia (7%), hyperglycemia (25%), hypertriglyceridemia (25%), nausea (47%), vomiting (16%), diarrhea (12%), anorexia (11%), pancreatitis, increased GGT, fever (19%), headache (16%), and rash (11%).

BLACK BOX WARNING

Abacavir (Ziagen™), or as combination product with zidovudine and lamivudine as Trizivir

- **Fatal hypersensitivity reactions reported in 5% of adults:**

- Signs or symptoms include: fever, skin rash, fatigue, gastrointestinal symptoms (nausea, vomiting, diarrhea, or abdominal pain), and respiratory symptoms (pharyngitis, dyspnea, or cough)
- Abacavir should be discontinued as soon as hypersensitivity reaction is suspected
- Abacavir **SHOULD NOT** be restarted
- If restarted, more severe symptoms will recur within hours 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 antiretroviral nucleoside analogues alone or in combination

Drug Interactions

- Abacavir increases the AUC (by 47%) of **amprenavir**. The manufacturer states that a dosage adjustment in either agent is not necessary in patients receiving both drugs.
- **Ethanol** use may increase the risk of toxicity (Increased ABC levels by 41%).
- **Methadone's** serum concentration may be decreased when used with abacavir, due to increased clearance. The manufacturer states that a small increase in methadone's dosage may be required.
- **Ribavirin** may increase the risk of lactic acidosis by an unknown mechanism.

Monitoring Parameters

- Body weight, temperature, complete blood counts, liver transaminases (eg. ALT and AST), LDH, anion gap, pH (<7.35), serum bicarbonate, BUN, serum creatinine, HIV RNA, CD4 count, amylase, and lipase.
- Serum lactate (>5mmol/L) and the lactate/pyruvate ratio should only be performed if lactic acidosis is suspected.

Patient Counseling Tips

- If a patient experiences the following: fever, skin rash, nausea, vomiting, diarrhea, abdominal pain, instruct the patient to discontinue therapy and contact their prescribing physician immediately.
- Reminder: **DO NOT RECHALLENGE THE PATIENT** with this medication.
- The oral solution may be stored at room temperature, but is best kept refrigerated.
- The patient should limit alcohol intake due to competition for alcohol dehydrogenase (one of the enzymes responsible for abacavir's metabolism). Abacavir blood levels can increase.
- May take this drug without regard to meals.
- The manufacturer's **Warning Card** (next page) should be distributed to individuals each time a new or refill prescription of abacavir is dispensed. The patient should carry the card at all times.

(Front of card)

WARNING CARD

ZIAGEN® (abacavir sulfate) Tablets and Oral Solution

Patients taking Ziagen may have a hypersensitivity reaction (a serious allergic reaction) **that can be life-threatening. IF YOU NOTICE A SKIN RASH OR TWO OR MORE OF THE FOLLOWING SETS OF SYMPTOMS WHILE TAKING ZIAGEN, STOP TAKING IT AND CALL YOUR DOCTOR IMMEDIATELY.**

- fever
 - nausea, vomiting, diarrhea, or abdominal pain
 - severe tiredness, achiness, or generally ill feeling
 - sore throat, shortness of breath, or cough
- You should carry this Warning Card with you.

(Back of Card)

WARNING CARD

ZIAGEN® (abacavir sulfate) Tablets and Oral Solution

If you must stop treatment with Ziagen because you have had this serious reaction to abacavir, **NEVER** take Ziagen again. If you take Ziagen again after you have had this serious reaction, **WITHIN HOURS** you may experience life-threatening symptoms that may include lowering of your blood pressure or death.

You should return all of your unused Ziagen to your doctor or pharmacist for proper disposal.
Please read the Medication Guide for additional information on Ziagen.

Didanosine (ddl, Videx[®], Videx EC[®])

Formulations

- Videx[®] EC: 125mg, 200mg, 250mg, 400mg (capsule, delayed release)
- Powder for Oral Solution: Buffered (single dose packet): 100mg, 167mg, 250mg
- Tablets, buffered (with calcium carbonate and magnesium hydroxide), chewable/dispersable (mint flavor): 25mg, 50mg, 100mg, 150mg, 200mg (Available in bottles of 60)

Adult Dose & Administration

Patient weight	Tablets	Buffered Powder	Sustained Release Capsule (EC)
<60kg	125 mg bid or 250mg qd	167mg bid	250mg qd
>60kg	200mg bid or 400mg qd	250mg bid	400mg qd

- Chewable/dispersable buffered tablets: Tablets should be thoroughly chewed or dispersed in water before swallowing; the tablets should NOT be swallowed whole. To disperse the tablets, 2 tablets should be added to at least 30ml of water and stirred until a uniform dispersion forms; the entire dispersion should be swallowed immediately. May also add 1oz of clear apple juice to initial dispersion if additional flavor is desired. ***The apple juice dilution is stable for 1 hour at room temperature.*** Avoid giving more than 4 tablets at a time.
- Buffered powder for oral solution: Pour contents of the packet into 4 ounces of water. Mix until dissolved and drink immediately. It may take up to 2 to 3 minutes for complete dissolution. Do not mix with fruit juice or other acidic solution since it will be unstable at acidic pH.

Dosage in renal/hepatic impairment

- Renal Impairment:

<u>Creatinine clearance (ml/min)</u>	<u>>60kg (daily dose)</u>			<u><60kg (daily dose)</u>		
	<u>Tablet</u>	<u>Powder</u>	<u>EC</u>	<u>Tablet</u>	<u>Powder</u>	<u>EC</u>
30-59	200mg	200mg	200mg	150mg	100mg(bid)	125mg
10-29	150mg	167mg	125mg	100mg	100mg	125mg
less than 10	100mg	100mg	125mg	75mg	100mg	avoid use

Hepatic impairment- Currently, there is insufficient data available to make specific recommendations concerning dosage adjustment, but these patients should be monitored closely for evidence of toxicity.

Use in Pregnancy/Lactation

- Classified as FDA pregnancy category B.

- **Human study:** A phase I (PACTG 249) of didanosine was conducted in 14 HIV-infected pregnant women enrolled at gestational age 26 to 36 weeks and treated through 6 weeks postpartum. The drug was well tolerated during pregnancy by the women and the fetuses. Dose modification is not needed.
- **Cases of fatal lactic acidosis** have been described in pregnant women receiving the combination of didanosine and stavudine along with other antiretroviral agents. The FDA and the manufacturer have issued a warning.
- Didanosine is excreted in the milk of lactating rats; it is not known if didanosine is excreted in human breast milk.

Adverse Effects

The major toxicities associated with didanosine use are:

Potentially fatal pancreatitis (1-7%):

- Monitor serum lipase and amylase levels.
- Abdominal pain, nausea and vomiting
- Manifestations generally become evident during the first 1 to 6 months of therapy and vary from mildly symptomatic hyperamylasemia to severe, hemorrhagic pancreatitis.
- Pancreatitis generally resolves within 1-3 weeks following discontinuance of didanosine.
- Potential risk factors to consider include history of substantial alcohol ingestion, high doses or prior history of pancreatitis.

Lactic acidosis and severe hepatomegaly:

- Increased concentrations of AST, ALT, alkaline phosphatase, GGT and bilirubin have been reported.
- Percentage of patients with elevated liver function test abnormalities vary (7-68%).
- Risk factors include: obesity and long term therapy with NRTIs; most reported cases in women.
- Manifestations include fever, malaise, weakness, nausea, vomiting, diarrhea, epigastric pain and rapidly increasing serum transaminase concentrations.

Peripheral neuropathy:

- Generally consists of tingling, burning, or aching in the hands or lower extremities, particularly in the soles of the feet, with intermittent, shooting “electrical” pain in the legs that generally lasts 1 hour or longer.
- Symptoms may be more severe at night.
- Usually occurs after 2 to 6 months of therapy.
- Reported most frequently in patients with advanced HIV, history of neuropathy or patients being treated with other medications (e.g. stavudine).
- Incidence of neurologic symptoms vary to as high as 26%.

Other potential effects: Retinal changes (including retinal depigmentation) and optic neuritis, diarrhea (note that buffered powdered preparations contain citrate/phosphate and sucrose vehicles that may cause diarrhea as well), skin rash (10%) and asymptomatic hyperuricemia.

BLACK BOX WARNING

Didanosine (Videx™, Videx-EC™)

- Fatal and nonfatal pancreatitis have occurred during therapy with didanosine alone or in combination with other antiretroviral agents
 - Didanosine should be withheld if pancreatitis is suspected
 - Didanosine should be discontinued if pancreatitis is confirmed
- Fatal lactic acidosis has been reported among pregnant women who received a combination of didanosine and stavudine with other antiretroviral combinations
 - Didanosine and stavudine combination should only be used during pregnancy if the potential benefit clearly outweighs the the potential risks
- Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of antiretroviral nucleoside analogues alone or in combination

Drug Interactions

- Drugs whose absorption depends on acidity should be administered 2hrs before buffered formulations of Didanosine. (eg. **Amprenavir, ketoconazole, and itraconazole**).
- Decreased Effect- Buffered formulations may decrease the absorption of **tetracyclines, and quinolones**; separate agents by 2 hours.
- **Pancreatoxins, such as alcohol, pentamidine, stavudine, valproic acid and zalcitabine** may increase the risk of pancreatitis. **Didanosine should be held in treatment of PCP with pentamidine.**
- It may decrease the absorption of **indinavir**, which leads to decreased levels. (Give indinavir 1 hour prior to ddI).
- Increased Toxicity-Concomitant administration of other drugs, which have the potential to cause peripheral neuropathy (eg. **Other NRTIs, stavudine, indinavir, hydroxyurea, metronidazole, cisplatin, dapsone, isoniazid, nitrofurantoin, phenytoin, and pentamidine**).
- **Allopurinol** may increase didanosine concentrations. (Increases AUC by 4-fold) (Concomitant use is not recommended).
- Didanosine may potentiate the adverse effects of **aluminum or magnesium containing antacids**. (ddI tablets contain magnesium).
- **Ganciclovir** may increase didanosine concentrations. (111% increase in AUC) (May be of significance if concurrently treating CMV disease; Monitor for toxicity).
- **Hydroxyurea** may precipitate didanosine- induced pancreatitis.
- **Methadone** may decrease didanosine concentrations. (66% decrease in the peak concentration).
- **Zalcitabine** may potentiate peripheral neuropathy (Concurrent use of of the drugs should be avoided).

- **Dapsone's** absorption is decreased due to buffers in the didanosine. This is important because of the use of dapsone for the treatment of PCP pneumonia.
- **Ribavirin** may increase the risk of lactic acidosis by an unknown mechanism.
- **Ritonavir** may decrease ddI absorption (Dosage adjustment of ddI usually is not necessary).
- **Tenofovir** may increase didanosine levels. Reduce dosage to 250mg po qd. In addition, **didanosine** combined with **tenofovir** with either **nevirapine** or **efavirenz** has been associated with early virologic failure in HIV treatment-naïve patients with high baseline viral loads.
- **Delavirdine** and didanosine given concomitantly may lead to a 32% decrease in the area under the concentration curve of delavirdine if doses of the drugs are administered simultaneously or a 20% increase in the area under the concentration of delavirdine if didanosine is administered 1 hour after delavirdine. This interaction is thought to be due to the buffer in the ddI preparation and is not expected to occur if delavirdine is administered concomitantly with delayed-released capsules containing enteric-coated pellets of didanosine. If delavirdine is used concomitantly with buffered didanosine preparations, delavirdine should be given 1 hour prior to didanosine.

Monitoring Parameters

- Serum potassium, uric acid, creatinine, BUN, hemoglobin, CBC with differential, liver transaminases (eg. AST and ALT), LDH, anion gap, pH (<7.35), serum bicarbonate, amylase, lipase, CPK, alkaline phosphatase, GGT, total bilirubin, and weight gain.
- According to the manufacturer, a retinal eye exam should be performed periodically in adults and every 6 months for pediatric patients.
- Serum lactate (>5mmol/L) and the lactate/pyruvate ratio should only be performed if lactic acidosis is suspected.

Patient Counseling Tips

- Take 30 minutes before or 2 hours after eating.
- Report numbness, tingling in fingers, toes, or feet.
- At least two, but not more than four, didanosine tablets must be taken with each dose in order for the antacid component to be effective.
- Avoid alcohol due to increased risk of pancreatitis.
- Avoid antacids.
- Didanosine buffered powder for oral solution: After dissolving in water, the solution may be stored at ambient room temperature for up to 4 hours.
- DO NOT swallow the tablets whole. Chew the tablets well or mix them in water. Many patients drop the tablets in at least 1 ounce of water and stir well before swallowing. One ounce of apple juice may be added to the water for flavor, but only use apple juice.
- Videx-EC sustained release capsules should be swallowed whole and are best taken at night.

Lamivudine (Epivir[®], 3TC)

Formulations

- Oral Solution 10mg/ml
- Tablet, Film-coated 150mg and 300mg
- Also available in fixed dosage as Combivir[®] (ZDV 300mg +3TC 150mg) and Trizivir[®] (ZDV 300mg +3TC 150mg +ABC 300mg) and Epzicom[®] (3TC 3000mg + ABC 600mg)

Adult Dose & Administration

- 150mg twice daily.
- If the patient is < 50kg: 2mg/kg twice a day.
- Or with ZDV as Combivir[®], 1 tablet twice a day.
- Or with ZDV and ABC as Trizivir[®], 1 tablet twice a day.
- Take lamivudine without regard to meals.

Dosage in renal/hepatic impairment

- Renal impairment

HIV	Dose
CrCl(ml/min)	
30-49	150mg qd
15-29	150mg first dose, 100mg qd
5-14	150mg first dose, 50mg qd
<5	50mg first dose, 25mg qd

- Hepatic impairment- No dosage adjustment necessary, as provided by the manufacturer.

Use in Pregnancy/Lactation

- Classified as FDA **pregnancy category C**. See tables on page 147 and page 149.
- In the Antiretroviral Registry, **NO increases in birth defects** have been observed with lamivudine.
- Lamivudine has been found to have a 3% incidence of birth defects, but this is unremarkable when compared to the total prevalence of birth defects in the U.S. population of 3.1%.
- Lamivudine is **excreted into human breast milk**.

Adverse Effects

- **Nervous System Effects**
 - Peripheral Neuropathy (12%) occurs. Paresthesia, weakness, and peripheral neuropathy have been reported in patients receiving lamivudine or the fixed combination with ZDV.
 - Headache, insomnia, malaise, fatigue, pain also have been reported.
- **Pancreatitis (0.5%)**
- **Hepatic Effects and Lactic Acidosis**
 - Elevations in AST/ALT (1.7% and 3.7% respectively); increased amylase (4.2%).
- **Gastrointestinal Effects**
 - Nausea, vomiting, diarrhea, anorexia, abdominal pain, cramps and dyspepsia.
 - Stomatitis and oral mucosal pigmentation.
- **Neutropenia**
- **Others:** myalgia and arthralgia, skin rash noted as given in combination with ZDV.

BLACK BOX WARNING

Lamivudine (Epivir™), or as combination product in Combivir™ and Trizivir™)

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of antiretroviral nucleoside analogues alone or in combination.

Epivir tablets and oral solution used to treat HIV infection contain a higher dose of lamivudine than Epivir- HBV tablets and oral solution (used to treat chronic hepatitis B). Patients with HIV should receive only dosage and formulations appropriate for treatment of HIV.

Drug Interactions

- **TMP/SMX (Septra®, Bactrim®)** increases lamivudine's AUC and decreases its renal clearance by 29%.
- **Ribavirin** increases the risk of lactic acidosis by an unknown mechanism.

Monitoring Parameters

- Amylase, lipase, serum creatinine, BUN, liver transaminases (eg. AST and ALT), LDH, anion gap, serum bicarbonate, bilirubin, CBC with a differential, viral load, symptoms of pancreatitis (eg. abdominal pain with nausea & vomiting).
- Serum lactate (>5mmol/L) and the lactate/pyruvate ratio should only be performed if lactic acidosis is suspected.

Patient Counseling

- Take exactly as prescribed.
- Can be taken without regard to meals.

Stavudine (d4T, Zerit[®])

Formulations

- Capsule (15 mg, 20 mg, 30 mg, 40mg) (Available in bottles of 60)
- Powder for oral solution (1 mg/mL)
The oral solution should be refrigerated and is stable up to 30 days.

Adult Dose & Administration

- ≥ 60 kg: 40 mg every 12 hours.
- < 60 kg: 30 mg every 12 hours.
- Take without regard to meals.

Dosing in renal impairment: (50% renally excreted)

CrCl 26 – 50 mL/minute

- ≥ 60 kg: 20 mg every 12 hours
- < 60 kg: 15 mg every 12 hours

CrCl 10 - 25 mL/minute

- ≥ 60 kg: 20 mg every 24 hours
- < 60 kg: 15 mg every 24 hours

Hemodialysis (dose after dialysis on day of dialysis)

- ≥ 60 kg: 20 mg every 24 hours
- < 60 kg: 15 mg every 24 hours

Dosing in hepatic impairment:

Not established.

Use in Pregnancy/Lactation

- Classified as FDA **pregnancy category C**.
- In the Antiretroviral Registry, **NO increases in birth defects** have been observed with stavudine.
- Stavudine has been found to have a 2.2% incidence of birth defects, but this is unremarkable when compared to the total prevalence of birth defects in the U.S. population of 3.1%.
- **Human study:** A phase I/II safety study of combination d4T and 3TC in pregnant HIV-infected women. Both drugs were well tolerated.
- Stavudine is excreted into the breast milk of lactating rats.
- Stavudine and didanosine combination should only be used during pregnancy if the potential benefit clearly outweighs potential risks.

Adverse Effects

- **Peripheral neuropathy** (up to 52%) (dose related)- **resume therapy at ½ of the recommended dose**. If neuropathy occurs upon resumption, permanent discontinuation should be considered. Symptoms include: numbness, tingling, or pain in the hands or feet.

- **Other Nervous System Effects:** Headache (54% reported), motor weakness (may mimic Guillian Barre syndrome and should discontinue if occurs).
- **Pancreatitis**
 - Increased amylase or lipase have been reported in 21-31% of patients receiving stavudine in conjunction with other antiretrovirals; up to 8% had amylase or lipase concentrations more than 2 times the upper limit of normal.
- **Hepatic Effects and Lactic Acidosis**
 - Increased serum concentrations of AST, ALT, GGT, and bilirubin have been reported.
 - Hepatitis and liver failure have been reported in patients receiving stavudine during postmarketing surveillance.
- **Skin Rash (40%)**
- **Gastrointestinal Effects:**
 - Diarrhea has been reported in up to 50% of patients; nausea and vomiting as high as 50% as well.

BLACK BOX WARNING

Stavudine (Zerit™)

- Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of antiretroviral nucleoside analogues alone or in combination
- Fatal lactic acidosis has been reported in pregnant women who received a combination of stavudine and didanosine along with other antiretroviral combinations
- Stavudine and didanosine combination should only be used during pregnancy if the potential benefit clearly outweighs the potential risks
- Fatal and non-fatal pancreatitis have occurred when stavudine was part of a combination regimen with didanosine with or without hydroxyurea

Monitoring Parameters

- Obtain liver function test at baseline, then periodically. Monitor for signs and symptoms of peripheral neuropathy (eg. numbness, tingling, or pain in the feet or hands) routinely. LDH, anion gap, pH (<7.35), serum bicarbonate, and amylase. CD₄ count and viral load should be evaluated as needed.
- Serum lactate (>5mmol/L) and the lactate/pyruvate ratio should only be performed if lactic acidosis is suspected.

Drug Interactions

- Concurrent use with **didanosine (ddI, Videx, Videx EC) and Hydroxyurea (Hydrea)** increases the risk of neuropathy, pancreatitis, lactic acidosis, or severe hepatomegaly.
- Concurrent use with drugs associated with peripheral neuropathy will increase the risk of experiencing peripheral neuropathy. These drugs include: **chloramphenicol, cisplatin, dapsone, ethionamide, gold, hydralazine, iodoquinol, isoniazid, lithium, metronidazole, nitrofurantoin, pentamidine, phenytoin, ribavirin, and vincristine.**
- Concurrent use with **zidovudine** leads to a competitive inhibition of the intracellular phosphorylation of stavudine, therefore decreasing its efficacy. Do not use. **Contraindicated.**
- **Methadone**, by decreasing stavudine's bioavailability, decreases the AUC and peak concentration of stavudine. (No dosage adjustment is necessary).
- **Ribavirin** increases the risk of lactic acidosis by an unknown mechanism.
- **St. John's wort** increases the clearance and decreases the plasma concentrations of stavudine through its induction of P450-3A4 and the P-glycoprotein drug transporter.
- **Probenecid** may inhibit the tubular secretion of stavudine.

Patient Counseling Tips

- The patient should be instructed to report symptoms of neuropathy.
- Report fever, chills, unusual fatigue or acute depression, acute abdominal or back pain, persistent muscle pain, weakness, nausea, vomiting, or unusual bruising or bleeding.
- This prescription can be taken without regard to meals.
- Avoid alcohol consumption due to an increased risk for pancreatitis.
- Following reconstitution, the admixture must be refrigerated and should be discarded after 30 days.

Tenofovir (Viread™)

Formulations

- Tablet (300 mg – fumarate)

Adult Dose & Administration

- 300 mg once daily
Tenofovir (TDF) should be administered at least 2 hours before didanosine (ddI, Videx, Videx EC). This medication can be taken without regard to food.
- The dosage of didanosine should be reduced to 250mg po qd if given with tenofovir (in patients weighing > 60kg; no recommended dosage if < 60kg). (Concurrent administration of tenofovir and didanosine can result in elevated concentrations of didanosine making patients more susceptible to toxic effects).

Dosing in renal impairment (Primarily renally excreted by GFR and active tubular secretion)

•	<u>CrCl (mL/min)</u>	<u>Dose</u>
	>50	300mg qd
	30-49	300mg q 48 hr
	10-29	300mg twice weekly
	ESRD	300mg q 7 days

Dosing in hepatic impairment: No dosage adjustment given.

Use in Pregnancy/Lactation

- Classified as FDA **pregnancy category B**. No studies of tenofovir have been conducted in pregnant women or neonates.
- Studies in rats have demonstrated that tenofovir is secreted into the breast milk. There are no data on whether tenofovir crosses the placenta or is excreted in breast milk in humans.

Adverse Effects

- **Nausea** (11%), **diarrhea** (9%), **vomiting** (5%), **asthenia** (8%), **hypertriglyceridemia**, Increased liver transaminases (eg. ALT and AST), increased creatine kinase, neutropenia, hyperglycemia, and hypophosphatemia.
- **Hepatic Effects and Lactic Acidosis**
 - Monitor appropriate labs (ALT, AST, bilirubin, alkaline phosphatase).

BLACK BOX WARNING

Tenofovir (Viread™)

- 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

Monitoring Parameters

- CBC with differential, reticulocyte count, serum creatine kinase, CD₄ count HIV RNA plasma levels, renal function tests (serum creatinine and BUN), liver transaminases (eg. ALT and AST), LDH, anion gap, serum bicarbonate, bone density (long-term), lipid panel, and serum phosphorous should be monitored periodically.
- Serum lactate (>5mmol/L) and the lactate/pyruvate ratio should only be performed if lactic acidosis is suspected.

Drug Interactions

- Concurrent doses of **didanosine (ddI, Videx, Videx EC)** and tenofovir may increase the serum levels of didanosine (Increased C_{max} by 28% and increased AUC greater than 40%). The mechanism of this interaction is unknown. This may increase possibility of didanosine-related toxicity. The manufacturer recommends that the dosage of didanosine be reduced to 250mg po qd when administered with tenofovir in patients weighing > 60kg.
- Didanosine combined with tenofovir in combination with either nevirapine or efavirenz has been associated with early virologic failure in HIV treatment-naïve patients with high baseline viral loads.
- Tenofovir effects may be increased with concurrent administration of **acyclovir, cidofovir, ganciclovir, valacyclovir, and valganciclovir.** (Due to competition for active tubular secretion or reduced renal function).
- **Lopinavir and/or ritonavir** may increase serum concentrations of tenofovir 31% with co-administration. The clinical significance is unknown but should be kept in mind in patients with renal insufficiency. The AUC of lopinavir and ritonavir was decreased but probably not significant (15 and 24% respectively).
- **Atazanavir** can increase tenofovir serum concentrations. The mechanism of this interaction is unknown. The manufacturer recommends monitoring patients for tenofovir-related toxicities as a result of this potential interaction.
- **Ribavirin** may increase the risk of lactic acidosis by an unknown mechanism.

Patient Counseling Tips

- Tenofovir can be taken with or without food (fatty meals may increase bioavailability).
- Patients should report unresolved nausea and vomiting; abdominal pain; tingling, numbness, or pain of toes or fingers; skin rash; or muscle weakness or tremors.

Zalcitabine (ddC, Hivid[®])

Formulations

- Tablet, Film-coated (0.375 mg, 0.75 mg). Available in bottles of 100. Tablets may be stored at room temperature in a tightly closed container.

Adult Dose & Administration

- 0.75 mg 3 times a day (2.25mg as the total daily dose).
- Tablets can be taken with or without food.

Dosing in renal impairment: (Zalcitabine is primarily excreted renally-70%)

- CrCl 10 – 40 mL/minute: 0.75 mg every 12 hours.
- CrCl < 10 mL/minute : 0.75 mg every 24 hours.

Dosing in hepatic impairment:

No dosage recommendations have been made by the manufacturer.

Use in Pregnancy/Lactation

- Classified as FDA **pregnancy category C**.
- No studies of zalcitabine have been conducted in pregnant women or neonates.
- It is unknown if ddC is excreted in breast milk.

Adverse Effects

- **Peripheral Neuropathy**
 - Moderate to severe peripheral neuropathy has been reported in 3 to 35% of patients receiving oral zalcitabine at usual dosage.
 - Occurs most often in patients with advanced HIV disease.
 - The neuropathy that develops is generally a sensorimotor neuropathy characterized initially as numbness and burning dysesthesia involving the distal extremities.
 - Manifestations often become evident during the first 7 to 24 weeks of therapy and involve pain and discomfort in the feet, followed several weeks later by a burning dysesthesia in the same area.
 - Patients may experience diminished light touch, pin prick, temperature, and vibration sensations in the area of the feet and up to the midcalf; ankle deep-tendon reflexes may be decreased or absent.
 - If the drug is not discontinued when these initial manifestations appear, sharp shooting pains or severe continuous burning pain may occur and can progress to severe pain which is potentially irreversible.
 - If zalcitabine is discontinued promptly when initial manifestations occur, the neuropathy is slowly reversible. However, manifestations may progress or worsen for an additional 3 to 4 weeks before they begin to diminish 3 to 18 weeks after the drug has been discontinued.
 - In some patients, manifestations of the neuritis are still evident 6 months after discontinuance of the drug.

- **Pancreatitis**
 - Occurs in up to 1.1% of patients.
 - Manifestations include vague abdominal pain, nausea and vomiting.
 - Monitor lipase and amylase.
 - Although the clinical importance is unclear, increases in serum triglyceride concentrations or increased serum glucose concentrations have been reported prior to the onset of manifestations of pancreatitis.
- **Hepatic Effects and Lactic Acidosis**
 - Lactic acidosis and severe hepatomegaly with steatosis have been reported rarely.
 - Most reported cases involve women; patients who are obese and long term antiretroviral therapy as risk factors.
 - AST, ALT GGT exceeding 5 times the upper limit of normal occurred in as many as 7.6% in some studies.
- **Gastrointestinal Effects**
 - Severe oral ulcers or stomatitis have been reported in up to 3% of patients.
 - Oral lesions appear within 1 to 4 weeks of therapy and usually are multiple and discrete; In some patients these lesions resolve within 1 to 2 weeks despite continued use of zalcitabine.
- **Other Adverse Effects**
 - Neutropenia, thrombocytopenia, arthralgia, myalgia, and other nervous system effects (e.g. headache, mood swings, confusion, somnolence etc).

BLACK BOX WARNING

Zalcitabine (Hivid™)

- Zalcitabine can cause **severe peripheral neuropathy**, use with caution in patients with pre-existing neuropathy.
- In rare cases, zalcitabine may cause pancreatitis, therapy should be withheld until pancreatitis is excluded.
- **Rare cases of hepatic failure and death** have been reported in patients with underlying hepatitis B infection (8.9% of patients have hepatic abnormalities).
- **Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases**, have been reported with the use of antiretroviral nucleoside analogues alone or in combination, including HIVID.

Monitoring Parameters

- Renal function (serum creatinine and BUN), viral load, CD₄ counts, CBC with a differential, serum amylase & lipase, triglycerides, liver transaminases (eg. ALT and AST), GGT, CPK, LDH, anion gap, serum bicarbonate, and calcium should be obtained periodically.

- Serum lactate (>5mmol/L) and the lactate/pyruvate ratio should only be performed if lactic acidosis is suspected.
- Monitor for signs of neuropathy: decreased deep tendon reflexes of the ankles, diminished light touch, pin prick, temperature, and vibration sensations in the area of the feet and midcalf.

Drug Interactions

- Concurrent use with drugs associated with peripheral neuropathy will increase the risk of experiencing peripheral neuropathy. These drugs include: **chloramphenicol, cisplatin, dapsone, ethionamide, gold, hydralazine, iodoquinol, isoniazid, lithium, metronidazole, nitrofurantoin, pentamidine, phenytoin, ribavirin, amphotericin B, foscarnet, aminoglycosides, and vincristine. Avoid with stavudine as well.**
- Do not use **pancreatoxins, such as didanosine (ddI, Videx, Videx EC), zidovudine, alcohol, pentamidine, or valproic acid** with zalcitabine due to an increased risk of pancreatitis.
- **Ribavirin** may increase the risk of lactic acidosis by an unknown mechanism.
- **Probenecid** increases ddC levels by 50% by inhibiting its renal tubular secretion. (The dose of zalcitabine should be reduced if warranted).
- **Trimethoprim** increases ddC AUC by 37%.
- **Antacids** decrease ddC levels by 25%. (Avoid simultaneous ingestion)
- **Cimetidine** decreases ddC clearance by inhibiting its renal tubular secretion, and may lead to toxicity. (The dose of zalcitabine should be reduced if warranted).

Patient Counseling Tips

- The patient should be instructed on adherence to therapy.
- Zalcitabine can be taken with or without food.
- Patients should report persistent nausea and vomiting; abdominal pain; tingling, numbness, or pain of toes or fingers; skin rash; or muscle weakness or tremors.
- Oral lesions usually resolve 3-10 days after discontinuance of the drug and may resolve in 2 weeks if the drug is continued.

Zidovudine (AZT™, Retrovir®)

Formulations

- Capsule (100 mg)
- Tablet, Film-coated (300 mg)
- Injection (10 mg/mL in 20 mL vials) (Retrovir IV infusion)
- Syrup, strawberry flavor (50 mg/5 mL)
- Combination products:
 - Combivir® -- lamivudine 150mg and zidovudine 300mg
 - Trizivir® --- abacavir 300mg, lamivudine 150mg and zidovudine(300mg)

Adult Dose & Administration

- Oral: 300 mg twice daily or 200 mg 3 times a day.
- Tablets can be taken without regard to meals.
- IV: 2 mg/kg/dose infused over 1 hour, then 1mg/kg intravenously until delivery .
- Combivir or Trizivir: 1 tablet twice daily

Dosing in renal impairment

- CrCl < 10 mL/minute: 100 mg every 8 hours.
- Patients on peritoneal or hemodialysis should receive 100mg every 6 to 8 hours.

Dosing in hepatic impairment (Metabolized to AZT glucuronide- GAZT)

- No dosage recommendation.

Use in Pregnancy/Lactation

- Classified as FDA **pregnancy category C**.
- In humans, in the placebo-controlled perinatal trial PACTG 076, the incidence of minor and major congenital abnormalities was similar between zidovudine and placebo groups and no specific patterns of defects were seen.
- In the Antiretroviral Pregnancy Registry, **NO increases in birth defects** have been observed.
- The incidence of birth defects is 2.8%. This is unremarkable when compared to the total prevalence of birth defects in the U.S. population of 3.1%.
- **ZDV is well tolerated in pregnancy at recommended adult doses and in the full-term neonate at 2mg/kg body weight orally every 6 hours.**

Adverse Effects

- **Hematologic Effects**
 - Bone marrow toxicity with resultant anemia and/or neutropenia.
 - Anemia may occur as early as 2 to 4 weeks after initiation of therapy but occurs most commonly after 4 to 6 weeks of therapy.
 - Granulocytopenia occurs most commonly after 6-8 weeks of therapy.
- **Nervous System Effects**
 - Headache has been reported in up to 63% of patients.
 - Malaise has been reported in up to 53% of patients; asthenia from 9 to 69% of patients.
 - Agitation, dizziness and fatigue have been reported in up to 8% of patients.
 - Other nervous system effects include seizures, confusion and tremor.
- **Musculoskeletal Effects**

- Myalgia and muscle pain may occur.
- Severe necrotizing myopathy, which generally affects the legs, and a polymyositis-like syndrome have been reported occasionally in patients and in most cases is apparent after 6.5 to 12 months of therapy. This can be characterized by myalgias, muscle tenderness and weakness, weight loss, atrophy and increased creatine kinase and LDH.
- **Dermatologic and Sensitivity Reactions**
 - Pigmentation of fingernails and toenails has been reported. A dark, bluish discoloration at the base of the fingernails can be evident 2 to 6 weeks after initiation of therapy; a similar brownish-gray pigmentation has been reported in others.
 - In some patients, the pigmentation of nails involve the entire nail while in other cases, there were transverse or longitudinal bands of color.
 - Pigmentation of nails reported with greater frequency in black patients.
 - Hypersensitivity reactions including low-grade fever, anaphylaxis have been reported.
- **Gastrointestinal Effects**
 - Nausea has been reported in up to 61% of patients.
 - Anorexia, constipation, diarrhea, dyspepsia, abdominal cramping or pain and vomiting may occur in 5 to 25% of patients.
 - Esophageal ulceration has been reported in a few patients who swallowed their nightly doses of zidovudine capsules while in a recumbent position. Patients should be advised to swallow capsules while in an upright position and with adequate amounts of water (at least 4 oz).
- **Others:** adipogenic effects have been reported.

BLACK BOX WARNING

Zidovudine (Retrovir™), or as combination products in Combivir™ and Trizivir™

- Zidovudine may be associated with **hematologic toxicities, including bone marrow suppression, granulocytopenia and severe anemia (seen in 41% patients)**, particularly in advanced HIV patients
- Prolonged zidovudine use has been associated with symptomatic myopathy (seen in 8% of patients)
- **Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases**, have been reported with the use of antiretroviral nucleoside analogues alone or in combination

Monitoring Parameters

- Monitor CBC and platelet count at baseline, then once monthly for the first 3 months, followed by once every 3 months thereafter. Increased MCV (early indicator of anemia associated with AZT), hemoglobin, hematocrit, serum creatinine kinase, liver transaminases (eg. ALT and AST), LDH, anion gap, serum bicarbonate, BUN, serum creatinine; Viral load and CD₄ count should be as needed. Observe for signs and symptoms of opportunistic infections.
- Serum lactate (>5mmol/L) and the lactate/pyruvate ratio should only be performed if lactic acidosis is suspected.

Drug Interactions

- **Atovaquone** increases AZT AUC by 35%. No dosage adjustment is necessary.
- Administration of zidovudine with **acetaminophen, cimetidine, indomethacin, lorazepam, probenecid, and aspirin** may inhibit the excretion of zidovudine.
- **Acyclovir, ganciclovir, pentamidine, pyrimethamine, Interferon- α , foscarnet, certain anti-neoplastics (flucytosine, vincristine, vinblastine, adriamycin) and dapsone** coadministration with zidovudine may alter RBC/WBC number or function (increased bone marrow toxicity).
- **Fatty meals** may decrease the effects of zidovudine.
- **Clarithromycin** decreases AZT AUC by 25%.
- **Fluconazole** may increase AZT AUC by 74% through inhibition of glucuronidation.
- **Methadone** increases AZT AUC by 50% in 4/9 patients studied.
- **Phenytoin** may decrease the clearance of AZT.
- **Stavudine** may decrease antiviral activity. Concurrent use contraindicated.
- **TMP/SMX** may increase the risk of anemia and neutropenia, increase AZT levels and decrease AZT clearance.
- **Valproic acid** increases AZT AUC by 79% by inhibiting first pass metabolism.

Patient Counseling Tips

- Can be taken without regard to meals.
- Report persistent nausea and vomiting, abdominal pain, tingling, numbness or pain in toes or fingers.
- Report skin rash or muscle weakness or tremors.
- Report signs of infection or unusual bleeding.

Emtricitabine (FTC-Emtriva®)

Formulation

- Oral capsules 200mg (Emtriva®)
- Truvada® (emtricitabine 200mg plus tenofovir 300mg tablet)

Adult Dose & Administration

- Emtriva® - 200mg once daily.
- Truvada® - One tablet given once daily.
- Can be taken without regard to food.

Dosing in Renal Impairment

- | <u>Creatinine Clearance (ml/min)</u> | <u>Dose</u> |
|--------------------------------------|---------------|
| 30-49 | 200mg q 48 hr |
| 15-29 | 200mg q 72 hr |
| < 15 | 200mg q 96 hr |

Hemodialysis patients: 200mg q 96 hr (dose after dialysis if dose is due on dialysis day).

Dosing in Hepatic Impairment

- No dosage adjustments recommended.

Use in Pregnancy/Lactation

- Classified as FDA Category B.
- Not known whether emtricitabine is distributed into human milk; because of the risk of HIV transmission, HIV-infected women should not breast-feed infants.

Adverse Effects

- Hepatic Effects and Lactic Acidosis
 - Lactic acidosis and severe hepatomegaly with steatosis have been reported rarely.
 - Most patients who have developed the above problems involved women; obesity and long-term therapy with a nucleoside type drug.
- Patients Coinfected with Hepatitis B Virus
 - Prior to initiation of emtricitabine patients should be tested for chronic hepatitis B virus.
 - Exacerbations of hepatitis B virus have been reported upon discontinuance of this drug.
- Others: mild to moderate headache, diarrhea, nausea and rash in conjunction with other antiretrovirals.

BLACK BOX WARNING

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases have been reported with the use of nucleoside analogues alone or in combination with other antiretrovirals.

Emtriva is not recommended for the treatment of chronic hepatitis B virus (HBV) infection and the safety and efficacy of Emtriva 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 discontinuance of Emtriva. Hepatic function has been monitored closely with both clinical and laboratory follow-up at least several months in patients who discontinue Emtriva and are co-infected with HIV and HBV. If appropriate, initiation of Hepatitis B therapy may be warranted.

Monitoring Parameters

- Obtain liver function tests (ALT, AST, alkaline phosphatase) while on this drug.
- Monitor patients for hepatomegaly.
- Serum lactate (>5mmol/L) and the lactate/pyruvate ratio should only be performed if lactic acidosis is suspected.

Drug Interactions

- No significant interactions noted to date.

Patient Education Tips

- Medication can be taken without regard to food.
- Take this medication concurrently with other antiretroviral agents prescribed.
- Report any signs of potential adverse effects.

PROTEASE INHIBITORS

Amprenavir(APV, Agenerase®)

Formulations

- Capsule, liquid-filled 50mg
- Oral Solution 15mg/ml
- The capsule and the solution are not interchangeable on a mg per mg basis.

Adult Dose & Administration

- 1400mg twice daily (oral solution).
- Can be taken with or without food, but avoid taking with high fat meals (note: vitamin E content of amprenavir(amprenavir 50mg capsule contains 36 units of Vit E and the solution contains 46 units of Vit E).
- Consider using fosamprenavir for more convenient dosing.

Dosage in renal/hepatic impairment

- The oral solution should NOT be used in patients with renal impairment OR hepatic impairment due to potential for accumulation of propylene glycol and related toxicity in the formulation.
- Renal impairment: no dosage adjustments recommended.
- Hepatic impairment (Substrate of CYP3A4):
 - For the capsules- Patients with hepatic impairment with Child Pugh score between 5-8; 450 mg bid; Child Pugh score between 9-12; 300mg bid.

Use in Pregnancy/Lactation

- Classified as FDA **pregnancy category C**.
- There have been no studies of amprenavir in pregnant women or neonates.
- The amprenavir oral solution contains propylene glycol, which is metabolized by the alcohol and aldehyde dehydrogenase enzyme pathway. Some patients, including infants and children below age four, pregnant women, patients with hepatic or renal failure, and patients treated with disulfiram or metronidazole, are unable to metabolize propylene glycol. This leads to accumulation and adverse events. **Thus, while the capsule form of amprenavir may be used in pregnancy, the oral solution is contraindicated in pregnant women and infants.**
- Amprenavir is excreted in the milk of lactating rats; it is not known if it is excreted in human milk. Do not breastfeed.

Adverse Effects

- **Avoid in patients with sulfa allergies.**
- **Gastrointestinal Effects**
 - Nausea , diarrhea or loose stools and vomiting may occur.
 - Taste disorders have been reported.
 - The incidence of nausea, vomiting and diarrhea varies but can occur frequently.
- **Dermatologic and Sensitivity Reactions**
 - Skin rash has been reported (up to 27% of patients studied).

- Rash reported in patients receiving this drug had a median onset of 11 days after initiation and a median duration of 10 days in early studies.
- Rash experienced during initial studies was maculopapular (with or without pruritis) and of mild to moderate intensity. Severe rash (Stevens-Johnson syndrome) has been reported in 1% of cases.
- **Nervous System Effects**
 - Oral/perioral paresthesia has been reported in up to 31% of patients in one study.
 - Peripheral paresthesia has been reported in up to 10% of patients studied.
 - Headache and fatigue have been reported as well.
- **Effects on Lipoproteins**
 - Hypertriglyceridemia and hypercholesterolemia have been reported in significant numbers of patients.
- **Hepatic Effects**
 - Increased AST and ALT have been reported.
- **Hyperglycemia and Diabetogenic Effects**
 - Hyperglycemia has been reported and serum glucose concentrations should be monitored accordingly.
- **Fat Maldistribution (Adipogenic Effects)**
 - Redistribution of body fat, including dorsocervical fat enlargement (buffalo hump), has been reported.
 - Redistribution or accumulation of body fat, including central obesity, dorsocervical fat enlargement, peripheral wasting, facial wasting, breast enlargement, and general cushingoid appearance has been reported with this and other protease inhibitors.
- **Hematologic Effects**
 - Spontaneous bleeding episodes have been reported in patients with hemophilia A or B.

BLACK BOX WARNING

Amprenavir (Agenerase™) Oral Solution

- Because of the potential risk of toxicity from **large amounts of the excipient propylene glycol in Agenerase Oral Solution**, it is contraindicated in the following patient populations:
 - children age < 4 years
 - pregnant women
 - patients with renal or hepatic failure
 - patients treated with disulfiram or metronidazole
- Oral solution should be used only when Agenerase capsules or other protease inhibitors cannot be used

Monitoring Parameters

- Hepatic/renal function; routine blood chemistry, body weight, liver transaminases, bilirubin, amylase, lipid profile, propylene glycol toxicity

including hyperosmolality, lactic acidosis, renal toxicity, seizures, stupor, tachycardia, and hemolysis in patients on amprenavir oral solution.

Drug Interactions

- Amprenavir is a CYP3A4 enzyme inhibitor, inducer *and* substrate. What this means is as follows:
 - As an inhibitor of CYP3A4, this drug may inhibit the metabolism of other drugs that are metabolized via this route. This may cause toxic accumulation of the drug(s) affected by this mechanism.
 - As an inducer of CYP3A4, amprenavir can increase the concentration of this enzyme and can potentially result in decreasing the concentration of *other* medications metabolized by this route.
 - As a “substrate”, this drug is metabolized by CYP3A4 and drugs that induce this enzyme will result in lower concentrations of amprenavir while drugs that inhibit this enzyme may cause amprenavir to accumulate to toxic levels.
 - This drug is a *less* potent inhibitor of CYP3A4 than ritonavir.
- **Antacids:** Separate amprenavir dosage by at least 1 hour from time antacid is administered; absorption of amprenavir may be reduced.
- **Antiarrhythmics:** PIs may increase levels of certain antiarrhythmics. Use amiodarone, flecainide, propafenone, or quinidine with caution.
- **Anticonvulsants:** Carbamazepine, fosphenytoin, phenytoin, phenobarbital, and primidone may decrease amprenavir’s levels. Serum concentrations of the anticonvulsants should be monitored.
- **Antidepressants:** Avoid with tricyclic antidepressants and nefazadone as concentrations may increase.
- **Antifungals (Azoles):** Levels of antifungals may be increased. Monitor amprenavir as well for potential adverse effects since it is a substrate as well.
- **Antimycobacterials:**
 - Do not use with **rifampin** (combination results in reduced serum concentrations of amprenavir).
 - Reduce **rifabutin** dosage to 150mg po qd or 300mg 3 times per week. If boosted with ritonavir, reduce rifabutin to 150mg QOD or 3 times per week.
 - Clarithromycin—no dosage adjustments required.
- **Antineoplastics:** PIs may increase the levels of docetaxel, paclitaxel, vinblastine, vincristine, and vinorelbine.
- **Benzodiazepines:** All PIs increase levels of alprazolam, diazepam, clonazepam, flurazepam, midazolam, and triazolam. **Midazolam and triazolam are contraindicated.**
- **Calcium channel blockers:** May increase the levels of calcium channel blockers. Bepiridil is contraindicated with amprenavir. Monitor patient accordingly.
- **Clozapine:** May increase clozapine levels.
- **Dalfopristin; quinupristin (Synercid®):** May increase PI levels.

- **Didanosine:** Non-enteric coated tablets may decrease the absorption of some PIs.
- **Disulfiram:** Propylene glycol in APV liquid may increase toxicity. (Contraindicated)
- **Erectile Dysfunction Agents:**
 - Sildenafil: Use cautiously. Start with reduced dose of 25mg q 48 hours and monitor for adverse effects.
 - Vardenafil: Start with a 2.5mg dose and do not exceed a single 2.5mg dose in 24 hours. Do not exceed 2.5mg in 72 hours if administered with ritonavir.
 - Tadalafil: Substantial increase in tadalafil AUC may result. Start with a 5mg dose and do not exceed a single dose of 10mg q 72 hours.
- **Ergot alkaloids:** May increase ergot levels leading to toxicity. (Contraindicated).
- **Grapefruit juice:** May increase PI levels.
- **HMG-CoA Reductase Inhibitors:** PIs may increase levels of certain statins. Lovastatin and simvastatin are contraindicated.
- **Immunosuppressants:** PIs may increase levels cyclosporine, sirolimus, and tacrolimus.
- **Methadone:** PIs may cause a 35% decrease in methadone levels, APV levels may also be decreased (May precipitate withdrawal in opiate-dependent patients) consider alternative antiretroviral agent if used together.
- **Nefazodone:** PIs may increase levels of nefazodone; Nefazodone may increase PI levels.
- **Neuroleptics:** Clozapine and pimozide levels may be increased.
- **NNRTIs:** See individual agents concerning recommended dosage adjustments for PI/NNRTI combinations.
- **Oral contraceptives:** Do not co-administer; alternative methods of contraception recommended; effectiveness of oral contraceptive reduced.
- **PIs:** See table on recommended dosage adjustments for dual PI combinations.
- **St. John's wort:** May induce CYP3A4 enzyme and decrease levels of PIs.
- **Tamoxifen:** May increase tamoxifen levels.
- **Venlafaxine:** May decrease levels of PIs.
- **Warfarin:** PIs may increase warfarin levels. (Monitor INR and make appropriate dosage adjustments).
- **Metronidazole and disulfiram** are contraindicated because they may block the metabolism of propylene glycol.

Patient Counseling Tips

- Do not use if the patient has a sulfa allergy.
- Women taking oral contraceptives, should also use a barrier method (e.g. condoms).
- Avoid taking with vitamin E and a high fat meal.
- Capsules should be stored at room temperature.

Fosamprenavir (f-APV, Lexiva[®])

Formulations

- 700mg tablets

Adult Dosage and Administration

- In antiretroviral naïve patients:
 - 1400mg two times daily, OR
 - 1400mg plus ritonavir 200mg once daily, OR
 - 700mg plus ritonavir 100mg twice daily.
- In protease inhibitor experienced patients, once daily dosing is not recommended
 - Fosamprenavir 700mg with ritonavir 100mg twice daily.
- Co administered with efavirenz:
 - Fosamprenavir 700mg with ritonavir 100mg twice daily; or
 - Fosamprenavir 1,400mg with ritonavir 300mg once daily.
- Co-administration with efavirenz unboosted is not recommended.
- Can be administered with or without food.

Dosage in Renal/Hepatic Impairment

- No dosage adjustment in renal impairment.
- For hepatic impairment:

○ Child Pugh Class	Dose
5-8	700mg bid
9-12	Not recommended

Ritonavir boosting should not occur with this drug in hepatic impaired patients.

Use in Pregnancy/Lactation

- This drug is classified as FDA Category C.
- Do not breastfeed.

Adverse Effects

- **Avoid in patients with a history of sulfa allergy.**
- Dermatologic
 - Skin rash (19%)
- Fat Redistribution: Redistribution and accumulation of body fat can occur including central obesity, dorsocervical enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement and “cushingoid appearance”.
- GI Effects
 - Diarrhea, nausea and vomiting may occur.
- Nervous System Effects
 - Headache
- Hepatic Effects
 - Increase in liver function tests possible (ALT, AST).
- Hyperlipidemia
 - Increase in cholesterol and triglyceride concentrations may occur. Treatment should be provided as needed.
- Hyperglycemia

- Increase in plasma glucose may occur and should be monitored.
- Possible increased bleeding episodes in patients with hemophilia.

Black Box Warning: No warning for this drug.

Monitoring Parameters

Obtain liver function tests (ALT, AST, alkaline phosphatase), serum triglyceride and total cholesterol concentrations, serum glucose, clotting time (INR).

Drug Interactions:

- Amprenavir is a CYP3A4 enzyme inhibitor, inducer *and* substrate. What this means is as follows:
 - As an inhibitor of CYP3A4, this drug may inhibit the metabolism of other drugs that are metabolized via this route. This may cause toxic accumulation of the drug(s) affected by this mechanism.
 - As an inducer of CYP3A4, amprenavir can increase the concentration of this enzyme and can potentially result in decreasing the concentration of *other* medications metabolized by this route.
 - As a “substrate”, this drug is metabolized by CYP3A4 and drugs that induce this enzyme will result in lower concentrations of amprenavir while drugs that inhibit this enzyme may cause amprenavir to accumulate to toxic levels.
 - This drug is a *less* potent inhibitor of CYP3A4 than ritonavir.
- **Antifungals (Azoles):** Ketoconazole may increase levels of amprenavir (note: ketoconazole levels can increase as well). Consider reducing ketoconazole dose if >400mg/day (if boosted with ritonavir do not exceed 200mg/day). Use others with similar caution.
- **Antiarrhythmics:** PIs may increase levels of certain antiarrhythmics. Use amiodarone, flecainide, propafenone, or quinidine with caution.
- **Anticonvulsants:** May reduce amprenavir levels; monitor concentrations of anticonvulsants as well.
- **Antimycobacterials:**
 - Rifampin: Contraindicated since rifampin will induce metabolism of amprenavir resulting in reduced serum concentrations (amprenavir concentrations reduced by 90%).
 - Rifabutin: Reduce rifabutin to 150mg qd or 300mg 3 times per week; If boosted with ritonavir, give rifabutin 150mg QOD or 3 times per week.
 - Clarithromycin: No dosage adjustment.
- **Benzodiazepenes:** Midazolam and triazolam are contraindicated since serum concentrations of these drugs may increase.
- **HMG-CoA Reductase Inhibitors:** PIs may increase levels of certain statins and cause severe toxicity from these agents (simvastatin, lovastatin atorvastatin).

- **Erectile Dysfunction Agents:**
 - Sildenafil: Use cautiously. Start with reduced dose of 25mg q 48 hours and monitor for adverse effects.
 - Vardenafil: Start with a 2.5mg dose and do not exceed a single 2.5mg dose in 24 hours. Do not exceed 2.5mg in 72 hours if administered with ritonavir.
 - Tadalafil: Substantial increase in tadalafil AUC may result. Start with a 5mg dose and do not exceed a single dose of 10mg q 72 hours.
- **H2 Antagonists and Proton Pump Inhibitors:**
 - These agents may result in reduced serum concentration of amprenavir. H2 antagonists (e.g. ranitidine) administration should not be administered concurrently. Proton pump inhibitor therapy should be avoided.
- **Methadone:** Levels of methadone may decrease. Monitor and titrate if needed.
- **Oral Contraceptives:** Avoid concurrent use (may reduce effectiveness of contraceptives).
- **St John's Wort:** Avoid concurrent use since this herbal product can induce enzymes to metabolize protease inhibitors and reduce serum concentration (this could potentially lead to virologic failure).

Patient Counseling:

1. Avoid if patient has allergy to sulfa drugs.
2. Women taking oral contraceptives should utilize an additional method (e.g. condom).

Indinavir (Crixivan®)

Formulations

- Capsules: 200mg, 333mg, 400mg
 - 200mg
 - 333mg
 - 400mg
 - Indinavir MUST BE dispensed in original container.

Adult Dose & Administration

- 800mg every 8 hours (1 hour before or 2 hours after meals, or with a light non-fat meal). OR
- 800mg every 12 hours if boosted with ritonavir 200mg (may take with or without food).
- Take with a full glass of water or skim milk. Patient should drink ≥ 48 oz of fluids daily; 6-8 oz glasses, preferably water, to prevent IDV-associated renal calculi.
- Separate dosing with ddI by 2 hours or use Videx EC formulation.

Dosage in renal/hepatic impairment

- Renal impairment: No dosage adjustment necessary.
- Hepatic impairment secondary to mild to moderate cirrhosis-- Decrease the dose to 600mg every 8 hours.

Use in Pregnancy/Lactation

- Classified as FDA **pregnancy category C**.
- **Human study:** A phase I/II safety study (PACTG 358) of indinavir (800mg tid) in combination with ZDV and lamivudine in pregnant HIV-infected women and their infants is being conducted. Early results reveal that the AUC for indinavir is lower during pregnancy than postpartum.
- In a phase I study in pregnant women and their infants (PACTG 358), transplacental passage of indinavir was minimal.
- Indinavir is excreted in the milk of lactating rats; it is not known if it is excreted in human milk. Do not breastfeed.

Adverse Effects

- **Lipid Effects:** May cause elevations in triglycerides and cholesterol.
- **Hyperglycemia**
- **Indirect hyperbilirubinemia** (14% - dose related). Occurs more frequently in dosages exceeding 2.4 grams daily.
- **Nephrolithiasis:** May present as flank pain with or without hematuria (12%). Nephrolithiasis appears to be dose-related since it has occurred more frequently in patients receiving indinavir dosages exceeding 2.4 g daily than those receiving less than this amount. If pain occurs, temporarily interrupt therapy (1-3 days) or consider discontinuing.

- **GI Effects:** Abdominal pain, nausea, diarrhea and vomiting may occur. Abdominal distention and dyspepsia have been reported.
- **Others:** Headache, asthenia, skin rash (possible Stevens-Johnson), increased bleeding in hemophiliacs, thrombocytopenia, metallic taste and alopecia have all been reported.

BLACK BOX WARNING

Indinavir (Crixivan™) None given

Monitoring Parameters

- Triglycerides, cholesterol, glucose, serum creatinine, BUN, bilirubin, liver transaminases, amylase, and complete blood count with a differential, hemoglobin, hematocrit, hematuria, urinalysis, and blood glucose should be monitored.

Drug Interactions

- Indinavir is a CYP3A4 enzyme inhibitor *and* substrate. What this means is as follows:
 - As an inhibitor of CYP3A4, this drug may inhibit the metabolism of other drugs that are metabolized via this route. This may cause toxic accumulation of the drug(s) affected by this mechanism.
 - As a “substrate”, this drug is metabolized by CYP3A4 and drugs that induce this enzyme will result in lower concentrations of indinavir while drugs that inhibit this enzyme may cause indinavir to accumulate to toxic levels.
- **Alcohol:** May increase the risk of kidney stones.
- **Antiarrhythmics:** PIs may increase levels of certain antiarrhythmics. Use amiodarone, flecainide, propafenone, or quinidine with caution.
- **Anticonvulsants:** Carbamazepine, fosphenytoin, phenytoin, Phenobarbital, and primidone may decrease indinavir’s levels. Indinavir may increase the levels of carbamazepine, ethosuximide, tiagabine, and zonisamide. (Monitor serum concentrations of the anticonvulsants).
- **Antifungals (Azoles):** Itraconazole and ketoconazole can increase levels of indinavir. Indinavir can also increase the levels of the azoles. Consider decreasing the dose of IDV to 600 mg po every 8 hours. No dosage adjustments for voriconazole.
- **Antimycobacterials**
 - Rifampin: concurrent use is contraindicated.
 - Rifabutin: Decrease rifabutin dose to 150mg qd or 300mg 3 times per week AND increase indinavir to 1000mg tid.
- **Antineoplastics:** PIs may increase the levels of docetaxel, paclitaxel, vinblastine, vincristine, and vinorelbine.

- **Benzodiazepines:** All PIs increase levels of alprazolam, diazepam, clonazepam, flurazepam, midazolam, and triazolam. Midazolam and triazolam are contraindicated.
- **Calcium channel blockers:** May increase the levels of calcium channel blockers.
- **Clozapine:** May increase clozapine levels.
- **Dalfopristin; quinupristin (Synercid®):** May increase PI levels.
- **Didanosine:** Non-enteric coated tablets may decrease the absorption of some PIs.
- **Erectile Dysfunction Agents:**
 - Sildenafil: Levels can increase; Start with reduced dose of 25mg q 48 hr.
 - Vardenafil: Do not exceed 2.5mg every 72 hours if administered with ritonavir.
 - Tadalafil: Start with 5mg dose and do not exceed 10mg every 72 hours.
- **Ergot alkaloids:** May increase ergot levels leading to toxicity. (Contraindicated).
- **Erythromycin:** Levels of PI and erythromycin may increase.
- **Grapefruit juice:** May decrease indinavir levels by 26%.
- **HMG-CoA Reductase Inhibitors:** PIs may increase levels of certain statins. Lovastatin and simvastatin are contraindicated. Begin with lowest dose of atorvastatin. No data available for pravastatin.
- **Immunosuppressants:** PIs may increase levels cyclosporine, sirolimus, and tacrolimus.
- **St. John's wort:** May decrease levels of IDV by 57%. Avoid concurrent use.
- **Tamoxifen:** May increase tamoxifen levels.
- **Warfarin:** PIs may increase warfarin levels.

Patient Counseling

- Do not take any over the counter medications or herbal medications unless you notify your healthcare provider.
- Avoid alcohol due to increased risk of kidney stones.
- IDV capsules are sensitive to moisture and should be dispensed and stored in the original container with a desiccant (drying agent).
- The manufacturer considers it acceptable to store a 1-week supply in a pillbox if kept in a cool, dry environment.
- Drink \geq 48 oz of fluids/day, preferably water, to ensure proper hydration to prevent nephrolithiasis.
- Take 1 hour before or 2 hours after a meal, or with a light non-fat meal; such as dry toast with jelly, juice, coffee with skim milk and sugar or corn flakes with skim milk.

Lopinavir/Ritonavir (Kaletra®)

Formulations

- Capsule: Lopinavir 133.3mg and ritonavir 33.3mg
- Solution: Lopinavir 400mg/5ml and ritonavir 100mg/5ml
 - Note: Oral Solution contains 42% alcohol

Adult Dose & Administration

- 3 capsules twice daily (400mg lopinavir/100mg ritonavir) OR 5ml twice daily.
- Dosage adjustment when taking nevirapine or efavirenz – 533mg lopinavir/133 mg ritonavir twice daily (i.e. 4 capsules or 6.7ml of oral solution).
- Take with food.

Dosage in renal/hepatic impairment

- Renal impairment: No adjustment necessary.
- Hepatic impairment: No dosage adjustment necessary. Use with caution due to an increase in the plasma concentration of lopinavir.

Use in Pregnancy/Lactation

- Classified as FDA **pregnancy category C**.
- Lopinavir and ritonavir are secreted into the breast milk of lactating rats; it is not known if either drug is excreted in human milk.

Adverse Effects

- GI Effects: Nausea, vomiting and diarrhea.
- Asthenia
- Fat Redistribution. This causes a redistribution of fat centrally causing buffalo hump, facial atrophy, and breast enlargement and may cause hyperglycemia.
- Lipid Effects:
 - Hypercholesterolemia , increased triglycerides.
- Hepatic Effects: Elevations in liver transaminases (AST/ALT) usually within first few months of therapy.
- Pancreatitis: increased amylase (5%), abdominal pain, nausea and vomiting.
- Hyperglycemia
- Increased bleeding in hemophiliacs.

BLACK BOX WARNING

Lopinavir/ritonavir (Kaletra™) None given

Monitoring Parameters:

- Amylase, lipase, liver transaminases (eg. ALT and AST), lipid profile, blood glucose, complete blood count with a differential.

Drug Interactions

- **Antiarrhythmics:** PIs may increase levels of certain antiarrhythmics. Do not use amiodarone, flecainide, propafenone, or quinidine with Kaletra.

- **Anticonvulsants:** Carbamazepine, fosphenytoin, phenytoin, phenobarbital, and primidone may decrease Kaletra's levels. Kaletra may increase the levels of carbamazepine, ethosuximide, tiagabine, and zonisamide.
- **Antifungals (Azoles):** Itraconazole (dosage adjustment for patients receiving 400mg/day or higher); (ketoconazole (>200mg qd not recommended), Voriconazole can increase levels of Kaletra at high doses but effects at "boosting" doses uncertain.
- **Antimycobacterials:**
 - Rifampin: No change in dose. Increased liver toxicity possible. Co-administration can lead to loss of virologic response if the only PI. If this is the case rifabutin can be used.
 - Rifabutin: Reduce dose to 150mg qod or 150mg 3 times per week
- **Antineoplastics:** PIs may increase the levels of docetaxel, paclitaxel, vinblastine, vincristine, and vinorelbine.
- **Benzodiazepines:** All PIs increase levels of alprazolam, diazepam, clonazepam, flurazepam, midazolam, and triazolam. Midazolam and triazolam are contraindicated. Kaletra may increase levels of zolpidem.
- **Calcium channel blockers:** May increase the levels of calcium channel blockers. Bepiridil is contraindicated with Kaletra.
- **Clarithromycin:** May increase clarithromycin levels.
- **Clozapine:** May increase clozapine levels.
- **Dalfopristin; quinupristin (Synercid®):** May increase PI levels.
- **Disulfiram:** Do not use with Kaletra (oral solution has alcohol).
- **Erectile Dysfunction Agents**
 - Siladenafil: Start with 25mg every 48 hours and monitor closely for adverse effects.
 - Vardenafil: Start with 2.5mg dose and do not exceed 2.5mg dose in 72 hours.
 - Tadalafil: Start with a 5mg dose and do not exceed a single dose of 10mg every 72 hours.
- **Ergot alkaloids:** May increase ergot levels leading to toxicity. (Contraindicated).
- **Erythromycin:** Levels of PI and erythromycin may increase.
- **HMG-CoA Reductase Inhibitors:** PIs may increase levels of certain statins. Lovastatin and simvastatin are contraindicated. If atorvastatin used, begin with lowest dose since levels can increase significantly.
- **Immunosuppressants:** PIs may increase levels cyclosporine, sirolimus, and tacrolimus.
- **Methadone:** PIs may decrease methadone levels. (May precipitate withdrawal in opiate-dependent patients).
- **Nefazodone:** PIs may increase levels of nefazodone; Nefazodone may increase PI levels.
- **Neuroleptics:** Clozapine and pimozide are to be avoided with Kaletra.
- **Oral contraceptives:** Effect of oral contraceptive reduced; Use alternative methods (e.g. condom).

- **St.John's Wort**: Avoid use with Kaletra since concurrent use may result in decreased concentrations of this antiretroviral.
- **Tamoxifen**: May increase tamoxifen levels.
- **Warfarin**: PIs may increase warfarin levels.

Patient Counseling

- Take with food.
- Administer the oral solution with a calibrated dosing syringe whenever possible (obtain from pharmacy).
- May interfere with oral contraceptives. Use back-up barrier method (e.g. condoms).

Nelfinavir (Viracept®)

Formulations

- Tablets, film coated 250mg and 625mg tablets
- Powder 50mg/g (contains 11.2 mg of phenylalanine derived from aspartame)

Adult Dose & Administration

- 750mg three times daily or 1250mg twice daily (five 250mg tabs or two 625mg tablets).
- Should be taken with food.

Dosage in renal/hepatic impairment

- Renal impairment: No dosage adjustment necessary.
- Hepatic impairment: No dosage adjustment necessary. Use with caution.

Use in Pregnancy/Lactation

- Classified as FDA **pregnancy category B**.
- In the Antiretroviral Pregnancy Registry, **NO increases in birth defects** have been observed with nelfinavir. The prevalence of birth defects with nelfinavir exposure was 2.9% compared with total prevalence of birth defects in the U.S. population of 3.1%.
- In a phase I study in pregnant women and their infants (PACTG 353), transplacental passage of nelfinavir was minimal.
- Nelfinavir is excreted in the milk of lactating rats; it is not known if it is excreted in human milk. Do not breastfeed.

Adverse Effects

- **GI Effects:** mild to moderate diarrhea.
- **Hyperlipidemia:** Monitor cholesterol and triglyceride levels.
- **Redistribution of fat (Adipogenic Effects)**
 - Redistribution or accumulation of body fat, including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, breast enlargement, and general cushingoid appearance, has been reported in patients receiving protease inhibitors including nelfinavir.
- **Hyperglycemia.**
- **Dermatologic and Sensitivity Reactions:** Skin rash has been reported (1-3% of adults reported); Hypersensitivity reactions including bronchospasm, fever and edema has been reported.
- **Increased bleeding in hemophiliacs**
- **Increased liver transaminases (3%):** Increase in ALT and AST, increased alkaline phosphatase, increased GGT.

BLACK BOX WARNING

Nelfinavir (Viracept™) None given

Monitoring Parameters

- Liver function tests (ALT, AST), triglycerides, cholesterol, complete blood count with a differential, CPK, alkaline phosphatase, GGT, hemoglobin, hematocrit, and plasma glucose.

Drug Interactions

- Nelfinavir is a CYP3A4 inducer, inhibitor and substrate.
 - Inducer: Nelfinavir can increase levels of this enzyme which can lead to increased metabolism of other drugs.
 - Inhibitor: Nelfinavir can competitively inhibit this enzyme which can lead to reduced metabolism of drugs being metabolized by CYP3A4.
 - Substrate: Nelfinavir can be metabolized by CYP3A4. Thus, drugs that inhibit this enzyme may cause Nelfinavir concentrations to increase. Drugs that induce this enzyme can cause Nelfinavir concentrations to decrease with potential loss of virologic activity.
- **Antiarrhythmics:** PIs may increase levels of certain antiarrhythmics. Use flecainide, propafenone, or quinidine with caution. (Amiodarone is contraindicated).
- **Anticonvulsants:** Carbamazepine, fosphenytoin, phenytoin, phenobarbital, and primidone may decrease nelfinavir's levels. Monitor anticonvulsant levels and virologic response.
- **Antifungals (Azoles):** No dosage adjustments necessary; monitor for toxicity of ketoconazole, itraconazole or voriconazole.
- **Antimycobacterials:**
 - Rifampin: Contraindicated since rifampin reduces nelfinavir levels significantly.
 - Rifabutin: Increased levels of rifabutin; give 150mg qd or 300mg 3 times weekly if dosage of nelfinavir is 750mg q 8hr; No change required if Nelfinavir 1250mg bid is given.
- **Antineoplastics:** PIs may increase the levels of docetaxel, paclitaxel, vinblastine, vincristine, and vinorelbine.
- **Benzodiazepines:** All PIs increase levels of alprazolam, diazepam, clonazepam, flurazepam, midazolam, and triazolam. Midazolam and triazolam are contraindicated.
- **Calcium channel blockers:** May increase the levels of calcium channel blockers.
- **Clozapine:** May increase clozapine levels.
- **Dalfopristin; quinupristin (Synercid®):** May increase PI levels.
- **Ergot alkaloids:** May increase ergot levels leading to toxicity. (Contraindicated)
- **HMG-CoA Reductase Inhibitors:** PIs may increase levels of certain statins.
 - Lovastatin and simvastatin are contraindicated.

- Atorvastatin: initiate therapy with low dose and monitor for adverse effects.
- Pravastatin: no data available.
- **Immunosuppressants:** PIs may increase levels cyclosporine, sirolimus, and tacrolimus.
- **Methadone:** PIs may decrease methadone levels. (May precipitate withdrawal in opiate-dependent patients).
- **Neuroleptics:** Clozapine and pimozide levels may be increased.
- **Oral contraceptives:** Decreased norethindrone levels by 18%, ethinyl estradiol levels 47%. Use alternative barrier method (e.g. condom).
- **Erectile Dysfunction Agents**
 - Sildenafil: Start with 25mg every 48 hours and monitor for toxicity of sildenafil (levels may be elevated).
 - Vardenafil: Start with a 2.5mg dose and do not exceed 2.5mg in 24 hours. Do not exceed 2.5mg in 72 hours if given with ritonavir (levels may be elevated).
 - Tadalafil: Start with 5mg dose and do not exceed a single dose of 10mg 72 hours.
- **St. John's wort:** May decrease levels of protease inhibitors (this could potentially result in virologic failure).
- **Tamoxifen:** May increase tamoxifen levels.
- **Venlafaxine:** May decrease levels of PIs.
- **Warfarin:** PIs may increase warfarin levels.

Patient Counseling Tips

- Take with food.
- Do not take powder formulation with acidic foods or juice because the resultant mixture would produce a bitter taste.
- When the oral powder is used, it should be added to a small amount of water, milk or soy-based formula or liquid dietary supplement, pudding or ice cream. It should NOT be diluted by adding water to the original container. The entire mixture must be taken within 6 hours.
- Tablets can be may be crushed and placed in a small amount of water and allowed to disperse. The dispersion may be swallowed or mixed with milk or food. The entire mixture must be taken within 6 hours.
- Women taking oral contraceptives, should use a backup barrier method as well (condoms, diaphragm plus contraceptive foam).
- Phenylketonurics should not take Viracept.

Ritonavir (Norvir®)

Formulations

- Capsule, liquid-filled 100 mg
- Solution : 600mg/7.5ml
- Present in Kaletra

Adult Dose & Administration

- **If used as a pharmacokinetic booster with other PIs:** 100-400mg per day in 1 to 2 divided doses
- **If used as sole PI: 600mg bid titrated to this amount with the schedule given below**
 - Day 1-2: 300mg bid
 - Day 3-5: 400mg bid
 - Day 6-13: 500mg bid **then,**
 - Day 14: 600mg bid

This escalation of the dosing reduces the risk of nausea.

- Administration with food improves tolerability of oral solution (unpleasant taste), but is not required for absorption. Mix the solution with chocolate milk or a liquid nutritional supplement to improve tolerability. This mixture must be consumed within 1 hour after preparation.
- Doses of ritonavir and ddI should be spaced 2 to 2.5 hours apart.

Dosing in renal impairment

- No dosage adjustment necessary.

Dosing in hepatic impairment

- No adjustment necessary for mild to moderate impairment.
- Use with caution severe hepatic impairment.

Use in Pregnancy/Lactation

- Classified as FDA **pregnancy category B.**
- In a phase I study in pregnant women and their infants (PACTG 354), transplacental passage of ritonavir was minimal.
- Ritonavir is excreted in the milk of lactating rats; it is unknown if it is excreted in human milk. Do not breastfeed.

Adverse Effects

- **GI Effects**
 - GI effects are the most frequent adverse events reported.
 - Nausea, vomiting, diarrhea, taste perversion, abdominal pain.
- **Nervous System Effects**
 - Circumoral paresthesia and peripheral paresthesias.
 - Asthenia
 - Others: headache, dizziness, insomnia or somnolence.
- **Hyperglycemia**

- **Lipid Effects**
 - Hypertriglyceridemia and hypercholesterolemia is significant.
- **Fat redistribution (adipogenic effects)**
 - Redistribution or accumulation of body fat, including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, breast enlargement and general cushingoid appearance has occurred.
- **Pancreatitis**
 - Pancreatitis has been reported with ritonavir.
- **Hepatic Effects**
 - Elevations in liver transaminase levels (exceeding 5 times normal) can occur as well as hepatitis and jaundice.
- **Others:** Possible increased bleeding in hemophiliacs.

BLACK BOX WARNING

Ritonavir (Norvir[®])

Co-administration of ritonavir 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 ritonavir on hepatic metabolism of certain drugs.

Monitoring Parameters

- Triglycerides, cholesterol, CBC with differential, liver function tests (ALT, AST, alkaline phosphatase, GGT), uric acid, hemoglobin, hematocrit, liver transaminases, amylase, lipase, and glucose should be periodically monitored.

Drug Interactions

- **Ritonavir is a potent inhibitor of cytochrome 3A4**
 - Inhibiting cytochrome P450 (3A4 isoenzyme system) prevents metabolism of other medications normally metabolized via this route.
 - Other enzyme systems are inhibited as well (e.g. CYP2D6, CYP1A2).
- **Amiodarone, bepridil, cisapride, flecainide, primozide, propafenone, quinidine, and benzodiazepines.;** Contraindicated to use in combination with ritonavir.
- **Anticonvulsants**
 - Monitor anticonvulsant levels; ritonavir increases carbamazepine levels.
- **Antifungal Agents**
 - Itraconazole-dosage adjustment may be needed for doses greater than 400mg.
 - Ketoconazole—do not exceed 200mg ketoconazole daily.
 - Voriconazole use is contraindicated with ritonavir.
- **Antimycobacterial Agents**
 - Rifampin: No change in dosage necessary. Increased hepatic toxicity possible. If ritonavir used as sole PI, virologic failure may occur. Consider use of rifabutin.
 - Rifabutin: Decrease dose to 150mg qod or dose 3 times weekly.
 - Clarithromycin: Adjust dosage in renal failure patients.
- **Erectile Dysfunction Agents**
 - Siladenafil: Begin therapy slowly by using 25mg every 48 hours and monitor for side effects of siladenafil.

- Vardenafil: Begin therapy with 2.5mg and do not exceed a single 2.5mg dose over 72 hour period.
- Tadalafil: Begin with a dose of 5mg and do not exceed a single dose of 10mg every 72 hours.
- **Ergot alkaloids** coadministration with ritonavir may cause vasospasm and ischemia.
- **HMG-CoA Reductase Inhibitors**
 - **Lovastatin and simvastatin** Potential for large increase in statin levels. Do not use with ritonavir.
 - **Pravastatin** may be used (adjust dosage according to lipid response).
- **Meperidine:** Concurrent use increases amount of normeperidine which can accumulate and possibly cause seizures. Long term use not recommended.
- **Metronidazole or Disulfiram:** Ritonavir may precipitate disulfiram reaction.
- **Methadone:** Decreased methadone concentrations leading to opiate withdrawal.
- **Theophylline:** Decreased theophylline concentrations. Increased dosage of theophylline may be required.
- Decreased dosage may be needed for each of the following to avoid accumulation with resultant toxicity: **Propoxyphene, antiarrhythmics (disopyramide, lidocaine, and mexilitine), anticonvulsants (carbamazepine, clonazepam, ethosuximide), antidepressants (bupropion, nefazodone, SSRIs), antiemetics (dronabinol), quinine, beta-blockers (metoprolol, timolol), calcium channel blockers, immunosuppressants (cyclosporine, tacrolimus), neuroleptics (perphenazine, risperidone, thioridazine), steroids, stimulants.**
- **Oral contraceptives:** Decreased ethinyl estradiol concentrations may occur. Use alternative barrier methods (condoms) in addition.
- **St. John's Wort:** Concurrent administration is not recommended since to avoid potential suboptimal concentrations of antiretroviral. Specific studies on ritonavir have not been done (studies relate to initial reports with other antiretrovirals)
- **Warfarin:** Monitor INR and make appropriate dosage adjustments.

Patient Counseling Tips

- This medication can be taken with food (capsule) or mixed with chocolate milk or liquid nutritional supplement (solution) to improve tolerability
- Patients should report persistent headache, confusion, severe diarrhea, swelling, numbness of tongue, mouth or lips, vomiting, fever, chills, or fatigue. Do not take with any over-the-counter medications, other medications, or herbal products (especially St. John's Wort) without consulting the physician.
- Instruct patient to keep Norvir capsules in the refrigerator; they however, can stay at room temperature if used within 30 days.
- The solution may be stored at room temperature.
- Patients should use a back-up barrier method if taking oral contraception (e.g. condoms)

Saquinavir (SQV, SQV-sgc, Fortovase[®], Invirase[®])

Formulations

- Saquinavir **hard gel capsule** (200 mg, Invirase)
- Saquinavir tablets (500mg, Invirase)
- Saquinavir **soft gel capsule** (200mg, Fortovase)
- **These formulations are not interchangeable.**

Adult Dose & Administration

- **Fortovase (soft gel) –Unboosted saquinavir**: 1200mg tid in combination with other antiretrovirals; **Boosted with ritonavir**: saquinavir 1000mg twice daily plus ritonavir 100mg bid.
- **Invirase** – Unboosted is **not** recommended.
 - **Boost** with 100mg ritonavir plus saquinavir 1000mg (Invirase) twice daily.
- **Food Effects**:
 - Invirase: Take within two hours of a meal when boosted with ritonavir.
 - Fortovase: Take with or up to 2 hours after a meal (with or without ritonavir).

Dosing in renal/hepatic impairment

Renal impairment: No dosage adjustment necessary.

Hepatic impairment: No dosage adjustment is necessary. Use with caution in patients with severe hepatic impairment.

Use in Pregnancy/Lactation

- Classified as FDA **pregnancy category B**.
- In a phase I study in pregnant women and their infants (PACTG 386), transplacental passage of saquinavir was minimal.
- **Human study**: A phase I/II safety and pharmacokinetic study (PACTG 386) of saquinavir (800mg bid) plus ritonavir (100mg bid) in pregnant HIV-infected women and their infants was well tolerated and achieved adequate saquinavir levels in the women.
- Saquinavir is excreted in the milk of lactating rats; it is not known if it is excreted in human milk. Do not breastfeed.

Adverse Effects

- **GI Effects**: nausea, diarrhea, abdominal discomfort.
- **Hyperglycemia**
- **Lipid Effects**
 - Hypertriglyceridemia and hypercholesterolemia may occur.

- **Fat redistribution (adipogenic effects)**

- Redistribution or accumulation of body fat, including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, breast enlargement, and general cushingoid appearance.
- **Hepatic Effects**
 - Severe cutaneous reaction associated with increased liver function test results.
 - Liver transaminase levels may be as high as 5 to 10 times normal.
- **Nervous System Effects**
 - Headache (5-9%), depression, insomnia reported.
- **Other adverse effects include:** rash, fatigue, increased bleeding in hemophiliacs, low WBC count.

BLACK BOX WARNING

Saquinavir (Fortovase™, Invirase™)

- Invirase (saquinavir mesylate) hard gelatin capsules and tables and Fortovase (saquinavir) soft gelatin capsules are not bioequivalent and cannot be interchangeably.
- Invirase may be used only if it is combined with ritonavir, which significantly inhibits saquinavir's metabolism to provide plasma saquinavir levels at least equal to those achieved with Fortovase.
- When using saquinavir as the sole protease inhibitor in an antiviral regimen, Fortovase is the recommended formulation.

Monitoring Parameters

- Triglycerides, cholesterol, glucose should be monitored periodically, complete blood count with a differential, CPK, hemoglobin, hematocrit, amylase, lipase, serum creatinine, BUN.

Drug Interactions

Saquinavir is a weak cytochrome P450 3A4 inhibitor (and substrate)
Inhibition of this enzyme will result in accumulation of concurrently administered drugs.

- **Antiarrhythmics:** PIs may increase levels of certain antiarrhythmics. Use amiodarone, flecainide, propafenone, or quinidine with caution.
- **Anticonvulsants:** Carbamazepine, fosphenytoin, phenytoin, phenobarbital, and primidone may decrease saquinavir's levels. Saquinavir may increase the levels of carbamazepine, ethosuximide, tiagabine, and zonisamide.
- **Antifungals (Azoles):**
 - Itraconazole, ketoconazole and voriconazole should be used with caution. Dosages may have to be reduced of these agents.

- **Antimycobacterials:**
 - Rifampin: Levels of saquinavir decreased by 84% (rifampin can induce enzymes). The combination should not be used.
 - Rifabutin: Contraindicated unless boosted. Rifabutin decreases saquinavir levels. Give rifabutin 150mg qod or 3 times weekly.
 - Clarithromycin: no dosage adjustment required.
- **Antineoplastics:** PIs may increase the levels of docetaxel, paclitaxel, vinblastine, vincristine, and vinorelbine.
- **Benzodiazepines:** All PIs increase levels of alprazolam, diazepam, clonazepam, flurazepam, midazolam, and triazolam. Midazolam and triazolam are contraindicated.
- **Calcium channel blockers:** These drugs may increase the levels of calcium channel blockers.
- **Clozapine:** May increase clozapine levels.
- **Dalfopristin; quinupristin (Synercid®):** May increase PI levels.
- **Erectile Dysfunction Agents:**
 - Sildenafil: Concentrations of sildenafil can increase. Start with a low dose of 25mg.
 - Vardenafil: No data, but vardenafil area under the concentration curve (AUC) may be substantially increased. Start with 2.5mg dose and do not exceed a 2.5mg dose in 24 hours. Do not exceed a single 2.5mg dose in 72 hours if administered with ritonavir.
 - Tadalafil: Substantial increase in tadalafil half-life can occur. Start with a 5mg dose and do not exceed a single dose of 10mg every 72 hours.
- **Ergot alkaloids:** May increase ergot levels leading to toxicity.
- **Erythromycin:** Levels of PI and erythromycin may increase.
- **Garlic:** Concomitant use of garlic supplements may result in substantial decrease in serum saquinavir concentrations; avoid concurrent use.
- **Grapefruit juice:** May increase oral bioavailability of saquinavir.
- **HMG-CoA Reductase Inhibitors:**
 - Simvastatin and Lovastatin: Do not use due to potential for toxic accumulation of these medications.
 - Atorvastatin: Use lowest possible dose of this medication and monitor for toxicity since this drug may accumulate when combined with saquinavir.
 - Pravastatin: No dosage adjustment is necessary.
- **Immunosuppressants:** PIs may increase levels cyclosporine, sirolimus, and tacrolimus.
- **Methadone:** Although PIs may decrease methadone levels, no adjustment is needed when boosted with ritonavir. Monitor to insure no opiate withdrawal symptoms appear.
- **Nefazodone:** PIs may increase levels of nefazodone; Nefazodone may increase PI levels.
- **Neuroleptics:** Clozapine and pimozide levels may be increased.
- **St. John's wort:** May decrease levels of protease inhibitors.
- **Tamoxifen:** May increase tamoxifen levels.

- **Venlafaxine:** May decrease levels of PIs.
- **Warfarin:** PIs may increase warfarin levels. (Monitor INR)

Patient Counseling Tips

- While on this medication, direct exposure to sunlight should be avoided. Do not take with any medication (including over-the-counter medications or herbals products) without consulting the physician.
- Soft gel capsules may be stored at room temperature for up to 3 months.

Atazanavir (ATV, Reyataz[®])

Formulations

- Capsules: 100mg, 150mg, and 200mg

Adult Dose & Administration

- The recommended dose is 400mg (two 200mg capsules) once daily.
- Atazanavir should be taken with food and avoid taking antacids at the same time
- When administered concomitantly with didanosine buffered formulations, atazanavir should be given (with food) 2 hours before or 1 hour after didanosine.
- If Reyataz[®] is given concomitantly with efavirenz or tenofovir the dosage should be boosted with ritonavir to maintain levels similar to unboosted levels obtained with the 400mg daily dosing. Co-administration with tenofovir or efavirenz can decrease atazanavir serum concentrations. Reyataz should be boosted in this situation as follows:
 - Reyataz 300mg + ritonavir 100mg once daily

• Dosage in Renal and Hepatic Impairment

- **Renal:** No dosage adjustment recommended

- **Hepatic:**

Child-Pugh Class	Dose
7-9	300mg qd
>9	not recommended

Use in Pregnancy/Lactation

- Classified as FDA **pregnancy category B**.
- There are no adequate and well-controlled studies in pregnant women.
- Atazanavir may cause hyperbilirubinemia (monitor for kernicterus in neonates and young infants).
- Unknown if this drug is excreted in human milk. Avoid breast-feeding.

Adverse Effects

- **Indirect Hyperbilirubinemia (35%)**
- **Cardiac Effects**
 - Abnormalities in AV conduction including prolongation of the PR interval
 - Cardiac conduction abnormalities normally are limited to first-degree AV block
 - Use with caution with drugs that prolong the PR interval (e.g. digoxin, verapamil and beta-blockers)
 - Use with caution in patients with cardiac conduction abnormalities
- **Hyperglycemia**
 - Monitor glucose for new onset diabetes or exacerbation of existing diabetes
- **Fat Redistribution**

- Redistribution or accumulation of body fat, including central obesity, dorsocervical fat enlargement (“buffalo hump”), peripheral wasting, facial wasting, breast enlargement, and general cushingoid appearance
- **Others:** Possible increased bleeding in hemophiliac patients

BLACK BOX WARNING
Atazanavir (Reyataz™) None given

Monitoring Parameters

- Bilirubin, liver transaminases, lipid profile, hemoglobin, and complete blood count with a differential and serum glucose.

Drug Interactions

Atazanavir inhibits cytochrome P-450 CYP isoenzymes 3A, 1A2 and 2C9. This will result in the serum accumulation of drugs and toxicity normally metabolized by these isoenzymes.

- **Antifungal Agents**
 - No dosage adjustments recommended at present. Monitor for toxicities.
- **Anticonvulsants**
 - Effects unknown. Monitor serum levels of anticonvulsants and clinical effects/toxicities of atazanavir
- **Antimycobacterials**
 - Rifampin: Should **not** be coadministered
 - Rifabutin: Atazanavir can increase levels of rifabutin. Give rifabutin 150mg qod or 3 times weekly
 - Clarithromycin: Levels of clarithromycin are increased by as much as 94% and can cause QT prolongation. **Decrease** dosage by 50%.
- **Didanosine buffered formulations:** can decrease the concentration of atazanavir. Atazanavir should be given with food 2 hours before or 1 hour after didanosine buffered formulations.
- **Erectile Dysfunction Agents:**
 - Sildenafil: reduce dosage to 25mg every 48 hours and monitor for adverse effects
 - Vardenafil: No data, but potential for increase in levels of vardenafil possible. It is recommended to start with a 2.5mg dose and do not exceed a 2.5mg dose in 24 hours
 - Tadalafil: Significant increase in tadalafil concentration may occur. Start therapy with a 5mg dose and do not exceed a single dose of 10mg every 72 hours
- **Efavirenz:** can decrease the concentrations of atazanavir. It is recommended that atazanavir 300mg with ritonavir 100mg be co-administered with efavirenz 600mg (all as a single daily dose with food).
- **HMG-CoA Reductase Inhibitors:**
 - Itraconazole: Although no data is available, monitor for toxicities.
 - Ketoconazole: If unboosted there are no recommendations for dosage change. If boosted with ritonavir (use with caution and do not exceed 200mg per day)
 - Voriconazole: Concomittant therapy with ritonavir is contraindicated.

- **Ritonavir:** can increase the concentrations of atazanavir. If coadministered, then give 300mg once daily with ritonavir once daily with food.
- **Tenofovir:** Co-administration can result in increased tenofovir levels by an unknown mechanism. Monitor patients for tenofovir-associated adverse effects.
- **Antacids:** can decrease the concentrations of atazanavir. Atazanavir should be administered 2 hours before or 1 hour after antacids.
- **Antiarrhythmics (amiodarone, lidocaine, and quinidine):** increased concentrations of the antiarrhythmics can occur. Monitor plasma concentrations of the antiarrhythmics and toxicity.
- **Warfarin:** can increase warfarin concentrations. Monitor INR and adjust the warfarin dosage if necessary.
- **Tricyclic Antidepressants (TCAs):** can increase TCA concentrations. Monitor the plasma concentrations of the TCAs to avoid toxicity.
- **Rifabutin:** can increase rifabutin levels. A rifabutin dose reduction of up to 75% is recommended. (Adjust TB medications in consultation with TB treatment expert)
- **Diltiazem:** can increase diltiazem concentrations. A dose reduction of diltiazem by 50% should be considered.
- **Felodipine, nifedipine, nicardipine, and verapamil:** atazanavir can increase the concentration of various calcium channel blockers. Dose titration of the calcium channel blocker should be considered.
- **H₂-receptor antagonists:** can decrease atazanavir concentrations. Administer at least 12 hours apart.
- **Cyclosporine, sirolimus, and tacrolimus:** can increase the concentrations of the immunosuppressants. Monitor plasma concentrations of the immunosuppressants.
- **Clarithromycin:** can increase clarithromycin or atazanavir concentrations. Reduce the dose of clarithromycin by 50%.
- **Oral contraceptives:** can increase the concentration of hormones; use smallest/most effective dose of the oral contraceptive
- Drugs that should not be coadministered with atazanavir: **rifampin, irinotecan, midazolam, bepridil, ergot derivatives, cisapride, lovastatin, simvastatin, pimozide, indinavir, proton-pump inhibitors, St. John's wort.**

Patient Counseling

- Take atazanavir with food.
- Administer atazanavir at least 2 hours before or 1 hour after antacids or buffered medications

Tipranivir (Aptivus®)

Formulation

- 250mg capsule

Adult Dose and Administration

- 500mg (two 250mg capsules) twice daily combined with ritonavir 200mg po bid.
- Approved for use in HIV-infected individuals who have tried and failed other regimens (including those with regimens containing protease inhibitors) in the past. It is not approved for initial therapy unless they are infected with a strain of HIV resistant to multiple protease inhibitors).
- Take with food to insure proper absorption.

Dosage in renal/hepatic impairment

- Data not available as of this printing.

Use in Pregnancy and Lactation

- Classified as FDA Pregnancy Category C.

Adverse Effects

- **Gastrointestinal**
 - Nausea, vomiting and diarrhea.
- **Hepatic Effects**
 - Drug induced hepatotoxicity may occur.
 - Use with caution in patients with hepatitis B and hepatitis C.
- **Allergic Reactions**
 - Avoid use in patients with a history of sulfa allergy.
- **Skin**
 - Mild to moderate rash may occur. Rash may be accompanied by joint pain, stiffness, throat tightness or itching.
 - Photosensitivity.
 - Women taking oral contraceptives are at increased risk for developing a rash.

- **Hypertriglyceridemia and hypercholesterolemia.**
- **Hyperglycemia**
- **Lipodystrophy**

Monitoring Parameters

- Liver function tests, serum glucose, serum triglyceride and cholesterol levels.

Drug Interactions

- **Tipranivir/ritonavir can decrease the levels of other protease inhibitors including amprenavir, fosamprenavir and saquinavir. It is recommended that tipranivir/ritonavir not be taken with other protease inhibitors until adequate studies are performed.**
- **Tipranivir/ritonavir decreases levels of abacavir by 40% and zidovudine by 35%. Dosage adjustment may be required but is not established at this time.**
- **Tipranivir/ritonavir may decrease levels of ddI. Take tipranivir/ritonavir 2 hours before or 2 hours after ddI.**
- **Antifungal agents**
 - **Fluconazole can increase tipranivir blood levels.**
 - **Tipranivir/ritonavir may increase itraconazole or ketoconazole levels.**
 - **Tipranivir/ritonavir may increase or decrease voriconazole levels.**
- **Antimycobacterial agents**
 - **Tipranivir may increase clarithromycin levels. Clarithromycin also can increase tipranivir levels but dosage adjustment is not needed at present.**
 - **Rifabutin levels are increased and the dosage of rifabutin should be decreased to 150mg qod.**
- **Antidepressants**
 - **Blood levels of desipramine may be increased with concomitant administration. Other agents have not been studied.**
- **Antihyperlipidemic Agents**
 - **Avoid simvastatin and lovastatin due to elevation in serum concentration of these agents. Pravastatin and fluvastatin are considered safe when combined with tipranivir/ritonavir. Tipranivir/ritonavir can increase levels of atorvastatin and little is known about rosuvastatin.**
- **Oral contraceptives**
 - **Serum levels of oral contraceptives will be reduced. Use an additional barrier method (e.g. condom).**
- **Increased levels of sildenafil, vardenafil and tadalafil may occur and lower dosages of these agents should be used.**

Patient Counseling Tips

- **Inform patients about potential adverse effects.**
- **Take medication with food to insure proper absorption.**
- **Advise women taking oral contraceptives to use an additional method of birth control (e.g. condom).**

NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS

Delavirdine (Rescriptor®)

Formulations

- Tablets : 100mg and 200mg

Adult Dose & Administration

- 400mg three times daily.
- Patients with achlorhydria should take the drug with an acidic beverage.
- Antacids and delavirdine should be separated by one hour.
- This drug may be taken without regard to food.
- For patients unable to swallow commercially available 100mg tablets, a dispersion may be prepared (only with the 100mg tablets) by adding 4 tablets to at least 3 oz of water (a slurry is produced); allow to stand for few minutes and stir until uniform dispersion; drink immediately; rinse glass and mouth following ingestion to ensure total dose administered. The 200mg tablets are not readily dispersed in water and should be swallowed intact.

Dosage in renal/hepatic impairment

- Renal impairment: No adjustment necessary.
- Hepatic impairment: Due to extensive hepatic metabolism, the manufacturer states that the drug should be used with caution.

Use in Pregnancy/Lactation

- Classified as FDA **pregnancy category C**.
- Whether delavirdine crosses the placenta is unknown.
- Delavirdine has not been evaluated in HIV-infected pregnant women.
- Delavirdine is excreted in the milk of lactating rats; it is not known if it is excreted in human milk.

Adverse Effects

- **Skin Rash**
 - During clinical trials, incidence was 4.3%. Severe reactions have occurred including Stevens-Johnson Syndrome.
 - Delavirdine-associated rash occurs mainly on the upper body and proximal arms with decreasing intensity of the lesions on the neck and face and progressively less on the rest of the trunk and limbs.
 - Rash is usually evident within the first few weeks following initiation of therapy and occurrence of rash after 1 month of therapy is uncommon.
- **Hepatic Effects**
 - Increase in ALT and AST, GGT (sometimes 5 times normal values).
 - Hepatic failure has been reported during postmarketing surveillance.
- **Central Nervous System Effects**
 - Headache, asthenia/fatigue, depressive symptoms, anxiety and insomnia have been reported.
- **GI Effects**

- Moderate or severe nausea was reported in 14.7-20% of patients.
- Vomiting, diarrhea and abdominal pain reported.

BLACK BOX WARNING

Delavirdine (Rescriptor™) None given

Monitoring Parameters

- Liver function tests (ALT, AST, GGT) and a complete blood count with a differential.

Drug Interactions

Delavirdine is a substrate that is metabolized by the cytochrome P-450 enzyme system (principally CYP3A and possibly CYP2D6). Thus, medications that stimulate these enzyme systems may reduce delavirdine serum concentrations and there could be loss of virologic control. Alternatively, delavirdine may impair metabolism of drugs metabolized by these systems and can result in toxic concentrations of drugs being metabolized by these enzyme systems.

- **Antacids:** Interferes with absorption of some NNRTIs. Concurrent antacid administration can decrease delavirdine AUC 41%. Patients should take antacids 1 hour before or at least 1 hour after delavirdine.
- **Antiarrhythmics:** NNRTIs may affect levels of certain antiarrhythmics. DLV increases serum concentrations of antiarrhythmics metabolized by the CYP 3A4 system (eg. Quinidine, lidocaine, amiodarone, flecainide).
- **Anticonvulsants:** Carbamazepine, fosphenytoin, phenytoin, Phenobarbital, and primidone may decrease NNRTIs levels. Co-administration of these agents is contraindicated.
- **Antifungals:**
 - Ketoconazole: no change in dose recommended for either agent.
 - Voriconazole: Metabolism of voriconazole may be inhibited by delavirdine. Voriconazole may inhibit NNRTI metabolism. Monitor for antifungal effect and NNRTI toxicity.
 - Fluconazole: No changes in doses for either medication.
- **Antimycobacterials:**
 - Rifampin: Delavirdine levels are decreased by 90%. Concurrent use is contraindicated.
 - Rifabutin: Concurrent administration is not recommended. Delavirdine concentrations decrease while rifabutin concentrations will increase.
 - Clarithromycin: Levels of both drugs will increase. Monitor appropriately.
- **Antineoplastics:** DLV increases levels of etoposide, paclitaxel, and vinblastine.
- **Benzodiazepines:** May affect levels of alprazolam, clonazepam, diazepam, estazolam, flurazepam, midazolam, and triazolam. DLV may increase the levels of these drugs.
- **Calcium channel blockers:** DLV may increase levels of CCBs.
- **Didanosine:** Buffers in non-enteric tablets may decrease the absorption of DLV.

- **Clarithromycin:** Clarithromycin levels increase 100%; DLV levels increase 44%.
- **Erectile Dysfunction Agents**
 - Sildenafil: Potential for increased concentrations and adverse effects exist. Start with reduced dose of 25mg every 48 hours and monitor for adverse effects.
 - Vardenafil: No data but cautious dosing is recommended. Start with a 2.5mg dose and do not exceed a 2.5mg dose in 24 hours.
 - Tadalafil: No data exists but potential for prolonging half-life of tadalafil exists. Recommended to start therapy with a 5mg dose and do not exceed a single dose of 10mg every 72 hours.
- **Ergot alkaloids:** DLV may increase ergot levels leading to toxicity.
- **HMG-CoA Reductase inhibitors:**
 - DLV may increase statin levels leading to toxicity. Do not use **lovastatin** or **simvastatin**.
 - Atorvastatin: Start with lowest dose and monitor for toxicity.
 - Pravastatin: no data available.
- **Immunosuppressants:** DLV may increase levels of cyclosporine, sirolimus, and tacrolimus.
- **Methadone:** DLV levels unchanged but no information on methadone.
- **Nefazodone:** May increase or decrease levels of nefazodone.
- **Oral contraceptives:** DLV may increase levels of estrogen-containing oral contraceptives.
- **SSRIs:** DLV may increase levels of citalopram, and sertraline; fluvoxamine may increase levels of DLV.
- **St. John's wort:** This herb may induce CYP 3A4 and decrease NNRTI levels.
- **Tamoxifen:** NNRTIs may increase or decrease tamoxifen levels.
- **Warfarin:** DLV may increase warfarin levels.

Patient Counseling

- May be taken without regard to food.
- Instruct patient to take delavirdine at least 1 hour before or after ingesting a dose of an antacid.
- Patients with achlorhydria should take the drug with an acidic beverage.

Efavirenz (Sustiva®)

Formulations

- Capsule: 50mg, 100mg , and 200mg
- Also available as a 600 mg tablet.

Adult Dose & Administration

- 600mg once daily taken on an empty stomach at or before bedtime.
- High calorie and high fat meals increase plasma concentrations (39% in capsules and 79% increase in those taking tablets).
- Capsules may be opened and sprinkled into a liquid or onto food.
- To reduce CNS adverse effects, give at bedtime for the first 2-4 weeks.

Dosage in renal/hepatic impairment

- Renal impairment: The renal clearance of the drug is negligible and a clinically important decrease in the clearance of efavirenz is not anticipated.
- Hepatic impairment: Use with caution in patients with hepatic insufficiency.

Use in Pregnancy/Lactation

- Classified as FDA **pregnancy category D**.
- No clinical trials with EFV in pregnant humans are planned. Efavirenz has been associated with birth defects in primates.
- It is unknown whether efavirenz is excreted in human breast milk. Do not breastfeed.

Adverse Effects

- **Skin rash**
 - Treatment-emergent rash generally occurs within the first 2 weeks of therapy.
 - The incidence or severity of the rash is not dose related.
 - Mild to moderate rash resolves in most patients within 1 month with continued therapy. Rash associated with blistering, desquamation, mucosal involvement or fever should be discontinued.
- **Central Nervous System Effects**
 - Approximately 52% of patients experience a central nervous system effect which includes: abnormal dreams, dizziness, somnolence, impaired concentration, amnesia, agitation hallucinations and euphoria.
- **Hepatic Effects**
 - Elevations in ALT, AST more than 5 times normal has been reported.
- **Gastrointestinal Effects**
 - Nausea, diarrhea, vomiting, dyspepsia and abdominal pain have been reported.

BLACK BOX WARNING

Efavirenz (Sustiva™) None given

Monitoring Parameters

- Serum transaminases, cholesterol, triglycerides, signs and symptoms of infection, ALT, AST, GGT, and amylase.

Drug Interactions

Efavirenz is metabolized by CYP3A4 (serves as substrate). Drugs that induce this enzyme will increase metabolic breakdown of efavirenz and reduce its serum concentrations. In addition, efavirenz induces this isoenzyme and can increase metabolism of other drugs while also inducing its own metabolic breakdown leading to lower concentrations. In vitro, efavirenz inhibits several other isoenzymes (CYP2C9, CYP2C19, CYP3A4) and can reduce the metabolism of drugs metabolized through this pathway.

- **Antacids:** Interferes with absorption of some NNRTIs. No interaction with efavirenz.
- **Antiarrhythmics:** EFV may increase antiarrhythmics metabolized by the CYP 3A4 system (eg. Quinidine). Concentration monitoring of these drugs is recommended if they are co-administered.
- **Anticonvulsants:**
 - Carbamazepine, phenobarbital and phenytoin: Use with caution and monitor anticonvulsant levels.
- **Antifungals**
 - Ketoconazole: No data to evaluate this interaction.
 - Voriconazole: Efavirenz levels increase significantly while voriconazole levels decreased. This combination is not recommended.
 - Fluconazole: No dosage changes recommended.
- **Antimycobacterials**
 - Rifampin: Efavirenz serum concentration is decreased with concurrent administration. Increase dosage of efavirenz to 800mg qd.
 - Rifabutin: Efavirenz levels are unchanged. Concentrations of rifabutin are decreased. Increase dosage of rifabutin to 450-600mg qd or 600mg 3 times weekly.
 - Clarithromycin: Efavirenz serum concentration is unchanged. Clarithromycin levels decrease by 39%.
- **Antineoplastics:** EFV can increase or decrease levels of etoposide, paclitaxel, and vinblastine.
- **Benzodiazepines:** May affect levels of alprazolam, clonazepam, diazepam, estazolam, flurazepam, midazolam, and triazolam. EFV may increase or decrease the levels of these BZPs.
- **Ergot alkaloids:** EFV may increase ergot levels leading to toxicity.
- **HMG-CoA Reductase inhibitors:**
 - Simvastatin and Lovastatin: Efavirenz is unchanged. Simvastatin levels can decrease. Adjust dose of simvastatin as needed to control lipids.

- Atorvastatin: Levels of atorvastatin are decreased while efavirenz levels are unchanged. Adjust dosage of atorvastatin to maintain cholesterol and triglycerides within normal limits.
- Pravastatin: no data available.
- **Immunosuppressants:** EFV may increase or decrease levels of cyclosporine, sirolimus, and tacrolimus.
- **Methadone:** EFV may decrease methadone levels by 60%.and can precipitate withdrawal in opiate-dependent patients. Titrate methadone dose to achieve desired effect.
- **Nefazodone:** May increase or decrease levels of nefazodone and nefazodone may increase levels of EFV.
- **Oral contraceptives:** EFV may increase levels of estrogen-containing OCs by 37%.
- **SSRIs:** EFV may increase levels of citalopram, and sertraline; fluvoxamine may increase levels of EFV.
- **St. John's wort:** This herb may induce CYP 3A4 and decrease NNRTI levels.
- **Tamoxifen:** NNRTIs may increase or decrease tamoxifen levels.
- **Warfarin:** EFV may increase or decrease warfarin levels.

Patient Counseling

- Avoid taking this medication with fatty meals as levels may increase further.
- Counsel concerning potential adverse effects.
- Inform patient of the possibility of a false cannabinoid (marijuana) test.

Nevirapine (Viramune®)

Formulations

- Suspension (50 mg/5mL)
- Tablets, 200mg
- These products may be stored at room temperature.

Adult Dose & Administration

- 200mg qd x 14 days; thereafter 200mg bid.
- This medication can be taken with or without food.
- Shake suspension well prior to each use.
- If therapy has stopped for > 7 days, restart with lower dosage (i.e. 200mg qd) and start 200mg bid after 14 days.
- The manufacturer recommends use of a low initial dosage because it appears to lessen the frequency of rash. This dosage regimen should be repeated whenever nevirapine therapy has been interrupted for more than 7 days.

Dosing in renal or hepatic impairment

- Renal Impairment: No dosage adjustment recommended.
- Hepatic Impairment: No data available; use with caution in patients with moderate to severe liver impairment.

Use in Pregnancy/Lactation

- Classified as FDA **pregnancy category C**.
- In the Antiretroviral Pregnancy Registry, NO increase in birth defects have been observed. The prevalence of birth defects with nevirapine was 2% compared with the total prevalence of birth defects in the U.S. of 3.1%.
- Nevirapine is excreted into human breast milk.
- Nevirapine crosses the placenta and achieves neonatal blood concentrations equivalent to that of the mother.
- The HIVNET 012 study in Uganda compared nevirapine (200mg orally to the mother at the onset of labor and 2mg/kg to the neonate within 72 hours of birth) with ZDV (600mg orally to the mother at the onset of delivery and 300mg every 3 hours until delivery, and 4mg/kg orally twice daily for the first 7 days of life to the neonate). In this study, nevirapine lowered the risk of HIV transmission by nearly 50% during the first 14-16 weeks of life compared with ZDV. However, the women in this African trial were not receiving any other antiretroviral therapy. Since then, studies have shown development of resistance to NVP after a single dose. Single dose NVP to prevent vertical transmission is not recommended in the U.S.

Adverse Effects

- **Rash**

- Occurs in 24-40% of patients.
- Rash is usually mild to moderate and consists of maculopapular erythematous cutaneous eruptions (with or without pruritis), and is located on the trunk, face and extremities. Severe and life-threatening skin reactions (eg Stevens-Johnson) has occurred.
- Most cases of rash have occurred within the first 6 weeks of therapy.
- Risk factors for developing serious cutaneous reactions include failure to follow the low dosage regimen during the first 14 days of therapy and delay in discontinuing nevirapine after the onset of initial symptoms.
- Do not use prednisone for the rash initially as there have been reports that concomitant use of prednisone increased the incidence and severity of rash during the first 6 weeks of therapy.
- **HOW TO HANDLE RASH IF IT OCCURS:**
 - If severe skin reactions or hypersensitivity reactions including severe rash or rash accompanied by fever, general malaise, muscle or joint aches, blisters, oral lesions, facial edema, hepatitis, eosinophilia, lymphadenopathy, or renal dysfunction, the drug should be discontinued and NOT restarted.
 - While nevirapine therapy can be continued in patients with mild or moderate rash (e.g. erythema, pruritis, maculopapular rash), dosage should not be increased until the rash has resolved.
 - Mild to moderate rash resolves within 2 weeks in about 50% of patients and within 1 month in about 75% of patients; these patients may be treated symptomatically with antihistamines, antipyretics and NSAIDS. The manufacturer states that nevirapine therapy can be continued in patients who experience urticaria; however, if the drug is discontinued in these patients, it should not be reinitiated.

- **Hepatic Effects**

- Severe, life-threatening hepatotoxicity, including fulminant and cholestatic hepatitis, hepatic necrosis and failure has occurred.
- Although clinical presentation of hepatotoxicity varies, frequently occurred features include: nonspecific prodromal signs of fatigue, malaise, nausea, jaundice, hepatomegaly with or without initially elevated transaminases. Manifestations can progress over several days to hepatic failure with transaminase elevation.
- Severe hepatic disease occurs most frequently during the initial 12-16 weeks of therapy but can occur anytime during treatment.

- **Others:** Headache, nausea, diarrhea, vomiting, abdominal pain.

BLACK BOX WARNING

Nevirapine (Viramune[®])

- 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/mm³, 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 nevirapine treatment.
- Patients should be monitored intensively during the first 18 weeks of nevirapine therapy to detect potentially life-threatening hepatotoxicity or skin reactions
- A 14 day lead-in period with nevirapine 200mg daily must be followed strictly.
- Nevirapine should not be restarted after severe hepatic, skin, or hypersensitivity reactions.

Monitoring Parameters

- LFTs should be obtained at baseline, 2 weeks, then periodically, dark urine, pale feces, pruritis, GGT (If the patient has asymptomatic elevations of GGT without elevations in other LFTs, then continue therapy), complete blood count with a differential, hemoglobin, and temperature.

Drug Interactions

Nevirapine is a substrate for the cytochrome P450 enzyme CYP3A4. Therefore, drugs that inhibit this enzyme system can elevate nevirapine serum concentrations. Nevirapine also induces this same enzyme and can therefore increase the metabolism of drugs that are inactivated via this pathway. This drug also is able to inhibit CYP3A4 and can result in the accumulation (and possible toxicity) of other drugs that are metabolized via this system.

- **Antiarrhythmics:** NNRTIs may affect levels of certain antiarrhythmics. NVP can decrease the concentration of antiarrhythmics metabolized by the CYP 3A4 system (eg. Quinidine, lidocaine).
- **Anticonvulsants:** Carbamazepine, fosphenytoin, phenytoin, phenobarbital, and primidone may decrease NNRTIs levels. Monitor anticonvulsant levels.
- **Antifungals:**
 - Ketoconazole: Nevirapine concentrations increase while ketoconazole levels can decrease significantly. These drugs should not be used together.
 - Voriconazole: Metabolism of this drug can be induced by nevirapine. However, voriconazole can inhibit the metabolism of nevirapine. Frequently monitor for nevirapine toxicity and antifungal therapeutic outcomes.
- **Antimycobacterials:**
 - Rifampin: Levels of nevirapine can decrease significantly. In addition, the possibility of additive hepatotoxicity exists. Combined use is not recommended but if it is used, therapy should be closely monitored.

- Rifabutin: Slight decrease in nevirapine concentrations. No dosage adjustment is recommended.
- Clarithromycin: Nevirapine levels increase by 26% and clarithromycin decreases by 30%; monitor for efficacy or use alternative agent.
- **Calcium channel blockers:** NVP may decrease levels of calcium channel blockers.
- **HMG-CoA Reductase inhibitors:** No data is available to interpret.
- **Immunosuppressants:** NVP may decrease levels of cyclosporine, sirolimus, and tacrolimus.
- **Methadone:** Nevirapine may decrease methadone levels. (May precipitate withdrawal in opiate-dependent patients).
- **Oral contraceptives:** NVP may decrease levels of estrogen-containing oral contraceptives by 20%. (The patient should use a barrier method of contraception).
- **SSRIs:** NVP may decrease levels of citalopram, and sertraline.
- **St. John's wort:** This herb may induce CYP 3A4 and decrease NNRTI levels.
- **Warfarin:** NVP may decrease warfarin levels.

Patient Counseling Tips

- Be sure to stress the importance of increasing dosage of drug after 14 days to BID dosing.
- Discuss the importance of reporting skin rash and other symptoms.
- Take medication without regard to food.

Enfuvirtide (Fuzeon[®])

Formulations

- Injectable (lyophilized powder)
- Each vial contains 108mg of enfuvirtide to be reconstituted with 1.1ml sterile water. Resultant concentration to use is 90mg/ml.

Adult Dose & Administration

- 90mg injected subcutaneously twice daily.
- Reconstituted solution should be refrigerated and used within 24 hours.

Use in Pregnancy/Lactation

- Classified as FDA **pregnancy category B**.
- No studies of enfuvirtide have been conducted in pregnant women or neonates.
- It is not known if enfuvirtide crosses the human placenta or is excreted in human milk.
- Do not breastfeed.

Adverse Effects

- **Local injection site reactions**
 - Pain, induration, nodules and cysts, pruritis and ecchymosis can occur.
- **Pneumonia**
 - Increased rate of bacterial pneumonia has been reported.
- **Hypersensitivity Reactions**
 - Less than 1% of patients will experience.
 - Symptoms include rash, fever, nausea, vomiting, chills, rigor, hypotension and elevated transaminases. If this occurs, rechallenging the patient is NOT recommended.

BLACK BOX WARNING: None

Drug Interactions

- Enfuvirtide does not affect other anti- HIV medications and may be used at the same time with other anti-HIV medications.

Monitoring Parameters

- Body weight, temperature, liver transaminases, complete blood counts, and routine serum chemistry, injection sites should be monitored.

Patient Counseling Tips

- Contact healthcare provider immediately for the following: fever, skin rash, nausea, vomiting, diarrhea, or abdominal pain.
- Encourage patients to use aseptic technique when handling medication.
- Inform doctor if pregnant or breast-feeding.

MISCELLANEOUS

Hydroxyurea (Hydrea®)

Formulations

- Capsule (500 mg)
- Droxi[®] capsules (200 mg, 300 mg, 400 mg)

Adult Dose & Administration

- 500mg bid
- 600mg bid has been used in a randomized, controlled clinical trial.
Capsules may be opened and content put in water; it will not dissolve completely.

Dosing in renal impairment

- Specific dosage has not been established.

Dosage in hepatic impairment

- A dosage recommendation is unavailable.

Use in Pregnancy/Lactation

- Classified as FDA **pregnancy category D**.
- Hydroxyurea should be avoided in pregnancy.
- Hydroxyurea is excreted in human milk.
- Do not breastfeed.

Adverse Effects

- Edema, drowsiness (high doses), hallucinations, constipation, headache, maculopapular rash, hyperuricemia, nausea, vomiting, diarrhea, **leukopenia**, and **elevated hepatic enzymes** are common side effects associated with this medication. Others include **pancreatitis, seizures, and megaloblastic erythropoiesis**.
- Use in HIV may result in an increased risk of persistent cytopenias, hepatotoxicity, teratogenicity, and neuropathy.

Monitoring Parameters

- CBC with differential, platelets, hemoglobin, renal function, LFTs, serum uric acid, amylase and lipase should be monitored periodically.

Drug Interactions

- Hydroxyurea used with **zidovudine, zalcitabine, or didanosine** will cause a synergistic effect.
 - The addition of hydroxyurea to a regimen of didanosine and stavudine or didanosine alone results in moderately enhanced antiretroviral activity.
 - The long term clinical outcome of adding hydroxyurea to antiretroviral regimens is unknown.
 - It is thought that the synergistic action arises because hydroxyurea depletes intracellular deoxynucleotidetriphosphate pools and reduces competition between reverse transcriptase inhibitors and endogenous

dNTPs for binding sites on HIV reverse transcriptase, which reduces the rate of HIV-1 DNA synthesis and results in inhibition of HIV replication.

- Use with caution in drugs that will cause pancreatitis.

Patient Counseling Tips

- Instruct the patient to be sure to take this medication as scheduled. The capsule contents can be added to water, and swallowed immediately. Be sure to wash hands thoroughly.
- Small, frequent meals, frequent mouth care, lozenges, or chewing gum help reduce nausea.
- Constipation may be relieved by increasing exercise, fluids, or dietary fiber.
- Mouth sores can be prevented by frequent mouth care.
- Strictly avoid during pregnancy or in patients contemplating pregnancy.

Non-Antiretroviral Formulary Medications

Glipizide (Glucotrol®)

Formulations

- Tablet 5mg, 10mg
- Tablet extended release 2.5mg XL, 5mg XL, 10mg XL

Adult Dose & Administration

- Initial dose is 5mg qd.
- The max dose is 40mg qd in divided doses using conventional tablets.
- Dosage adjustments may be made in increments of 2.5-5mg daily at intervals of 3-7 days or 5mg daily at intervals of at least 7 days for XL tablets.
- If administering conventional tablets >15mg qd, it should be in divided doses.
- The max dosage for the XL is 20mg qd.
- Take 30 minutes before a meal (preferably breakfast)
- The extended release tablets should be swallowed whole and should NOT be divided, chewed, or crushed.

Dosage in renal/hepatic impairment

- Hepatic insufficiency: Start dose at 2.5mg.
- Renal Failure: CrCl <10ml/min, some investigators recommend not using.

Adverse Effects

- Headache, anorexia, constipation, **hypoglycemia**, **weight gain**, dizziness (7%), SIADH, arthralgia, myalgia, leg cramps, increased serum LDH, AST, and alkaline phosphatase, diarrhea, epigastric fullness, heartburn, nausea, vomiting (>10%), rash, photosensitivity (<10%). Rare side effects include leukopenia, thrombocytopenia, agranulocytosis, aplastic and hemolytic anemia.

Monitoring Parameters

- Urine for ketones and glucose, signs of hypoglycemia, plasma osmolality, arginine vasopressin (if suspected SIADH), serum creatinine, BUN, blood glucose, HbA1c, LDH, AST, alkaline phosphatase, and complete blood count with a differential.

Drug Interactions

- Decreased effect: **beta-blockers** (may impair glucose tolerance), **cholestyramine**, **hydantoins**, **rifampin**, **thiazide diuretics** (may cause hyperglycemia), **charcoal** (binds drug), **diazoxide** (adverse effect is hyperglycemia).
- Increased effect: **histamine 2 antagonists (cimetidine)**, **Warfarin**, **androgens**, **azoles (eg. fluconazole)**, **salicylates**, **gemfibrozil**, **tricyclic antidepressants**, **probenecid**, **methyldopa**, **antacids (magnesium hydroxide)**, **beta-blockers**, **sulfonamides (cotrimoxazole, sulfadiazine, Septra)**, **NSAIDs** (cause binding displacement), **and digitalis glycosides**.

Patient Counseling

- Do not skip meals, carry source of glucose, and a medical alert bracelet should be worn.
- Patients on the XL form should not be alarmed if the capsule is noticed in the feces.
- Take XL with breakfast. Conventional tablets are administered as a single daily dose given each morning before breakfast (approximately 30 minutes prior to a meal to achieve maximum reduction in postprandial blood glucose concentration)
- Swallow XL tablets whole.
- Store at room temperature.
- Avoid alcohol while taking this medication to prevent a disulfuram (Antabuse)-like reaction.
- Educate the patient about the signs of hypoglycemia, i.e. palpitations, sweating, dizziness.
- Use sunscreen when outdoors due to increased susceptibility to sunlight.

Glyburide (Micronase[®], Diabeta[®], Glynase[®])

Formulations

- Tablet 1.25mg, 2.5mg, 5mg
- Tablet micronized 1.5mg, 3mg, 6mg

Adult Dose & Administration

- Tablet: 2.5-5mg qd given with first meal of the day; Maintenance 1.25-20mg per day given in divided or single dose.
- Micronized tablet: 1.5-3mg qd given with first meal of the day; Maintenance 0.75-12mg per day given in single or divided doses.
- Max dosage for the regular tablet = 20mg/day.
- Max dosage for the micronized tablet = 12mg/day.
- Micronized formulations of glyburide are NOT bioequivalent with conventional formulations, and dosage should be retitrated when transferring patients from micronized to conventional formulations or vice versa.
- May be taken with food.

Dosage in renal/hepatic impairment

- Renal Impairment: If the CrCl<50ml/min, use is not recommended.
- Hepatic impairment: Use conservative doses.

Adverse Effects

- **Hypoglycemia, weight gain**, SIADH, cholestatic jaundice, allergic skin reactions, increased AST, ALT, and alkaline phosphatase, parasthesia, joint pain, nocturia, headache, anorexia, constipation, diarrhea, epigastric fullness, heartburn, nausea, vomiting (>10%), rash, photosensitivity (<10%). Rare side effects include leukopenia, thrombocytopenia, agranulocytosis, and aplastic and hemolytic anemia.

Monitoring Parameters

- Hemoglobin A1c, fructosamine, hypoglycemia, complete blood count with a differential, plasma osmolality and arginine vasopressin (if SIADH is suspected), blood glucose, ALT, AST, and alkaline phosphatase.

Drug Interactions

- CYP3A3/4 substrate.
- **Protein-bound Drugs:** Because glyburide is highly protein bound, it could be displaced by oral anticoagulants, hydantoin, salicylates, NSAIDs, and sulfonamides.
- **Phenylbutazone:** This drug may potentiate the hypoglycemic effect of glyburide. Monitor for signs and symptoms of hypoglycemia if used concomitantly.

- **Thiazide diuretics:** These diuretics may exacerbate diabetes mellitus due to their hyperglycemic effect.
- **Alcohol:** Disulfiram- (Antabuse) like reactions have occurred.
- **Beta-blockers:** Beta- blockers may impair glucose tolerance, increase the frequency or severity of hypoglycemia, and block hypoglycemia-induced tachycardia.
- **Drugs that may enhance the hypoglycemic effect:** chloramphenicol, MAOIs, fluoroquinolone antibiotics (eg. ciprofloxacin), and probenecid.
- **Drugs that may decrease the hypoglycemic effect:** nonthiazide diuretics (eg. furosemide), corticosteroids, phenothiazines, thyroid agents, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blockers, rifampin, and isoniazid.

Patient Counseling

- Do not skip meals, carry source of glucose, and a medical alert bracelet should be worn.
- Best if taken with the first meal of the day.
- Avoid alcohol while using this medicine due to a disulfiram- (Antabuse) like reaction.
- Educate the patient about the signs of hypoglycemia, i.e. weakness, drowsiness, confusion, anxiety, and extreme hunger.
- Use sunscreen when outdoors due to increased susceptibility to sunlight.

Metformin (Glucophage®)

Formulations: (As hydrochloride)

- Tablets, film-coated 500mg, 850mg, 1000mg
- Tablets, Extended release 500mg

Adult Dose & Administration

- Usual dosage in the management of type II diabetes: 500mg bid given with morning and evening meals OR 850mg qd given with meals.
- Regular tablets: 2500 mg a day is the max dose.
- Regular tablets may also be given tid.
- Extended release tablets: Initial dosage is 500mg qd.
- Extended release tablets: Max dose is 2000mg a day
- Take with food

Dosage in renal/hepatic impairment

- Contraindicated in renal dysfunction (Cr >1.5mg/dl males and Cr>1.4mg/dl).
- Avoid in hepatic failure due to increased chance of lactic acidosis.

Adverse Effects

- Headache, anorexia, constipation, **diarrhea**, epigastric fullness, heartburn, nausea, vomiting (>10%), rash, photosensitivity (<10%), **decreased vitamin B12**, agitation, dizziness, **lactic acidosis** (<0.1%), and metallic taste.

Monitoring Parameters

- Urine for glucose and ketones, fasting blood glucose, renal function (at least once yearly), liver transaminases, serum B12, LFTs, and hemoglobin. If lactic acidosis is suspected, get serum lactate levels, pH, anion gap, and lactate/pyruvate ratio.

Drug Interactions

- **Antidiabetic drugs:** Hypoglycemia may occur when metformin is used concomitantly with a sulfonylurea agent and/or insulin.
- **Diuretics:** Thiazide diuretics can exacerbate diabetes mellitus by causing hyperglycemia. (Consider an alternate diuretic or increase the dose of metformin)
- **Nifedipine:** Results in increased absorption of metformin.
- **Cimetidine:** Cimetidine may reduce the urinary excretion of metformin by competing for renal tubular organic cationic transport systems.
- **Amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, and vancomycin** are cationic drugs that may reduce the urinary excretion of metformin by competing for renal tubular organic cationic transport systems.

- **Beta-blockers:** Beta- blockers may impair glucose tolerance, increase the frequency or severity of hypoglycemia, and block hypoglycemia-induced tachycardia.
- **Alcohol:** Combined use can increase the risk of hypoglycemia and lactic acidosis, since alcohol decreases lactate clearance and hepatic gluconeogenesis and may increase insulin secretion.
- **Protein-bound drugs:** Binding of metformin to plasma proteins is negligible, and there is a decreased chance for an interaction as opposed to the sulfonylureas.
- **ACE inhibitors:** ACEIs may reduce fasting blood glucose concentrations in nondiabetic individuals and have been associated with unexplained hypoglycemia in diabetics whose blood glucose is controlled with insulin or oral agents.
- **Drugs that may cause hyperglycemia:** corticosteroids, oral contraceptives, thiazide diuretics, sympathomimetics, phenothiazines, niacin, calcium-channel blockers, and isoniazid.

Patient Counseling

- Do not use excessive alcohol while taking metformin.
- Monitor for signs of hypo/hyperglycemia.
- Carry a source of sugar, wear a medical alert bracelet, and eat regularly.
- Take with food or milk.
- Avoid alcohol due to an increased risk of lactic acidosis.

Atorvastatin (Lipitor®)

Formulations

- Tablets: 10 mg, 20 mg, 40 mg

Adult Dose & Administration

- 10 mg – 20mg daily initially, (maximum 80mg/day).
- May be taken without regard to meals.

Dosing in renal impairment

- No adjustment necessary.

Dosing in hepatic impairment

- Use of this medication in active hepatic disease is strictly contraindicated.

Adverse Effects

- **Increased liver transaminases** (Usually return to normal upon discontinuation), **myalgia** (1-6%), increased CPK, arthralgia (4-5%), diarrhea, flatulence, abdominal pain, upper RTI (2-16%), nausea, vomiting, heartburn, rash (1-4%), fatigue, dizziness, possible cataract formation, hyperglycemia, hypoglycemia, possible decrease in adrenal and gonadal hormone secretion, and respiratory difficulty with diaphragmatic muscle pain. Headache (3-17%) is the most commonly reported event of this medication. Cholestatic jaundice, angina, and **rhabdomyolysis with renal failure** are rare but life-threatening possible events.

Monitoring Parameters

- Lipid levels after 2 – 4 weeks of therapy.
- LFTs should be obtained at baseline, 12 weeks, and then periodically. Levels should also be obtained if there is an increase of dose.
- CPK if suspected myopathy.
- Tachyphylaxis has been noted after approximately one year of therapy with certain statins.

Drug Interactions

- Less myopathy/rhabdomyolysis risk is associated with atorvastatin than lovastatin or simvastatin.
- Coadministration of **grapefruit juice, amprenavir, clarithromycin, cyclosporine, diltiazem, fluvoxamine, erythromycin, fluconazole, indinavir, itraconazole, ketoconazole, miconazole, nefazodone, nelfinavir, verapamil, troleandomycin, clofibrate, fenofibrate, gemfibrate, cimetidine, ranitidine, omeprazole, or niacin** may increase serum levels of atorvastatin and risk of rhabdomyolysis development.
- Atorvastatin increases **digoxin and ethinyl estradiol** serum levels.
- **Colestipol, antacids, and St. John's Wort** may reduce atorvastatin drug levels.

- **Warfarin** levels may increase due to protein binding displacement (Increased PT).
- **Cholestyramine** lowers the absorption of atorvastatin.
- **Diltiazem:** Concomitant administration of diltiazem and certain statins has resulted in increases (4 to 5 fold) in plasma concentrations of the antilipemic agents.
- **Grapefruit juice:** Inhibits the metabolism of all of the statins except pravastatin. Clinicians recommend separating grapefruit juice and statin therapy by many hours (eg. grapefruit juice in the morning and statin in the evening).
- **Cimetidine:** Inhibits the metabolism of the statins and increases their plasma concentrations.

Patient Counseling Tips

- Medication may be taken with food, if desired; and without regard to time of day.
- If possible, the patient should avoid grapefruit juice or at least separate the two by 6-8 hours.
- Avoid non-prescription Tagamet[®].
- Have the patient report any unusual muscle pain immediately.
- If drug interactions are going to be a problem for a patient, pravastatin is the best choice due to its 47% renal elimination.

Gemfibrozil (Lopid®)

Formulations

- Film coated tablet (600 mg)

Adult Dose & Administration

- 600mg bid; 30 minutes before breakfast and dinner.
- Some patients may require up to 1.5g daily in divided doses.

Adverse Effects

- **Dyspepsia** was the most commonly reported event of this medication. Others include nausea, vomiting, diarrhea, constipation, headache, mental depression, **decreased hemoglobin**, decreased hematocrit, decreased WBCs, cholelithiasis, atrial fibrillation, rash, **increased blood glucose**, **myopathy**, arthralgia.

Pregnancy

- There are no adequate and controlled studies using gemfibrozil in pregnant women. Animal studies have shown adverse fetal events using doses as high as 0.5-3 times that of usual human dosage.

Monitoring Parameters

- Serum cholesterol and LFTs at baseline, 12 weeks, and periodically thereafter.
- Complete blood count with a differential, alkaline phosphatase, hemoglobin, hematocrit, blood glucose, and CPK if suspected myopathy.
- **Drug Interactions Bexarotene, glyburide, chlorpropamide, and warfarin:** Gemfibrozil may increase blood levels.
- **HMG-CoA reductase inhibitors:** co-administered may increase the risk of rhabdomyolysis development (eg atorvastatin).
- **Rifampin:** reduces serum levels of gemfibrozil.
- **Cyclosporine** serum levels are reduced when co-administered with gemfibrozil.
- **Beta blockers:** due to their ability to increase triglycerides and decrease HDL, may blunt Lopid's® response.
- **Thiazide diuretics:** may increase cholesterol.
- **Estrogens:** may increase triglycerides.

Patient Counseling Tips

- The patient should report persistent dizziness or blurred vision, abdominal or epigastric pain, diarrhea, nausea, or vomiting.
- Take gemfibrozil before the morning and evening meals (30 minutes prior).

Pravastatin (Pravachol®)

Formulations

- Tablet (10 mg, 20 mg, 40 mg, and 80mg)

Adult Dose & Administration

- Begin at 10, 20, or 40 mg once daily; then titrate up until a response is seen, up to 80 mg once daily.
- Dosage should be increased at intervals of no less than 4 weeks until the desired effect is achieved.
- This medication can be taken without regard to meals.
- The patient should be on the standard cholesterol-lowering diet for 3 – 6 months and continued through therapy.
- This medication is usually given at bedtime.

Dosing in renal & hepatic impairment

- Patients with renal or hepatic impairment and geriatric patients should receive an initial dose of 10mg qd.
- Pravastatin should not be used in patients with active liver disease or unexplained, persistent increases in serum aminotransferases.

Adverse Effects

- **Increased liver transaminases** (Usually return to normal upon discontinuation), **myalgia** (1-6%), increased CPK, arthralgia (4-5%), diarrhea, flatulence, abdominal pain, upper RTI (2-16%), nausea, vomiting, heartburn, rash (1-4%), fatigue, dizziness, possible cataract formation, hyperglycemia, hypoglycemia, possible decrease in adrenal and gonadal hormone secretion, and respiratory difficulty with diaphragmatic muscle pain. Headache (3-17%) is the most commonly reported event of this medication. Cholestatic jaundice, angina, and **rhabdomyolysis with renal failure** are rare but life-threatening possible events.

Monitoring Parameters

- Lipid levels after 2 – 4 weeks of therapy.
- LFTs should be obtained at baseline, 12 weeks, and then periodically. Levels should also be obtained if there is an increase of dose.
- CPK if suspected myopathy.

Drug Interactions

- Coadministration of **amprenavir, clarithromycin, cyclosporine, diltiazem, fluvoxamine, erythromycin, fluconazole, indinavir, itraconazole, ketoconazole, miconazole, nefazodone, nelfinavir, verapamil, troleandomycin, clofibrate, fenofibrate, gemfibrate, cimetidine, ranitidine, omeprazole, or niacin** may increase serum levels of pravastatin and risk of rhabdomyolysis development.
- **Digoxin and ethinyl estradiol** serum levels are increased when co-administered with pravastatin.
- **Colestipol, antacids, and St. John's Wort** may reduce pravastatin drug levels.
- **Warfarin** levels may increase due to protein binding displacement (Increased PT).
- **Cholestyramine** lowers the absorption of pravastatin.
- **Diltiazem:** Concomitant administration of diltiazem and certain statins (not pravastatin) has resulted in increases (4 to 5 fold) in plasma concentrations of the antilipemic agents.
- **Phenytoin:** Administration has resulted in a 27-40% increase in peak plasma concentrations of fluvastatin and a 5-20% increase in the respective parameters of phenytoin.
- **Grapefruit juice:** Inhibits the metabolism of all of the statins except pravastatin. Clinicians recommend separating grapefruit juice and statin therapy by many hours (eg. grapefruit juice in the morning and statin in the evening).
- **Oral antidiabetic agents:** Concomitant administration of glyburide and tolbutamide with certain statins (fluvastatin, simvastatin) reportedly has resulted in increased bioavailability of the antidiabetic agents through P450 inhibition.
- **Antileukotrienes and Fluvoxamine:** Inhibit the CYP3A4 isoenzyme and may inhibit the metabolism of most statins.
- **Cimetidine:** Inhibits the metabolism of the statins and increases their plasma concentrations.
- Ethanol: Excessive consumption increases the risk of liver damage.

Patient Counseling Tips

- The patient should be placed on a standard cholesterol-lowering diet for 3 – 6 months before receiving pravastatin and continued through therapy.
- The patient should be instructed to report unexplained muscle pain, tenderness or weakness; malaise or fever.
- If possible, the patient should avoid grapefruit juice or at the least separate the two by 6-8 hours.
- Avoid non-prescription Tagamet[®].
- If drug interactions are going to be a problem for a patient, pravastatin is the best choice due to its 47% renal elimination.
- Contraindicated during pregnancy or breast feeding.

Rosuvastatin (Crestor®)

Formulation:

- Tablets: 5mg, 10mg, 20mg and 40mg

Adult Dose & Administration

- Usual starting dose is 10mg qd.
- Dosage range is 5mg-40mg qd.
- An initial dosage of 20mg qd can be used in marked hypercholesterolemia (LDL>190 mg/dl); the 40mg dose is reserved for those who are not managed properly after receiving 20mg qd dosing.

Dosing in Renal and Hepatic Impairment

- Administer 5mg qd if creatinine clearance is less than 30ml/min; do not exceed 10mg.
- No adjustments noted for hepatic impairment.

Adverse Effects:

Major adverse effects include increases in liver enzymes and myopathy/rhabdomyolysis. Liver enzyme changes generally occur in the first 3 months of treatment. If an increase in ALT or AST of more than 3 times the upper limit of normal persists, reduction of dose or withdrawal of rosuvastatin should occur. These enzyme changes generally occur within the first 3 months of therapy. This drug should be used with caution in patients with a history of liver failure and should not be used in those with active liver disease or unexplained persistent transaminase levels. These effects are reported with other statin agents used to lower cholesterol .

Monitoring Parameters:

Full lipid profile (total cholesterol, triglycerides, HDL), liver function tests (ALT, AST, alkaline phosphatase).

Drug Interactions:

Clearance of rosuvastatin is not dependent upon cytochrome P450 3A4 and therefore it does not interact with many of the antiretrovirals and other drugs eliminated by this pathway. Significant drug interactions to consider are:

- Coadministration of this drug (80mg)with gemfibrozil (600mg twice daily for 7 days) increases concentrations of rosuvastatin significantly.
- Coadministration of an antacid (eg magnesium and aluminum combinations) with rosuvastatin results in a 54% decrease in rosuvastatin concentration. The antacid must be given 2 hours after rosuvastatin.
- Crestor given with cyclosporine can result in increased levels of rosuvastatin. This will require a lower dosage of Crestor.
- Crestor combined with warfarin therapy can result in increased INR values in these patients.

Patient Counseling:

1. Encourage patient to take medication as prescribed.
2. Consult healthcare provider prior to combining this drug with other prescription or nonprescription medications.

Megestrol Acetate (Megace®)

Formulations

- Suspension: 40mg/ml with alcohol 0.06% (236.6ml)
- Tablet: 20mg and 40mg

Adult Dose & Administration

- Cachexia associated with AIDS: 800mg qd has resulted in an average weight gain of 5kg; Lower dosages have also been successful (100-400mg qd).

Dosage in renal/hepatic impairment

- No adjustment is necessary.

Adverse Effects

- **GI Effects:**
 - Diarrhea, nausea and vomiting has occurred in up to 5% of patients.
- **Genitourinary Effects**
 - Impotence and decreased libido have been reported.
- **Cardiovascular Effects**
 - Mild elevation in blood pressure (approximately 10mm Hg) has been reported.
- **Others:** insomnia, headache, depression, paresthesia, asthenia.
- **Edema**, breakthrough bleeding, amenorrhea, weakness (>10%), depression, fever, allergic rash, fluid retention, nausea, stomach cramps, hepatotoxicity (1-10%), hepatomegaly, increased LDH, leukopenia, anemia, weight gain, DVT, diarrhea (5%), increased salivation, oral candidiasis (4%), impotence, decreased libido, hypertension, **hyperpnea** (due to stimulation of respiration).

Monitoring Parameters

- Monitor for tumor response; observe for signs of thromboembolic phenomena, and thromboembolic disorders, complete blood count with a differential, LDH, liver transaminases, blood pressure, temperature, respiratory rate, body weight, hemoglobin, hematocrit.

Drug Interactions

- **Dofetilide:** Megestrol can inhibit the cationic renal tubular secretion of dofetilide, resulting in increased plasma concentrations and the risk of QT prolongation and torsade de pointes.

Patient Counseling

- Patients may experience sensitivity to sunlight, change in appetite, decreased libido, or increased body hair.

- Report swelling in face, lips, or mouth, warmth, redness, or swelling in extremities.

Nandrolone (Deca-Durabolin®)

Formulations

- Injection as phenopropionate in oil; 25mg/ml (5ml); 50mg/ml (2ml)
- Injection as decanoate in oil; 50mg/ml (1ml, 2ml); 100mg/ml (1ml, 2ml); 200mg/ml (1ml)
- Injection repository, as decanoate; 50mg/ml (2ml); 100mg/ml (2ml); 200mg/ml (2ml)

Adult Dose & Administration

- **AIDS wasting; 100mg/week up to 600mg/week.**
- Inject deeply IM preferably in the gluteal muscle.

Dosage in renal/hepatic impairment

- Not available.

Adverse Effects

- **Acne**, gynecomastia, bladder irritability, **priapism** (>10%), insomnia, chills, decreased libido, **hepatic dysfunction**, nausea, diarrhea, **iron deficiency anemia**, **sodium and water retention**, **hypertension**, **virilization in women**, hypercalcemia, hypoglycemia, **hypertriglyceridemia**, increased alkaline phosphatase, hirsutism, **decrease in clotting factors and increased PT** (1-10%).

Monitoring Parameters

- Liver transaminases, complete blood count with a differential, hemoglobin, hematocrit, alkaline phosphatase, blood pressure, calcium levels, blood glucose, lipid profile, PT, and INR.

Drug Interactions

- Increased toxicity: **oral anticoagulants** (anticoagulant dosage may need to be decreased due to clotting factor suppression), **insulin, oral hypoglycemic agents, and adrenal steroids.**

Patient Counseling

- Virilization may occur in female patients; report menstrual irregularities.
- Males should report persistent penile erections.
- All patients should report persistent GI distress, diarrhea, dark urine, pale stools, and yellowing of skin or sclera.
- Diabetic patients should monitor glucose closely.

Oxandrolone (Oxandrin®)

Formulations

- Tablet 2.5mg and 10mg

Adult Dose & Administration

- 2.5mg 2-4 times per day for 2-4 weeks.
- Dosages range from 2.5mg to 20mg, depending upon the individual.
- Dosage regimens may be repeated intermittently.

Dosage in renal/hepatic impairment

- Use with caution with either renal impairment (due to propensity to cause edema) or hepatic impairment.

Adverse Effects

- Acne, gynecomastia, bladder irritability, **priapism (>10%)**, insomnia, chills, decreased libido, hepatic dysfunction, nausea, diarrhea, **iron deficiency anemia, sodium and water retention, hypertension**, virilization in women, hypercalcemia, hypoglycemia, **hypertriglyceridemia**, increased alkaline phosphatase, hirsutism, **decrease in clotting factors and increased PT (1-10%)**.

Monitoring Parameters

- Liver transaminases, complete blood count with a differential, hemoglobin, hematocrit, alkaline phosphatase, blood pressure, calcium levels, blood glucose, lipid profile, PT, and INR (international normalized ratio).

Drug Interactions

- Increased toxicity: **oral anticoagulants** (anticoagulant dosage may need to be decreased due to clotting factor suppression), **insulin, oral hypoglycemic agents, and adrenal steroids.**

Patient Counseling

- High protein, high caloric diet is recommended.
- Restrict salt intake
- Glucose tolerance may be altered in diabetics.
- Virilization may occur in female patients; report menstrual irregularities.
- Males should report persistent penile erections.
- All patients should report persistent GI distress, diarrhea, dark urine, pale stools, and yellowing of skin or sclera.

Testosterone Cypionate (Depo-Testosterone®)

Formulations

- In oil as cypionate **100mg/ml** (1ml, 10ml); **200mg/ml** (1ml, 10ml); Depo-Testosterone

Adult Dose & Administration

- Androgen replacement in the hypogonadal male can generally be achieved with 75-150mg IM every 7-10 days. Dosages vary for use in AIDS Wasting Syndrome (dosages of 200mg q 2weeks or 300mg q 3 weeks given IM).
- Administer into upper quadrant of gluteus maximus muscle, IM.

Dosage during renal/hepatic impairment

- Hepatic impairment: Reduce dose during hepatic impairment.
- Renal impairment: Use with caution due to the potential for edema.

Adverse Effects

- **Acne**, breast soreness, **menstrual problems**, **virilism**, bladder irritability, **priapism** (>10%) **edema**, flushing, hirsutism, nausea, vomiting, sleeplessness, impotence, **prostatic carcinoma** (1-10%), polycythemia.

Monitoring Parameters

- Liver function tests periodically, testosterone levels 14 days after initiation of therapy and every 3-4 months thereafter for the first year; digital rectal examination at baseline, 3-6 months after initiation, and then annually; lipid profile at baseline and repeated at 6-12 months; virilism in females, priapism, annual hematocrit and hemoglobin (due to erythropoietic potential).

Drug Interactions

- CYP3A3/4 and 3A5-7 enzyme substrate.
- Increased toxicity: Effects of **oral anticoagulants** may be increased.
- May decrease blood glucose and **insulin** requirements in diabetic patients.

Patient Counseling

- Virilization may occur in some patients, report menstrual irregularities, male's persistent penile erections, all patients should report persistent GI distress, diarrhea, dark urine, pale stools, and jaundice.

Testosterone Gel (Androgel®)

Formulation:

- 2.5 gram, 5.0 gram (delivers 25mg and 50mg respectively).
- Androgel is a clear colorless hydroalcoholic gel containing 1% testosterone.
- Approximately 10% of the applied testosterone is absorbed into systemic circulation.

Dosage

- Androgel is indicated for replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone.
- The recommended starting dose is 5.0gram packet (delivering 50mg) applied once daily (preferably in the morning) to clean, dry intact skin of the shoulders and upper arms or abdomen. Allow to air dry for a few minutes before covering with clothing. DO NOT apply to the genitals.

Adverse Effects

- Local skin reactions (irritation).
- Prostate disorders (2.8%) and includes enlargement and elevated PSA.
- Decreased libido, increase in liver transaminases, headache, increase in lipoprotein levels (eg cholesterol).

Monitoring Parameters:

- Measure serum testosterone levels 14 days after initiation of therapy to insure adequate dosing. If desired levels or effects are not achieved, can use next higher concentration.

Drug Interactions:

- Concurrent administration with corticosteroids may increase incidence of edema.
- Testosterone can reduce levels of thyroid binding globulin once absorbed.

Patient Counseling

- Apply gel to hands and rub medication into upper arm, shoulder or abdomen.
- Wash hands thoroughly after administration of medication.
- Store at room temperature.

Dronabinol (Marinol®)

Formulations

- **2.5mg, 5mg and 10 mg capsules**

Adult Dose and Administration

- **Appetite Stimulation: 2.5mg po twice daily before lunch and supper. If patient cannot tolerate, may decrease to 2.5mg/day as a single dose in the evening or at bedtime. The dosage may be increased gradually to a maximum of 20mg daily.**

Dosage in Renal and Hepatic Impairment

- **No dosage adjustment necessary.**

Adverse Effects

- **Central nervous system stimulation**
 - **Easy laughing, elation, heightened awareness, feeling of being “high”**
- **Palpitations**

Pregnancy and Lactation

- **FDA pregnancy category C.**

Drug Interactions

- **No significant drug interactions noted.**

Patient Counseling

- **Be aware of central nervous system stimulation and adjust lifestyle accordingly**
- **Inform healthcare provider if pregnant**

Hepatitis A Vaccine (Havrix®)

Formulations

- Prefilled injection syringe-adult (1440 ELISA units/mL)

Adult Dose & Administration

- 1440 ELISA units(1 mL) initial dose with a booster in 6 – 12 months.
- Shake well to achieve a homogeneous mixture.
- The injection site (IM) should be in the deltoid muscle with a 23 gauge or smaller needle with firm pressure applied to the site for at least 2 minutes.
- Intramuscular administration has been determined a reasonable, safe route by the ACIP for patients with a history of hemophilia, and high risk of bleeding. The vaccine should be scheduled shortly after anti-hemophilia or similar therapy.
- **Documentation:** All vaccine administration should be full documented in the patient's permanent record to include: date of administration, vaccine manufacturer, lot number, administration site, name, title and address of administrator.

Dosing in renal/hepatic impairment

- No dosage adjustment necessary.

Adverse Effects

- **Local Effects:**
 - Soreness or pain at the injection site (56% of patients).
 - Induration, erythema, tenderness, warmth and swelling.
- **Systemic Effects**
 - Headache (14%), pharyngitis, nasal congestion, dysgeusia, elevation of CPK and liver function tests, myalgia and fatigue, fever.

Monitoring Parameters

- Observe for local skin reactions and fever.

Drug Interactions

- **Immune globulin-** passively acquired antibody to hepatitis A virus (anti-HAV) from administration of immune globulin, appears to interfere with the active immune response produced by the hepatitis A viral vaccine.
- **Immunosuppressive agents-** patients may require additional doses of the vaccine.

Patient Counseling Tips

- Instruct the patient of the risk of hematoma development at the injection site.

Hepatitis B Vaccine (Engerix B®)

Formulations

- Suspension for injection-adults (20 mcg/mL)

Adult Dose & Administration

- 20mcg (1ml) IM administered at 0, 1 and 6 months.
- Shake well prior to each administration.
- The injection site should be in the deltoid muscle with a 23 gauge or smaller needle with firm pressure applied to the site for at least 2 minutes.
- Individuals at high risk for bleeding following IM injection (e.g. hemophiliacs) may receive the injections subcutaneously, lower levels are achieved and subcutaneous nodules have been observed.
- **Documentation:** All vaccine administration should be full documented in the patient's permanent record to include: date of administration, vaccine manufacturer, lot number, administration site, name, title and address of administrator.(this should be the address where the record id kept. name, title and address in the patient record.

Dosing in renal/hepatic impairment

- No dosage adjustment necessary.

Adverse Effects

- Nausea, vomiting, diarrhea, **injection site reactions**, **hypotension**, agitation, chills, and urticaria have been reported possible events associated with this medication.

Monitoring Parameters

- Observe injection site for local irritation/reaction.
- Administering this drug to immunodeficient patients (e.g. HIV/AIDS) may lower the effectiveness of the vaccine.

Drug Interactions

- Coadministration of **immunosuppressants** lowers the effects of the vaccine.

Patient Counseling Tips

- Instruct the patient on the importance of returning to receive all of the injections.

Hepatitis A Inactivated & Hepatitis B (Recombinant) Vaccine TWINRX®

Formulation

- **White suspension in vials and prefilled TIP-LOK® syringes containing a 1.0ml single dose.**
- **1.0ml dose contains 720 ELISA units of inactivated hepatitis A virus and 20mcg of recombinant hepatitis B surface antigen.**

Adult Dose and Administration

- **The vaccine is used as supplied and no dilution is necessary.**
- **Primary immunization for adults consists of 3 doses, given on a 0, 1 and 6 month schedule intramuscular route.**
- **Shake well prior to administration.**
- **The injection site (IM) should be in the deltoid muscle with a 23 gauge or smaller needle with firm pressure applied to the site for at least 2 minutes**
- **Intramuscular administration has been determined a reasonable, safe route by the ACIP for patients with a history of hemophilia, and high risk of bleeding. The vaccine should be scheduled shortly after anti-hemophilia or similar therapy.**
- **Documentation: All vaccine administration should be documented in the patient's permanent record to include: date of administration, vaccine manufacturer, lot number, administration site, name, title and address of administrator.**

Dosage in renal and hepatic impairment

- **No dosage adjustment necessary.**

Adverse Effects

- **Local effects**
 - **Induration**
 - **Pruritis, ecchymoses**
- **Systemic Effects**
 - **Headache, arthralgia, abdominal pain, rash.**

Drug Interactions

- **Administer with caution to people on anticoagulants and those with thrombocytopenia since bleeding may occur following intramuscular administration**
- **If administered to immunosuppressed persons or those receiving immunosuppressive therapy, the expected immune response may not be obtained**

Patient Counseling Tips

- **Inform patient as to the importance of completing the immunization series**

Pneumococcal Vaccine (Pneumovax[®])

Formulations

- Injection: 25mcg each of 23-polysaccharide isolates/0.5ml dose (0.5ml, 1ml, 5ml)

Adult Dose & Administration

- 0.5ml
- Do not inject IV, avoid intradermal, administer SC or IM in deltoid muscle or lateral mid thigh.
- Revaccination is in approximately 5 years.

Dose in renal/hepatic impairment

- No dosage adjustment needed.

Adverse Effects

- **Local irritation at injection site (>10%), fever, arthralgia, hypersensitivity, myalgia, headache, nausea, vomiting, adenitis, lymphadenitis, asthenia, and thrombocytopenia (rare).**

Monitoring Parameters

- Body temperature, and complete blood count if thrombocytopenia is suspected.

Drug Interactions

- Decreased effect with **immunosuppressive agents (eg. corticosteroids, alkylating agents, antimetabolites, corticotropin, and radiation), immunoglobulin, and other live vaccines within 1 month.**

Patient Counseling

- If a fever, headache, myalgia, or arthralgia develops, take an over the counter NSAID.

Amitriptyline (Elavil®)

Formulations

- Tablet, film-coated (10 mg, 25 mg, 50 mg, 75 mg, 100 mg, 150 mg)
Be sure to protect this medication from light.

Adult Dose & Administration

- Used on ADAP formulary at present as adjunctive therapy for peripheral neuropathy.
- Initiate at low doses (e.g. 10-25mg at bedtime). May increase the dosage depending upon response (50-100 mg/day at bedtime or in divided doses).

Dosing in hepatic impairment

- This medication should be used with caution, and the patient monitored carefully.

Adverse Effects

- **Anticholinergic effects** (tachycardia, constipation, mydriasis, increased intraocular pressure, urinary retention, and blurred vision), **sedation**, and increased appetite are all commonly reported events associated with this medication. Increased liver transaminases, increased alkaline phosphatase, **orthostasis**, flattening of the T-wave, rarely agranulocytosis, thrombocytopenia, and/or leukopenia.
- Tolerance usually develops towards the sedative, anticholinergic, and orthostatic effects of this drug.

Monitoring Parameters

- Blood pressure and pulse should be monitored initially, then as needed during therapy. Evaluation of mental status, weight, and EKG is suggested if symptoms warrant. Others include complete blood count with a differential, intraocular pressure, liver transaminases, alkaline phosphatase, arginine vasopressin if SIADH is suspected.

Drug Interactions

- Coadministration of **anticholinergics, CNS depressants, and carbamazepine** increases the risk for adverse effects.
- **Monoamine Oxidase Inhibitors** should not be used within two weeks of amitriptyline administration to avoid hypertensive crises and seizures.
- **Carbamazepine, phenobarbital, and rifampin** will increase the metabolism of amitriptyline.
- **Ethanol, valerian root, St. John's Wort, kava kava, and gotu kola** will increase CNS depression when used with amitriptyline.
- **Grapefruit juice** will block the metabolism of amitriptyline, and should be avoided.
- **SSRIs** inhibit the metabolism of TCAs, thus increasing plasma concentrations. (the dosage of the TCA may need to be reduced).

- **Guanethidine** – TCAs block the uptake of guanethidine into adrenergic neurons and prevent the hypotensive effect.
- **Clonidine**'s hypotensive effect is also inhibited.
- **Phenothiazines and haloperidol**: have been shown to inhibit metabolism and increase blood concentrations of TCAs. Both drugs should be carefully adjusted when given with a TCA.
- **Cimetidine**: reduces the hepatic metabolism of some TCAs. A reduction in TCA dosage may be necessary if used concomitantly.
- **Warfarin**: Amitriptyline has increased prothrombin time in patients on warfarin. The mechanism may involve inhibition of the anticoagulant's metabolism or decrease in intestinal motility, thereby increasing the time available for absorption of warfarin.

Patient Counseling

- Avoid alcohol, and grapefruit consumption while taking this medication.
- Do not discontinue use abruptly
- This medication may turn the urine blue-green, and cause drowsiness.
- If dry mouth is persistent, sips of water, sugarless gum, or hard candy may help.
- A response to the medication may take up to 3 – 6 weeks.
- The patient should rise slowly in the morning due to possible postural hypotension.
- Avoid during pregnancy
- Avoid while breastfeeding since the drug is secreted in human milk and potentially can adversely affect the nursing infant.

Nortriptyline (Pamelor®)

Formulations

- Capsule as hydrochloride 10mg, 25mg, 50mg, and 75mg
- Solution as hydrochloride 10mg/5ml (473ml)

Adult Dose & Administration

- Currently on ADAP formulary as adjunctive therapy to treat peripheral neuropathy.
- Begin therapy with 10-25mg at bedtime and increase dosage accordingly to control peripheral neuropathy.
- Use in pregnancy only if benefits outweigh the risk.

Dosage in renal/hepatic impairment

- Lower doses and slower titration, dependent on individualization of dosage, is recommended.

Adverse Effects

- **Arrhythmias, postural hypotension, tachycardia**, (myocardial infarction has been associated with this drug and other tricyclic antidepressants but a causal relationship has not been established), agitation, anxiety, ataxia, extrapyramidal side effects, hypomania, itching, breast enlargement, galactorrhea, gynecomastia, decrease libido, constipation, nausea, vomiting, numbness, tremor, mydriasis, eye pain, tinnitus, diaphoresis. Increased liver transaminases, increased alkaline phosphatase, SIADH, rarely agranulocytosis, thrombocytopenia, and/or leukopenia.
- Tolerance usually develops towards the sedative, anticholinergic, and orthostatic effects of this drug.

Monitoring Parameters

- Monitor blood pressure, pulse rate, mental status, and weight prior to and during therapy. Others include complete blood count with a differential, intraocular pressure, liver transaminases, alkaline phosphatase.

Drug Interactions

- Nortriptyline is metabolized by cytochrome P450 coenzymes CYP1A2 and 2D6 (substrate). Therefore, drugs that induce these enzyme systems can result in lower serum concentrations of this drug whereas drugs that inhibit these enzyme systems could cause serum nortriptyline levels to increase to toxic levels.
- Decreased effect: **carbamazepine phenobarbital, and rifampin** may increase the metabolism of nortriptyline.
- Nortriptyline inhibits the antihypertensive effects of **bethanidine, clonidine, guanadrel, guanabenz and/or guanfacine**.
- Increased effect/toxicity: **amphetamines, tolazamide, CNS depressants, and chlorpropamide**. Death has occurred when used with MAO inhibitors.

- **Cimetidine, grapefruit juice, indinavir, methylphenidate, ritonavir, quinidine, diltiazem, and verapamil** may inhibit metabolism.
- Combined use with a **beta agonist** or other drugs that prolong QT interval may predispose patients to cardiac arrhythmias.
- Coadministration of **anticholinergics, CNS depressants, and carbamazepine** increases the risk for adverse effects.
- Serotonin Syndrome has been reported with concurrent use of **MAOIs, and ritonavir**. Concurrent use with MAOIs is contraindicated and 2 weeks should elapse after discontinuation of either an MAOI or a TCA and initiation of the other class of drugs.
- **Ethanol, valerian root, St. John's Wort, kava kava, and gotu kola** will increase CNS depression when used with nortriptyline.
- **Grapefruit juice** will block the metabolism of nortriptyline, and should be avoided.
- **SSRIs** inhibit the metabolism of TCAs, thus increasing plasma concentrations. (the dosage of the TCA may need to be reduced)
- **Guanethidine** – TCAs block the uptake of guanethidine into adrenergic neurons and prevent the hypotensive effect.
- **Clonidine's** hypotensive effect is also inhibited.
- **Phenothiazines and haloperidol:** have been shown to inhibit metabolism and increase blood concentrations of TCAs. Both drugs should be carefully adjusted when given with a TCA.
- **Cimetidine:** reduces the hepatic metabolism of some TCAs. A reduction in TCA dosage may be necessary if used concomitantly.

Patient Counseling

- The patient should rise slowly in the morning due to possible postural hypotension.
- Avoid alcohol, and grapefruit consumption while taking this medication.
- Do not discontinue this medication abruptly.
- This medication may turn the urine blue-green, and cause drowsiness.
- If dry mouth is persistent, sips of water, sugarless gum, or hard candy may help.
- A response to the medication may take up to 3 – 6 weeks.

Gabapentin (Neurontin®)

Formulations

- Capsule (100 mg, 300 mg, 400 mg)
- Oral solution (250 mg/5 mL)
- Tablet, film-coated (600 mg, 800 mg)

Adult Dose & Administration

- 300 – 3600 mg daily in three divided doses.
- Maximum dosage per day is 2.4g.
- The maximum time interval between multiple daily doses should not exceed 12 hours. The first dose on the first day should be given at bedtime to avoid somnolence and dizziness. This medication can be taken without regard to meals.
- The capsules and tablets should be stored at room temperature, and the oral solution should be refrigerated.
- This drug is on the ADAP Formulary as an adjunctive therapy for the management of peripheral neuropathy

Dosing in renal impairment

- CrCl > 60 mL/minute: 900-3600mg/day in three divided doses.
- CrCl 30 – 59 mL/minute: 400-1400mg/day in two divided doses.
- CrCl 15 – 29 mL/minute: 200-700mg/day (qd dosing).
- CrCl 15 mL/minute: 100-300 mg/day.
- CrCl < 15ml/min: reduce proportionately utilizing value for CrCl 15ml/min.

Dosing in hepatic impairment

No data available.

Pregnancy: FDA Category C. See table on page 147.

Adverse Effects

- **Somnolence** (19%), **dizziness** (17%), **ataxia** (17%), fatigue (adults), and viral infections (3 – 12 year old children) have been reported during therapy with this medication (1%). Others include dry mouth (1.7%), nausea (8.4%), vasodilation (1.7%), dyspepsia (2.2%), edema (1.7%), rhinitis (4.1%), pharyngitis (2.8%), diplopia (5.9%), myalgia (2%), impotence (1.5%), and leukopenia (1.1%).

Monitoring Parameters

- Monitor serum levels of concurrently used anticonvulsants.
- Complete blood count with a differential, and CPK if myalgia is suspected.

Drug Interactions

- **Cimetidine** will increase serum concentrations of gabapentin.
- Gabapentin will increase serum concentrations of **norethindrone**.
- **Antacids** will reduce the bioavailability of Gabapentin by 20%.

- **Ethanol, valerian root, St. John's Wort, kava kava, and gotu kava** will increase CNS depression.
- **Evening primrose** will lower the seizure threshold.

Patient Counseling Tips

- Take this medication as directed.
- Neurontin may cause dizziness, use caution when driving or during hazardous tasks.
- The patient should report persistent diarrhea, fever, or palpitations immediately.
- Avoid alcohol and CNS depressants.
- Take first dose at bedtime to avoid somnolence and dizziness.
- This medication can be taken without regard to meals.
- Abrupt discontinuation of this medication will lower the seizure threshold.
- Avoid herbal products unless healthcare provider has been consulted.

Lamotrigine (Lamictal®)

Formulations

- Tablet: 25 mg, 100 mg, 150 mg, 200 mg
- Dispersible/Chewable tablet – black currant flavor (2 mg, 5 mg, 25 mg)
- This medication should be stored at room temperature and protected from light.

Adult Dose & Administration

- Primary purpose on ADAP formulary is adjunctive treatment of peripheral neuropathy. Other indications include:
- Adjunctive treatment for Lennox-Gastaut or partial seizures:
In combination with drugs containing valproic acid
Initial: 25 mg every other day for 2 weeks; then 25 mg every day for 2 weeks.
Maintenance: 100 – 400 mg daily in 1 – 2 divided doses. This dose may be increased by 25 – 50 mg every day for 1 – 2 weeks in order to achieve maintenance dose.

In combination with drugs not containing valproic acid
Initial: 50 mg daily for 2 weeks, then 100 mg in 2 doses for 2 weeks.
Maintenance: Daily dose can be increased by 100 mg every 1 – 2 weeks to be given in 2 divided doses.
- Bipolar disorder:
25 mg daily for 2 weeks, followed by 50 mg daily for 2 weeks, followed by 100 mg daily for 1 week. Thereafter, the daily dose should be increased by 100 mg weekly, up to a maximum of 500 mg daily.

This medication may be taken without regard to meals.

If the calculated dose cannot be achieved using whole tablets, the dose should be rounded down to the nearest whole tablet when determining the dose.

The dispersible tablet may be chewed, dispersed in water, or swallowed whole. When dispersing into water; add just enough water to cover the tablet and allow it to stand for approximately 1 minute until dispersed, swirl and consume immediately. Use a small amount of water or diluted fruit juice if swallowing whole.

Use caution writing, interpreting, and dispensing this product. The manufacturer reports a high number of medication errors.

Dosing in renal impairment

- Use with caution in patients with renal impairment.

Dosing in hepatic impairment

Experience in hepatically-impaired patients is limited. The manufacturer suggests that all doses should be reduced by 50% in patients with moderate (Child-Pugh Class B) and 75% in patients with severe (Child-Pugh Class C) hepatic impairment.

Adverse Effects

Headache, dizziness, ataxia, somnolence, nausea, vomiting, diarrhea, dyspepsia, **rash** (10%), possible **Stevens-Johnson syndrome**, hot flashes, pruritis, palpitations, pharyngitis, cough, neck pain, arthralgia, **dysmenorrhea**, vaginitis, amenorrhea, diplopia, blurred vision, and rhinitis. It is recommended that Lamictal not be restarted in patients who discontinued due to rash associated with prior treatment with Lamictal, unless the potential benefits clearly outweigh the risks.

Monitoring Parameters

- Monitor seizures for frequency and duration, and serum levels of concurrent anticonvulsants. Signs and symptoms of hypersensitivity reactions. Check menstrual regularity in female patients.

Drug Interactions

- **Lamotrigine** increases the amount of toxic metabolites produced from the metabolism of carbamazepine.
- **Valproic acid, and sertraline** will increase serum concentration levels of lamotrigine.
- **Acetaminophen, carbamazepine, phenytoin, and phenobarbital** will lower serum levels of lamotrigine.
- **Lamotrigine** will lower serum concentrations of valproic acid.
- **Ethanol** will increase the risk of CNS depression.
- **Evening primrose** will lower the seizure threshold.
- **Oral Contraceptives:** There have been reports of decreased concentrations of this drug once oral contraceptive therapy was initiated. In addition, reports of increased lamotrigine concentrations following discontinuation of oral contraceptives as well. Dosage adjustments may be required for those patients receiving or discontinuing oral contraceptive agents.

Patient Counseling Tips

- May cause GI upset.
- The dispersible tablet may be chewed, dispersed in water, or swallowed whole. When dispersing into water; add just enough water to cover the tablet and allow it to stand for approximately 1 minute until dispersed, swirl and consume immediately.
- Use a small amount of water or diluted fruit juice if swallowing whole.
- Take without regard to food.

Diphenoxylate (Lomotil®) with atropine

Formulations

- Schedule V controlled substance
- Oral solution (2.5mg diphenoxylate hydrochloride/0.025 mg atropine per 5 mL (4 mL, 10 mL, 60 mL)
- Tablet (2.5 diphenoxylate/0.025 mg atropine)
- This medication should be protected from light.

Adult Dose & Administration

- 5mg qid
- Maintenance – 5 – 15 mg in 2 – 3 divided doses.
- If no response occurs after 48 hours, then the drug will probably be ineffective.

Dosing in renal/hepatic impairment

- Renal impairment: No adjustment necessary.
- Hepatic impairment: Use this drug with caution in patients with cirrhosis, abnormal LFTs, and/or advanced liver disease due to reports of hepatic coma.

Adverse Effects

- Nervousness, dizziness, drowsiness, nausea, abdominal discomfort, pruritis, euphoria, **dry mouth, urinary retention, paralytic ileus, toxic megacolon, pancreatitis, sedation**, angioedema, **tachycardia, blurred vision**, and respiratory depression are possible events that are associated with the use of the medication.

Monitoring Parameters

- Monitor for signs for atropinism (dryness of skin and mucus membranes, thirst, tachycardia, flushing). Note the number and consistency of stools and observe for symptoms of toxicity, fluid and electrolyte loss, hypotension, and respiratory depression. Others include amylase and lipase (if suspected pancreatitis), urinary output, bowel sounds, and respiratory rate (if suspected respiratory depression).

Drug Interactions

- Concurrent use of **MAOIs and CNS depressants** will increase the risk of adverse effects, and increase the half-life of the drug.
- **Ethanol** will increase CNS depression.

Patient Counseling Tips

- Instruct the patient to use caution when driving or performing hazardous tasks. The patient should report persistent diarrhea, fever, or palpitations immediately. **Avoid alcohol and CNS depressants.**

Prochlorperazine (Compazine®)

Formulations

- Capsule sustained action as maleate: 10mg, 15mg
- Suppository, rectal: 2.5mg, 5mg, 25mg
- Syrup as edisylate; 5mg/5ml (120ml)
- Tablet as maleate; 5mg, 10mg
- Vials: 2ml (5mg/ml) and 10ml (5mg/ml)

Adult Dose & Administration

- Antiemetic:
 - Oral tablets 5-10mg 3-5 times/day with a max of 40mg/d.
 - Rectal: 25mg bid.
- Antipsychotic:
 - Oral 5-10mg 3-4 times/day up to 150mg/day may be required in some patients.

Dosage in renal/hepatic impairment

- No adjustment is necessary.

Adverse Effects

- Bradycardia, cardiac arrest, dizziness, drowsiness, tachycardia, cerebral edema, dizziness, drowsiness, **extrapyramidal signs**, headache, discoloration of skin, photosensitivity, breast enlargement, amenorrhea, pruritis, **tardive dyskinesia**, changes in libido, ejaculatory disturbances, incontinence, polyuria, **agranulocytosis**, hemolytic anemia, hepatotoxicity, tremor.

Monitoring Parameters

- Monitor blood pressure, signs of EPS, heart rate, menstrual regularity, complete blood count with a differential, hemoglobin, hematocrit, and contact dermatitis.

Drug Interactions

- Decreased effect: **barbiturates, carbamazepine, Benztropine** may inhibit the effect of prochlorperazine.
- Increased effect/toxicity: **chloroquine, propranolol, and sulfadoxine-pyrimethamine**. Concurrent use with a TCA may produce increased toxicity and altered therapeutic effect.

Patient Counseling

- May cause drowsiness and impair judgment.
- Photosensitivity reactions can occur so avoid excessive sunlight.
- Notify MD if any involuntary movements occur.
- Avoid alcohol and other CNS depressants.

Acyclovir (Zovirax®)

Formulations

- Capsules 200mg
- Suspension 200mg/5ml
- Tablets 400mg, 800mg
- Parenteral 25mg/ml, 50mg/ml, 5mg/ml in 0.9% NaCl, and 500mg (IV infusion only)

Adult Dose & Administration

- Oral:
 - Genital Herpes – 200mg every 4 hours while awake for 10 days.
 - Herpes Simplex virus – 400mg every 4 hours while awake for 7-14 days.
 - Varicella (chickenpox) – 20mg/kg (not to exceed 800 per dose) 4 times daily for 5 days.
 - Herpes Zoster (Shingles) – 800mg every 4 hours 5 times daily for 7-10 days.
 - Maintenance – 400mg bid.
- IV: Acyclovir should be administered over 1 hour and NOT by rapid IV infusion (over less than 10 minutes) or rapid IV injection.
- The usual IV dosage for Herpes Simplex Virus infection is 5mg/kg every 8 hours for 7 days.
- The usual IV dosage for Varicella-Zoster infections is 20mg/kg every 8 hours for 7 days (this is also the maximum dosage).

Dosing in Renal Impairment

- For HIV-infected patients with impaired renal function, the following oral dosages of acyclovir have been suggested based on a usual dosage regimen of 200-800mg every 4-6 hours and the patient's CrCl.

CrCl (ml/min)	Adjusted Dosage Regimen
>80	No adjustment
50-80	200-800mg every 6-8 hours
25-50	200-800mg every 8-12 hours
10-25	200-800mg every 12-24 hours
<10	200-400mg every 24 hours
Hemodialysis	Supplement usual dosage after each hemodialysis.

- Parenteral Dosage

CrCl (ml/min)	Adjusted Dosage Regimen
>80	No adjustment
50-80	No adjustment
25-50	5mg/kg every 12-24 hours
10-25	5mg/kg every 12-24 hours
<10	2.5mg/kg every 24 hours
Hemodialysis	Administer usual dose after hemodialysis

Dosing in Hepatic Impairment

- No recommendations made by the manufacturer.

Adverse Effects

- **Local reactions** at injection site, **increased BUN and/or serum creatinine** (5-10%)(especially when given by rapid IV infusion), renal failure, headache, paresthesia, asthenia, vertigo, dizziness, fatigue, insomnia, nausea, diarrhea, **thrombotic thrombocytopenic purpura/hemolytic uremic syndrome, thrombocytosis, thrombocytopenia, transient leukopenia, megaloblastic hematopoiesis, anemia, neutropenia**, fever, and pain.

Monitoring Parameters

- BUN, serum creatinine, complete blood count with a differential, hemoglobin, hematocrit.

Drug Interactions

- **Zidovudine**- increased risk of neurotoxicity. (Monitor patient closely).
- **Probenecid**- Increased AUC and plasma concentrations of acyclovir due to decreased renal clearance.
- **Antifungal agents**- Amphotericin B has been shown to potentiate the antiviral effect of acyclovir .
- **Interferon**- Synergism with acyclovir.
- **Methotrexate**- Parenteral acyclovir should be used with caution in patients who have exhibited prior neurologic reactions to intrathecal methotrexate.

Patient Counseling Tips

- Medicine may not work if a herpes breakout is more than 3 days old.
- Acyclovir may be taken with or without food.
- Patient should stay well hydrated to avoid renal adverse effects.
- Acyclovir will not prevent the spread of herpes.

Atovaquone (Mepron®)

Formulations

- Oral: Suspension 750mg/5ml

Adult Dose & Administration

- Atovaquone should be administered with a high fat meal to maximize bioavailability.
- Pneumocystis Carinii Pneumonia-
 - Treatment: 750mg bid with food for 21 days.
 - Prophylaxis: 1500mg once daily with food.
- Toxoplasmosis-
 - Treatment: 1500mg bid with meals combined with pyrimethamine 200mg x 1, then 75mg/day or sulfadiazine 1.5g qid.
- Babesiosis- 750mg bid for 7-10 days.
- Malaria- 500mg bid for 3 days, when used in conjunction with doxycycline.

Dosage in Renal and Hepatic Impairment

- The pharmacokinetics of atovaquone in individuals with renal or hepatic impairment and the possible need for caution and/or dosage adjustment remain to be fully determined.

Adverse Effects

- **Rash** (39%), GI effects (**nausea, vomiting, and diarrhea are very common**), fever, **headache** (28%), **asthenia** (22%), anemia, increased alkaline phosphatase (8%), decrease in hemoglobin, increased ALT and AST, increased BUN, increased serum creatinine, hyponatremia (10%), fever (40%), oral candidiasis (10%), rhinitis (24%), and hyperglycemia.

Monitoring Parameters

- Complete blood count with a differential, alkaline phosphatase, ALT, AST, BUN, serum creatinine, sodium level, body temperature, volume status, and blood glucose.

Drug Interactions

- Atovaquone is 99.9% bound to plasma proteins.
- **Rifampin** – reduces atovaquone levels by 50%; rifabutin probably has a similar effect. Avoid combination or increase dose of atovaquone

Patient Counseling Tips

- Take with food for best absorption.

Azithromycin (Zithromax®)

Formulations

- Suspension- 100mg per 5ml, 200mg per 5ml, and single dose packets containing 1g per packet.
- Film coated tablets- 250mg and 600mg
- Tablets 250mg (Z-Pak) given as a 5 day regimen of 6 tablets
- Tablets 500mg (Tri-Paks) given as a 3 day regimen of 3 tablets
- Parenteral: (For IV infusion only) 500mg

Adult Dose and Administration

- The usual dosage is 500mg on the first day, followed by 250mg once daily for 4 additional days.
- Primary prevention of Mycobacterium avium Complex- the usual oral dosage is 1.2g weekly. It can be given alone or in combination with rifabutin (300mg daily).
- Treatment and secondary prevention of Mycobacterium avium Complex- 500 mg daily with ethambutol, with or without rifabutin.
- Treatment of Mycobacterium avium Complex- 250mg or 500mg 3 times weekly in combination with rifabutin and ethambutol.
- May be given without regard to meals.

Dosage in Renal and Hepatic Impairment

- Caution should be exercised in patients with hepatic dysfunction due to azithromycin's liver metabolism. Caution should be exercised in patients with renal impairment since experience with azithromycin in such patients is limited.

Adverse Effects

- **Diarrhea**, nausea, abdominal pain, vomiting, dyspepsia, rash, **photosensitivity**, increased ALT, AST, LDH, and alkaline phosphatase, increased potassium, increased BUN, serum creatinine, and/or serum phosphate levels, palpitations, and headache.

Monitoring Parameters

- ALT, AST, LDH, alkaline phosphatase, potassium, BUN, serum creatinine, and serum phosphate.

Drug Interactions

- Drugs Affecting Hepatic Microsomal Enzymes
- **Antacids**- Results in a decreased rate of absorption of azithromycin as evidenced by 24% reduction in peak serum concentrations.
- **Theophylline**- May increase serum theophylline concentrations.
- **Nucleoside Reverse Transcriptase Inhibitors**- Concomitant administration may increase the mean peak plasma concentrations, AUCs, and clearance of NRTIs.

Patient Counseling Tips

- Use this medication for the full treatment time, even if you feel better after a few days.
- The oral liquid must be used within 10 days of filling the prescription.
- Because of increased photosensitivity, use sunscreen when outdoors.
- May be taken without regard to meals.
- Report severe or persistent diarrhea.
- Separate antacid dosing by 1 hour to avoid decrease in absorption.

Clarithromycin (Biaxin[®])

Formulations

- Suspension – 125mg/5ml or 250mg/5ml
- Tablets, Film coated- 250mg, 500mg
- Tablets, extended-release, film coated- 500mg

Adult Dose and Administration

- May be given without regard to meals.
- Extended- release tablets should be taken with food, swallowed whole, not chewed, broken or crushed.
- The suspension may be administered with milk.
- The usual dosage is 250-500mg every 12 hours for 10-14 days.
- Mycobacterium avium Complex (MAC)-
 - Treatment and secondary prevention: 500mg every 12 hours
 - Primary prophylaxis: 500mg every 12 hours
- Note: Avoid in pregnancy except where no alternate therapy is appropriate.

Dosage in Renal and Hepatic Impairment

- In patients with a CrCl of < 30ml/min with or without hepatic impairment, the dosage should be halved or the dosing interval doubled.

Adverse Effects

- **Diarrhea, nausea**, abnormal taste, abdominal discomfort, increased ALT, AST, GGT, alkaline phosphatase, LDH and/or total bilirubin, hepatomegaly, **increased prothrombin time**, decreased WBC count, elevated BUN and serum creatinine, headache, and allergic reactions.

Monitoring Parameters

- ALT, AST, GGT, alkaline phosphatase, LDH and total bilirubin, PTT, complete blood count with a differential, BUN, and serum creatinine.

Drug Interactions

- **Pimozide**- Macrolides inhibit the metabolism of pimozide resulting in increased plasma concentrations. Since pimozide prolongs the QT interval, such increased plasma concentrations may lead to serious cardiac events. (Contraindicated).
- **Cisapride**- QT prolongation (Contraindicated).
- **Carbamazepine**- Clarithromycin may decrease carbamazepine's AUC and peak plasma concentration. (Use with caution) .
- **HMG-CoA Reductase Inhibitors (Statins)**- increased serum concentrations of the statins via inhibition of P450 isoenzymes.
- **Rifabutin and Rifampin**- May increase the metabolism of clarithromycin.
- **Theophylline**- Increased serum theophylline concentrations. (Adjust theophylline dosage if necessary).

- **Ritonavir**- Increased AUC and peak plasma concentration of clarithromycin 77% and 31%, respectively. (If the patient has a CrCl of 30-60ml/min, reduce the clarithromycin dosage by ½; if the patient has a CrCl of <10ml/min, reduce the clarithromycin dosage by 75%).
- **Fluconazole**- Serum concentrations and the AUC for clarithromycin increased by an average of 33% and 18%, respectively.
- **Digoxin**- May elevate digoxin levels. (Monitor digoxin levels carefully).
- **Oral anticoagulants**- Possible enhanced effect of the oral anticoagulants (Monitor the prothrombin time).

Patient Counseling Tips

- May be taken with or without food.
- Use this medication for the full treatment time, even if you feel better in a few days.
- Take the extended-release tablet with food or milk.
- The oral liquid must be used within 14 days after the prescription is filled.
- Report severe or persistent diarrhea to the physician.
- Shake the suspension well prior to each dose.

Dapsone

Formulations

- Tablets- 25mg and 100mg

Adult Dose and Administration

- Leprosy- 100mg daily in conjunction with rifampin and clofazimine given for 12 months.
- Pneumocystis carinii Pneumonia-
Treatment: 100mg once daily has been given in conjunction with trimethoprim for 21 days.
Prophylaxis: 50mg twice daily in conjunction with pyrimethamine and leucovorin or dapsone in conjunction with pyrimethamine.
- Toxoplasmosis-
Prophylaxis: 50mg once daily in conjunction with pyrimethamine and leucovorin.

Dosing in Renal and Hepatic Impairment

- No recommendations made by the manufacturer.

Adverse Effects

- Dose-related **hemolytic anemia (exacerbated in patients with G-6- PD deficiency)**, **methemoglobinemia**, cyanosis, **leukopenia**, exfoliative dermatitis, toxic erythema, toxic epidermal necrolysis, urticaria, peripheral neuropathy with motor loss, insomnia, headache, psychosis, anorexia, nausea, vomiting, toxic hepatitis, cholestatic jaundice, increased ALT, AST, alkaline phosphatase, LDH, phototoxicity, drug-induced lupus, and tachycardia.

Monitoring Parameters

- Complete blood count with differential, hemoglobin, hematocrit, ALT, AST, LDH, alkaline phosphatase, reticulocyte count and heart rate.

Drug Interactions

- **Didanosine**- The buffer system of the ddI preparation interferes with the absorption of the dapsone.
- **Clofazimine**- May increase the urinary excretion of dapsone.
- **Drugs Associated with Adverse Hematologic Effects**- Concomitant use of pyrimethamine and dapsone may result in an increased risk of hematologic adverse effects. (Monitor the patient closely)
- **Rifampin**- Decreases serum dapsone concentrations (A change in dapsone's dosage is not necessary).
- **Trimethoprim**- Increases plasma dapsone concentrations during concomitant therapy.

Patient Counseling Tips

- May be taken with food to avoid stomach upset; May cause sulfa allergy

Ethambutol (Myambutol®)

Formulations

- Tablets, film-coated 100mg and 400mg

Adult Dosage and Administration

- **Initial Treatment:** 15mg/kg daily when used for conventional therapy. (max 1500mg/day).
- **Retreatment:** 25mg/kg daily for 60 days or (until smears appear negative) with at least one other antitubercular drug; then decrease to 15mg/kg daily single dose.
- When ethambutol is used in conjunction with other antituberculosis agents for the treatment of disseminated Mycobacterium avium complex infections, a dosage of 15mg/kg daily has been recommended by ATS.

Dosing in Renal and Hepatic Impairment

- If the CrCl = 70-100 ml/min, the dosage should not exceed 15mg/kg daily.
- If the CrCl is < 70 ml/min, the dosage should be further reduced.
- Some clinicians have suggested that the usual dose be administered every 24-36 hours in patients with a CrCl of 10-50ml/min and every 48 hours in patients with a CrCl <10ml/min.

Adverse Effects

- **Optic neuritis, constriction of visual fields**, central and peripheral scotomas, loss of red-green color discrimination, dermatitis, headache, fever, GI upset, arthralgia, vomiting, peripheral neuritis, increased serum uric acid, and abnormal LFTs.
- **Contraindicated in patients with optic neuritis and children under 13 years of age.**

Monitoring Parameters

- Visual testing should be performed prior to initial therapy. Testing should be done monthly in patients receiving more than 15mg/kg/day. Examinations should include ophthalmoscopy, finger perimetry, and testing of color discrimination. Patients developing adverse ocular effects may show subjective visual symptoms either before or simultaneously with decreases in visual acuity. ALL patients should be questioned about blurred vision and acuity.
- serum uric acid levels, ALT, and AST
- Monitor patient for gout.

Drug Interactions

- **None reported**

- **Patient Counseling Tips**

- May take with food to avoid GI upset.
- This medication may cause blurred vision and the patient should exercise caution while driving.
- Report any changes in vision to the healthcare provider.

Fluconazole (Diflucan[®])

Formulations

- Suspension: 350 mg bottle (50mg/5ml when reconstituted) and 1400mg bottle (200mg/5ml when reconstituted)
- Tablets 50mg, 100mg, 150mg, 200mg
- Fluconazole in Dextrose for IV infusion only- 2mg/ml (200 or 400mg) in 5.6% Dextrose
- Fluconazole in Sodium Chloride for IV infusion only- 2mg/ml (200 or 400mg) in 0.9% Sodium Chloride

Adult Dose and Administration

- Administered orally or by IV infusion.
- Can be given orally without regard to meals.
- IV infusions should be administered once daily at a rate not exceeding 200 mg/hr.
- Oral and IV dosages are identical.
- Oropharyngeal or Esophageal Candidiasis: 200mg on the first day, followed by 100mg or 200mg doses given once daily.
- Vulvovaginal Candidiasis: A single (1 day only) 150mg oral dose.
- Cryptococcal Infections: 400mg on the first day, followed by 200mg to 400mg doses given once daily. **Higher doses of fluconazole (800-1000mg daily) have been used in some patients with HIV for the treatment of cryptococcal meningitis.**
- Coccidioidomycosis: 200-800mg once daily.
- Blastomycosis or Histoplasmosis: 400-800mg daily.
- Prophylaxis of Fungal infections: 100-200mg daily. **400mg given once weekly has also been used in HIV patients.**

Dosing in Renal Impairment

- The dosage must be modified in response to the degree of impairment. The manufacturer recommends that adults with impaired renal function receive an initial loading dose of 50-400mg of fluconazole, then patients with creatinine clearances exceeding 50ml/min should receive 100% of the usual daily dose and those with creatinine clearances of 50ml/min or less should receive 50% of the usual daily dose.

Dosing in Hepatic Impairment

- No recommendations by the manufacturer.

Adverse Effects

- **Hepatotoxicity**, cholestasis, **hepatitis**, hepatic failure, nausea, vomiting, diarrhea, abdominal pain, rash accompanied by eosinophilia and pruritis, Stevens-Johnson syndrome, headache, dizziness, anemia, leukopenia, thrombocytopenia, fever, edema, and oliguria.

Monitoring Parameters

- Liver transaminases, alkaline phosphatase, and complete blood count with a differential.

Drug Interactions

- **Amphotericin B**- antagonism can occur with these agents. (Use with caution)
- **Flucytosine**- the combination is synergistic, and additive.
- **HIV Protease Inhibitors**- If used concomitantly with Indinavir or Ritonavir, increased peak plasma concentration and AUC of the antiretroviral agent has been reported. Dosage adjustment of the PI is probably unnecessary.
- **NRTIs**- fluconazole appears to interfere with the metabolism and clearance of zidovudine.
- **Rifabutin** - Concomitant administration of fluconazole and rifabutin resulted in substantially increased plasma concentrations and AUCs of rifabutin. **Rifampin**: Concomitant administration of fluconazole and rifampin resulted in a 25% decrease in the AUC and 20% decrease in the plasma half-life of fluconazole. (May need to increase the dose of fluconazole.)
- **CNS agents**- Increases in the serum concentrations of amitriptyline and carbamazepine have occurred when given with fluconazole.
- **Warfarin**- increased PT (Monitor PT carefully.)
- **Cyclosporine and Tacrolimus**- increased cyclosporine and tacrolimus concentrations.
- **Cisapride**- increased concentrations of cisapride (Contraindicated)
- **Antacids and H₂ antagonists**- decreased GI absorption of fluconazole.
- **Phenytoin**- increased plasma concentrations of phenytoin. (Adjust phenytoin's dosage based upon plasma concentrations.)
- **Sulfonylureas**- reduced metabolism of the anti-diabetic agents has resulted.
- **Theophylline**- increased serum theophylline concentrations.
- **Thiazide diuretics**- resulted in a 14% increase in fluconazole concentrations. No dosage adjustment necessary.
- **Zidovudine**: significant increase in zidovudine AUC following the administration of fluconazole.

Patient Counseling Tips

- The tablet may be swallowed whole or crushed.
- The suspension must be discarded after 14 days.

Erythropoietin or Epoetin Alfa (Epogen[®], Procrit[®])

Formulations

- Injection for IV or subcutaneous use 2000 units/ml, 3000 units/ml, 4000 units/ml, 10,000 units/ml, 20,000 units/ml, 40,000 units/ml

Adult Dose and Administration

Usual Dosage

Subcutaneous (SQ) injections either three times weekly or once weekly. Treatment regimen should be individually tailored to each patient.

- **Initial:** 100-300 U/kg/day SQ three times a week (TIW) for 8 weeks. (monitor hematocrit weekly with no more than a 4-point rise in a 2-week period).
- **Dosage Increase:** If response is unsatisfactory after 8 weeks, the dose of EPO can be increased by 50 to 100 U/kg TIW. Response should be evaluated every 4-8 weeks thereafter and the dose adjusted accordingly by 50-100 U increments TIW. *If response is unsatisfactory at 300 units. It is unlikely to be achieved at higher doses.*
- **Maintenance:** After achieving desired response, titrate dose to maintain desirable hematocrit level. (75-150 units/kg per week for up to 6 months)
- **Anemia of Chronic Renal Failure:** initial dosage of 50-100 units/kg 3 times weekly until the hematocrit approaches 36% or the hemoglobin approaches 12 g/dL.
- **Zidovudine-associated Anemia in HIV-infected patients-** 100 units/kg IV or s.c. 3 times weekly for 8-12 weeks.
- **Cancer Patients Receiving Chemotherapy:**
 - 150 units/kg SQ three times weekly; reduce by 25% if hemoglobin reaches 12 g/dl or if there is > 1g/dl increase in any 2 week period. Can increase to 300 u/kg thereafter if inadequate response OR
 - 40,000 units SQ weekly; after 4 weeks increase to 60,000 SQ weekly if hemoglobin not increased by 1g/dl. If patient does not respond to this increase, do not increase further.

EPO is not indicated for the treatment of anemia in HIV-infected patients due to other factors such as iron or folate deficiencies, hemolysis or gastrointestinal bleeding, which should be managed appropriately.

Dosing in Renal or Hepatic Impairment

- No recommendations given by the manufacturer.

Adverse Effects

- **Hypertension, seizures (tonic-clonic), possible thrombotic complications** associated with epoetin-alfa induced increases in erythrocyte count, predialysis increases in BUN, creatinine, uric acid, and phosphate, flu-like syndrome (characterized by diaphoresis, chills, shivering, malaise, myalgia, bone pain and arthralgia, fever and abdominal pain/cramps).

Monitoring Parameters

- Hematocrit should be determined at least once a week in HIV-infected patients with zidovudine-induced anemia, blood pressure, BUN, serum creatinine, electrolytes, evaluation of iron stores (including transferrin saturation and serum ferritin) should be performed once a month for 3 months, and complete blood count with a differential. Obtain serum erythropoietin levels (optional).

Drug Interactions

- **Androgens**- these agents may stimulate residual endogenous erythropoietin secretion and decrease the required dosage of epoetin alfa.
- **Probenecid**- may inhibit renal tubular secretion of endogenous erythropoietin.

Patient Counseling Tips

- Avoid in patients with uncontrolled hypertension.
- Inform patients that flu-like symptoms are transient.

Itraconazole (Sporanox®)

Formulations

- Capsules 100mg
- Solution 10mg/ml
- Injection for IV infusion 10mg/ml (250mg for delivery of 200mg)

Adult Dose and Administration

- Because of differences in bioavailability, itraconazole capsules and oral solution should not be used interchangeably on a mg-for-mg basis.
- **Blastomycosis or Histoplasmosis**: capsules should be initiated at 200mg once daily.
- The manufacturer recommends increasing oral itraconazole dosage in 100mg increments daily up to a maximum dosage of 400mg daily.
- Oral doses exceeding 200mg per day should be divided into 2 doses daily. If given IV, use 200mg twice daily for 4 doses, then the dosage should be decreased to 200mg once daily.
- **Aspergillosis**: capsules can be given at 200-400mg daily. If IV, give 200mg twice daily for 4 doses, then decrease the dose to 200mg once daily.
- **Oropharyngeal and Esophageal Candidiasis**: The oral solution should be vigorously swished in the mouth (10ml at a time) for several seconds and then swallowed. The recommended dosage of oral solution for oropharyngeal candidiasis is 200mg (20ml) daily for 1-2 weeks. The recommended dosage of oral solution for esophageal candidiasis is 100mg (10ml) daily.
- **Primary prophylaxis**: capsules; 200mg once daily.

Dosage in Renal and Hepatic Impairment

- Adjustment of oral itraconazole dosage in patients with renal impairment does not appear to be necessary.
- Contraindicated in patients with renal impairment since severe renal impairment reduced the clearance of hydroxypropyl-beta-cyclodextrin (an excipient contained in itraconazole injection).

Adverse Effects

- Nausea, constipation, dyspepsia, dysphagia, flatulence, gastritis, taste perversion, ulcerative stomatitis, rash, pruritis, headache, dizziness, congestive heart failure, peripheral edema, pulmonary edema, **increased liver transaminases, hypokalemia**, adrenal insufficiency, gynecomastia, and albuminuria.

Monitoring Parameters

- Edema, pulmonary function, liver transaminases, potassium levels, adrenocorticosteroids, and proteinuria.
- Do not administer for the treatment of onychomycosis in patients with evidence of ventricular dysfunction such as congestive heart failure (CHF) or history of CHF.

Drug Interactions

- **Antiarrhythmic agents**- Concomitant use of quinidine or dofetilide and itraconazole is contraindicated due to prolongation of the Q-T interval.

- **Antilipemic agents**- The concentrations of HMG-CoA reductase inhibitors may be increased by itraconazole.
- **Antiretroviral Agents**: Co-administration with nevirapine and other non-nucleoside reverse transcriptase inhibitors is not recommended since these agents can induce the metabolism of ketoconazole and potentially itraconazole. Monitor use with protease inhibitors as well since co-administration may result in increased concentration of these drugs by itraconazole.
- **Benzodiazepines**- increased plasma concentrations of benzodiazepines.
- **Pimozide**- contraindicated due to cardiac dysarrhythmias and/or sudden death.

Patient Counseling Tips

- Should be taken with food.
- Report any symptoms of nausea, vomiting, abdominal pain or signs of jaundice
- Caution patient concerning signs and symptoms of congestive heart failure and if symptoms occur, discontinue medication and call provider immediately.

Leucovorin (Folinic Acid)

Formulations

- Tablets: 5mg, 10mg, 15mg, 25mg
- Parenteral: 50mg, 100mg, 200mg, 350mg

Adult Dose and Administration

Therapy is usually oral, but should be parenteral if there is vomiting, NPO status, or the dose is >25mg

- **Toxoplasmosis Treatment:** Pyrimethamine 50-75mg/day + leucovorin 10-20mg/day x 6 weeks.
- **Maintenance:** Pyrimethamine 25-50mg/day + leucovorin 10-25mg/day.
- **Toxoplasmosis Prophylaxis:** Pyrimethamine/leucovorin, 25mg every week (with dapsone + pyrimethamine).
- Because of the calcium concentration of the solution, the IV infusion rate should not exceed 16 ml (160mg of leucovorin) per minute.
- Prevention and Treatment of Hematologic Toxicity Associated with Folic Acid Antagonists: When large doses or overdoses of methotrexate are given, leucovorin can be administered by IV infusion in doses up to 75mg within 12 hours, followed by 12mg IM every 6 hours for 4 doses. When average doses of methotrexate are given, 6-12mg of leucovorin may be given IM every 6 hours for 4 doses.

Dosing in Renal or Hepatic Impairment

- No recommendations made by the manufacturer.

Adverse Effects

- **Nontoxic** in therapeutic doses.
- **Thrombocytosis, and hypersensitivity reactions.**

Monitoring Parameters

- Hematocrit, hemoglobin, and complete blood count with a differential.

Drug Interactions

- **Fluorouracil-** leucovorin increases the toxicity of fluorouracil.

Patient Counseling Tips

- Do not give to a patient with pernicious anemia due to possible masking of neurologic effects of that anemia.

Miconazole (Lotrimin[®], Monistat[®], Micatin[®], Desenex[®])

Formulations

- Aerosol 1%, 2%
- Aerosol Powder 2%
- Cream 1%, 2%
- Lotion 1%, 2%
- Powder 2%
- Solution 1%
- Tincture 2%
- Suppositories 100mg, 200mg

Adult Dose and Administration

- Topical: applied twice daily in the morning and evening. (Dermatophytoses, Superficial Mycoses, and Cutaneous Candidiasis).
- Suppository: 200mg vaginally once daily at bedtime for 3 consecutive days or 100mg of miconazole nitrate (one suppository or 5g of the 2% cream) vaginally. (Vulvovaginal Candidiasis).

Dosing in Renal or Hepatic Impairment

- No recommendations made by the manufacturer.

Adverse Effects

- **Irritation, burning**, contact dermatitis, headache, hives, and **rarely pelvic cramps**.

Monitoring Parameters

- Monitor for improvement in the patient's condition.

Drug Interactions

- **Coumarin anticoagulants**- increased PT time, INR, and/or bleeding or bruising have been reported in some patients receiving intravaginal miconazole.
- Topical miconazole is minimally absorbed and thus would not lead to any drug interactions.

Patient Counseling Tips

- Wear clean cotton underwear instead of nylon or rayon, or wear underwear with cotton crotch.
- The suppository may be moistened with water for easier insertion. Petroleum jelly should be avoided.
- A sanitary pad may be used in case of leakage of the drug, but tampons should be avoided.

Filgrastim (Neupogen®)

Formulations

- Injection for IV or subcutaneous use 300µg and 480µg

Adult Dose and Administration

- **Neutropenia associated with HIV infection:** 5-10µg/kg given by SQ injection once daily for 2-4 weeks.
- Chemotherapy-induced Neutropenia: 5µg/kg daily SQ. for up to 2 weeks.
- Bone Marrow Transplantation: 10µg/kg daily given by IV infusion over 4-24 hours or SQ. over 24 hours for 3 days, then reduce the dose to 5µg/kg daily.
- Peripheral Blood Progenitor Cell Transplantation: 10µg/kg daily given by SQ. for at least 4 days prior to the first leukapheresis to collect peripheral blood progenitor cells (PBPC) and continued until the last leukapheresis is performed.
- Myelodysplastic Syndromes: 0.3-10µg/kg have been given once daily by SQ. injection or dosages of 50-400µg/m² have been given once daily by IV infusion over 30 minutes.

Dosing in Renal or Hepatic Impairment

- No recommendations made by the manufacturer.

Adverse Effects

- Medullary **bone pain**, nausea, vomiting, abdominal pain, rash, erythema, swelling, pruritis (at injection site), **leukocytosis** (occasionally > 100,000/mm³), anemia, possible **thrombocytopenia**, myelodysplasia, increased serum uric acid levels, increased LDH, alkaline phosphatase, leukocyte alkaline phosphatase (LAP), and splenomegaly.

Monitoring Parameters

- Complete blood count with a differential, serum uric acid levels, LDH, alkaline phosphatase, LAP, and palpate the spleen for signs of enlargement.

Drug Interactions

- **Antineoplastic agents**- Because filgrastim stimulates proliferation of neutrophil precursors and because many antineoplastic agents target rapidly proliferating cells, filgrastim doses should not be administered within 24 hours before or after a dose of one of these agents.
- **Lithium**- due to its myeloproliferative effect, should be used with caution.

Patient Counseling Tips

- Unopened vials should be stored in the refrigerator.
- Medicine should be removed from the refrigerator 1 hour prior to administration.
- The medicine should be clear and colorless.
- Avoid crowds and individuals with colds or the flu.
- Do not clean litter boxes or handle pet excreta.
- No fresh-squeezed juices, unpasteurized milk, raw fish, shellfish, or under-cooked meat.

Pyrimethamine (Daraprim®)

Formulations

- Tablets 25mg

Adult Dose and Administration

- Tablets may be crushed.
- **Toxoplasmosis:** Initial dose of 50-75mg daily for 1-3 weeks, then
- Reduced by 50% and continued for an additional 4-5 weeks.
- Most clinicians state that the treatment of choice for toxoplasmosis in adults is 25-100mg of pyrimethamine (with 10-25mg of leucovorin) administered daily for 3-4 weeks concomitantly with sulfadiazine given in a dosage of 1-1.5g 4 times daily for 3-4 weeks.
- **Pneumocystis carinii Pneumonia:** Pyrimethamine 50mg + oral leucovorin 25mg once weekly in conjunction with dapsone 50mg once daily.

Dosing in Renal or Hepatic Impairment

- No recommendations made by the manufacturer.

Adverse Effects

- **Folic acid depletion** leading to reversible **bone marrow depression**, megaloblastic anemia, leukopenia, thrombocytopenia, agranulocytosis, diarrhea, vomiting, abdominal cramps, ataxia, tremors, seizures, respiratory failure, hypersensitivity, increased liver transaminases, alkaline phosphatase, increased bilirubin, hepatomegaly, hepatitis, hematuria, and disorders of cardiac rhythm.
- **Use in pregnant women only if the potential benefit justifies the potential risk to the fetus.**

Monitoring Parameters

- Complete blood count with a differential, liver transaminases, alkaline phosphatase, bilirubin, hematuria, ECG if arrhythmia suspected.

Drug Interactions

- **P-aminobenzoic acid (PABA)-** interferes with the action of pyrimethamine and probably should not be used in patients receiving pyrimethamine.
- **Lorazepam-** mild hepatotoxicity has been reported with the concomitant use of these two drugs.

Patient Counseling Tips

- May be taken with food if GI irritation occurs.
- Consult healthcare provider before stopping this medication.

Rifabutin (Mycobutin®)

Formulations

- Capsule 150mg

Adult Dose and Administration

- Mycobacterium Avium Complex (MAC): 300mg once daily in combination with other anti-mycobacterial medications.
- May be administered with food.
- Active Tuberculosis: 5mg/kg (maximum of 300mg) daily in combination with other antituberculous medications.

Dosing in Renal or Hepatic Impairment

- Renal Impairment: A 50% dosage adjustment is recommended if creatinine clearance is less than 30ml/min. No adjustment is required if clearance is higher than this value.
- Hepatic Impairment: No dosing guidelines available.

Adverse Effects

- **Neutropenia (ANC < 750/mm³), leukopenia, anemia, thrombocytopenia**, rash, nausea, vomiting, abdominal pain, taste perversion, diarrhea, dyspepsia, eructation, headache, fever, myalgia, arthralgia, uveitis, brown-orange discoloration of tears, increased liver transaminases, alkaline phosphatase, and discolored urine.

Monitoring Parameters

- Complete blood count with a differential, liver transaminases, and alkaline phosphatase.

Drug Interactions

- **Delavirdine**- may reduce the metabolism of rifabutin. Co-administration not recommended.
- **Efavirenz**- may decrease plasma concentrations of rifabutin.
- **HIV protease inhibitors**-
 - **Amprenavir and rifabutin**: can affect the kinetics of both drugs, resulting in a decrease in the AUC of the protease inhibitor and an increase in the AUC of rifabutin.
 - **Indinavir and rifabutin**: results in a decrease in the AUC of indinavir and a substantial increase in the AUC of rifabutin (increase the dose of indinavir to 1000mg every 8 hours and decrease the rifabutin dose by 50%).
 - **Lopinavir and rifabutin**: results in increased concentrations of rifabutin and its metabolite (reduce the rifabutin dose to a max of 150mg 3 times weekly).
 - **Nelfinavir and rifabutin**: can result in alterations in the kinetics of both drugs (Use 50% of the usual dose of rifabutin and 1250mg bid of nelfinavir).
 - **Ritonavir and rifabutin**: dosage should be decreased to a max of 150mg 3 times weekly.
- **NRTIs**-
 - **Zidovudine**:- half-life is decreased by 28%.

Patient Counseling Tips

- This medication may be taken with or without food.
- Birth control pills may not be effective while taking this medication and a barrier method of contraception is recommended.
- Avoid wearing soft contact lenses because they may be permanently discolored.
- This medication may color the tears, feces, and urine. (Orange-brown) Will return to normal when finish taking medication.
- Inform healthcare provider concerning all medications taken.

Terconazole (Terazol[®])

Formulations

- Cream 0.4% (Terazol[®] 7), and 0.8% (Terazol[®] 3)
- Suppositories 80mg (Terazol[®] 3)

Adult Dose and Administration

- **Vaginal Cream-**
 - 0.4% product- insert intravaginally at bedtime for 7 consecutive days.
 - 0.8% product- insert intravaginally at bedtime for 3 consecutive days.

Dosing in Renal and Hepatic Impairment

- No recommendations made by the manufacturer.

Adverse Effects

- **Vulvovaginal burning**, pruritis, irritation, itching, **headache** (21-30%), abdominal pain, dysmenorrhea, and fever.

Monitoring Parameters

- Monitor for signs of improvement.

Drug Interactions

- Efficacy of intravaginal terconazole is not affected by concomitant use of oral contraceptives, nor does administration of intravaginal terconazole appear to affect estradiol or progesterone concentrations in women receiving low-dose oral contraceptives.

Patient Counseling Tips

- Refrain from sexual intercourse during treatment; an ingredient in the cream may weaken certain latex products like condoms or diaphragm; do not use such products within 72 hours of using medication.
- Call healthcare provider immediately if these symptoms occur:
 - Burning or irritation in vaginal area
 - Stomach pain
 - Fever
 - Foul smelling discharge
- Wear clean cotton underwear instead of nylon or rayon, or underwear with a cotton crotch.
- The suppository may be moistened with water for easier insertion. Petroleum jelly should be avoided.
- A sanitary pad may be used in case of leakage of the drug, but tampons should be avoided.

Trimethoprim-Sulfamethoxazole (Septra[®])(Bactrim[®])

Formulations

- Suspension: Trimethoprim 40mg/5ml and Sulfamethoxazole 200mg/5ml
- Tablets: Trimethoprim 80mg and Sulfamethoxazole 400mg or Trimethoprim 160mg and Sulfamethoxazole 800mg (Bactrim DS[®] or Septra DS[®])
- Parenteral- For IV infusion: Trimethoprim 16mg/ml and Sulfamethoxazole 80mg/ml

Adult Dose and Administration

- Dosage of TMP/SMX is expressed in terms of the trimethoprim content of the fixed combination containing 5mg of sulfamethoxazole to 1mg of trimethoprim.
- **Pneumocystis carinii Infections:** trimethoprim 15-20mg/kg daily, given in 3-4 divided doses. The usual duration of therapy is 14-21 days.
- Primary and secondary prevention in HIV-infected adults, 160mg once daily is recommended.
- **Toxoplasmosis:** For primary prophylaxis in HIV patients, an oral trimethoprim dosage of 160mg once daily is recommended.
- **Granuloma Inguinale (Donovanosis):** 160mg bid for at least three weeks is recommended.
- **Pertussis:** 320mg daily given in 2 divided doses daily has been recommended.
- **Plague:** 320-640mg daily in 2 equally divided doses for 7 days.
- **Cholera:** 160mg bid for 3 days, in conjunction with fluid and electrolyte replacement.

Dosage in Renal and Hepatic Impairment

- In renal dysfunction, the manufacturer recommends that the usual daily dose be reduced 50% in patients with CrCl of 15-30ml/min. The manufacturer recommends not using this drug in patients with a CrCl of <15ml/min.

Adverse Effects

- Hemolytic anemia from G6PD deficiency can occur (can occur in patients with normal or abnormal G6PD levels), epidermal necrolysis, exfoliative dermatitis, **Stevens-Johnson syndrome**, serum sickness, allergic myocarditis, aplastic anemia, agranulocytosis, leukopenia, neutropenia, thrombocytopenia, eosinophilia, nausea, vomiting, glossitis, stomatitis, pancreatitis, headache, insomnia, fatigue, apathy, peripheral neuritis, hepatitis, fever, chills, **crystalluria**, increased BUN and serum creatinine, increased LFTs, and hypotension.
- Consider desensitization in patients with severe sulfa allergies who may require treatment with this drug.
- Use with caution when co-administering with AZT, Combivir or Trizivir to avoid additive toxicity

Monitoring Parameters

- Complete blood count with a differential, amylase, lipase, abdominal pain, liver transaminases, LDH, alkaline phosphatase, GGT, BUN, and serum creatinine.

Drug Interactions

- **Warfarin-** TMP/SMX may prolong the PT time by inhibiting the metabolic clearance of warfarin.
- **Phenytoin-** Due to the fact that TMP/SMX is folate depleting it may potentiate the anti-folate properties of phenytoin.
- **Methotrexate-** Sulfonamides can displace methotrexate from plasma protein binding sites resulting in increased free methotrexate concentrations.
- **Digoxin-** increases in serum digoxin concentrations have been reported.
- **Indomethacin-** increases serum sulfamethoxazole concentrations.
- **Oral hypoglycemic agents-** potentiation of hypoglycemic effect.
- **Pyrimethamine-** increased risk of megaloblastic anemia.

Patient Counseling Tips

- Store the suspension at room temperature.
- May be taken with or without food.
- This medication may increase the risk of phototoxicity.
- Contraindicated in women who are breast feeding.
- Call healthcare provider immediately for the following symptoms:
 - Skin rash, itching, sore throat, fever or chills, mouth sores, unusual bruising or bleeding, yellowing of the skin or eyes, paleness or joint aches.

**Pertinent Tables Concerning Antiretroviral Therapy
From
Guidelines for the Use of Antiretroviral Agents in HIV-1 Infected Adults and Adolescents**

www.aidsinfo.nih.gov

May 4, 2006

Antiretroviral Regimens Recommended for Treatment of HIV-1 Infection in Antiretroviral Naïve Patients (page 134)

Antiretroviral Drugs and Components Not Recommended as Initial Therapy (page 135)

Antiretroviral Regimens or Components That Should Not Be Offered At Any Time (page 136)

Strategies to Improve Adherence to Antiretroviral Therapy (page 137)

Potentially Life-Threatening and Serious Adverse Effects (page 138)

Adverse Events with Potential Long Term Complications (page 142)

Adverse Effects Compromising Quality of Life and/or With Potential Impact on Medication Adherence (page 143)

Drugs That Should Not Be Used with PI or NNRTI Antiretrovirals (page 144)

Drug Effects on Concentration of PIs (page 145)

Drug Effects on Concentration of NNRTIs (page 146)

Summary of Guidelines For Changing An Antiretroviral Regimen For Suspected Treatment Regimen Failure (page 147)

Preclinical and Clinical Data Relevant to the Use of Antiretrovirals During Pregnancy (page 148)

Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy (page 149)

FDA Categorization of Drug Risks to Fetus (page 152)

Table 6. Antiretroviral Regimens Recommended for Treatment of HIV-1 Infection in Antiretroviral-Naïve Patients

Regimens should be individualized based on the advantages and disadvantages of each combination such as pill burden, dosing frequency, toxicities, drug-drug interaction potential, co-morbid conditions, and level of plasma HIV RNA. Clinicians should refer to [Table 6](#) to review the pros and cons of different components of a regimen and to [Tables 10-12](#) for adverse effects and dosages of individual antiretroviral agents. Preferred regimens are in bold type; regimens are designated as “preferred” for use in treatment-naïve patients when clinical trial data suggest optimal and durable efficacy with acceptable tolerability and ease of use. Alternative regimens are those where clinical trial data suggest efficacy, but it is considered alternative because of disadvantages compared to the preferred agent, such as antiviral activity, durability, tolerability, drug interaction potential, or ease of use. In some cases, based on individual patient characteristics, a regimen listed as alternative in this table may actually be the preferred regimen for a selected patient. Clinicians initiating antiretroviral regimens in the HIV-1-infected pregnant patient should refer to “*Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV-1 Transmission in the United States*” at <http://aidsinfo.nih.gov/guidelines/>.

	Regimens	No. of pills
Preferred Regimens NNRTI-based	Efavirenz + (lamivudine or emtricitabine) + (zidovudine or tenofovir DF) (AII) – [note: efavirenz is not recommended for use in 1 st trimester of pregnancy or in women with high pregnancy potential*]	2-3
	PI-based lopinavir/ritonavir (co-formulation) + (lamivudine or emtricitabine) + zidovudine (AII)	6-7
Alternative Regimens NNRTI-based	efavirenz + (lamivudine or emtricitabine) + (abacavir or didanosine or stavudine) (BII) – [note: efavirenz is not recommended for use in 1 st trimester of pregnancy or in women with high pregnancy potential*]	2-4
	nevirapine + (lamivudine or emtricitabine) + (zidovudine or stavudine or didanosine or abacavir or tenofovir) (BII) – [note: High incidence (11%) of symptomatic hepatic events was observed in women with pre-nevirapine CD4 ⁺ T cell counts >250 cells/mm ³ and men with CD4 ⁺ T cell counts >400 cells/mm ³ (6.3%). Nevirapine should not be initiated in these patients unless the benefit clearly outweighs the risk.]	3-6
	PI-based atazanavir + (lamivudine or emtricitabine) + (zidovudine or stavudine or abacavir or didanosine) or (tenofovir + ritonavir 100mg/d) (BII)	3-6
	fosamprenavir + (lamivudine or emtricitabine) + (zidovudine or stavudine or abacavir or tenofovir or didanosine) (BII)	5-8
	fosamprenavir/ritonavir[†] + (lamivudine or emtricitabine) + (zidovudine or stavudine or abacavir or tenofovir or didanosine) (BII)	5-8
	indinavir/ritonavir[†] + (lamivudine or emtricitabine) + (zidovudine or stavudine or abacavir or tenofovir or didanosine) (BII)	7-12
	lopinavir/ritonavir + (lamivudine or emtricitabine) + (stavudine or abacavir or tenofovir or didanosine) (BII)	5-8
	nelfinavir + (lamivudine or emtricitabine) + (zidovudine or stavudine or abacavir or tenofovir or didanosine) (CII)	5-8
	saquinavir (s/gc, hgc, or tablets)[‡]/ritonavir[†] + (lamivudine or emtricitabine) + (zidovudine or stavudine or abacavir or tenofovir or didanosine) (BII)	7-15
	3 NRTI-based abacavir + zidovudine + lamivudine - only when a preferred or an alternative NNRTI- or a PI-based regimen cannot or should not be used (CII)	2

* Women with child bearing potential implies women who want to conceive or those who are not using effective contraception

† Low-dose (100–400 mg) ritonavir per day

‡ sgc = soft gel capsule; hgc = hard gel capsule

Table 9. Antiretroviral Drugs and Components Not Recommended as Initial Therapy

Antiretroviral Drugs/Components (arranged in alphabetical order)	Reasons for not recommending as initial therapy
Delavirdine (DII)	<ul style="list-style-type: none"> • Inferior virologic efficacy • Inconvenient dosing (three times daily)
Didanosine + tenofovir + NNRTI (DII)	<ul style="list-style-type: none"> • High rate of early virologic failure when didanosine and tenofovir are used in combination with efavirenz or nevirapine • Rapid selection of resistant mutations • Potential for immunologic non-response
Enfuvirtide (DIII as initial regimen)	<ul style="list-style-type: none"> • No clinical trial experience in treatment-naïve patients • Requires twice daily subcutaneous injections
Indinavir (Unboosted) (DIII)	<ul style="list-style-type: none"> • Inconvenient dosing (three times daily with meal restrictions)
Ritonavir as sole PI (DIII)	<ul style="list-style-type: none"> • High pill burden • Gastrointestinal intolerance
Saquinavir soft gel capsule (Unboosted) (DII)	<ul style="list-style-type: none"> • High pill burden • Inferior virologic efficacy
Tipranavir (boosted with ritonavir) (DIII)	<ul style="list-style-type: none"> • Lack of data in treatment-naïve patients
Zalcitabine + zidovudine (DII)	<ul style="list-style-type: none"> • Inferior virologic efficacy • Higher rate of adverse effects than other 2-NRTI alternatives

Table 10. Antiretroviral Regimens or Components That Should Not Be Offered At Any Time

	Rationale	Exception
Antiretroviral Regimens Not Recommended		
Monotherapy (EII)	<ul style="list-style-type: none"> • Rapid development of resistance • Inferior antiretroviral activity when compared to combination with three or more antiretrovirals 	<ul style="list-style-type: none"> • Pregnant women with pretreatment HIV RNA <1,000 copies/mL using ZDV monotherapy for prevention of perinatal HIV transmission and not for HIV treatment for the mother[†]; however, combination therapy is generally preferred.
2-NRTI regimens (EII)	<ul style="list-style-type: none"> • Rapid development of resistance • Inferior antiretroviral activity when compared to combination with three or more antiretrovirals 	<ul style="list-style-type: none"> • For patients currently on this treatment some clinicians may continue if virologic goals are achieved (DII)
Abacavir + tenofovir + lamivudine (or emtricitabine) as a triple-NRTI regimen (EII)	<ul style="list-style-type: none"> • High rate of early virologic non-response seen when this triple NRTI combination was used as initial regimen in treatment-naïve patients 	<ul style="list-style-type: none"> • No exception
Tenofovir + didanosine + lamivudine (or emtricitabine) combination as a triple-NRTI regimen (EII)	<ul style="list-style-type: none"> • High rate of early virologic non-response seen when this triple NRTI combination was used as initial regimen in treatment-naïve patients 	<ul style="list-style-type: none"> • No exception
Antiretroviral Components Not Recommended As Part of Antiretroviral Regimen		
Amprenavir oral solution (EIII) in: <ul style="list-style-type: none"> • pregnant women; • children <4 yr old; • patients with renal or hepatic failure; and • patients on metronidazole or disulfiram 	<ul style="list-style-type: none"> • Oral liquid contains large amount of the excipient propylene glycol, which may be toxic in the patients at risk 	<ul style="list-style-type: none"> • No exception
Amprenavir + fosamprenavir (EII)	<ul style="list-style-type: none"> • Amprenavir is the active antiviral for both drugs, combined use have no benefit and may increase toxicities 	<ul style="list-style-type: none"> • No exception
Amprenavir oral solution + ritonavir oral solution (EIII)	<ul style="list-style-type: none"> • The large amount of propylene glycol used as a vehicle in amprenavir oral solution may compete with ethanol (the vehicle in oral ritonavir solution) for the same metabolic pathway for elimination. This may lead to accumulation of either one of the vehicles. 	<ul style="list-style-type: none"> • No exception
Atazanavir + indinavir (EIII)	<ul style="list-style-type: none"> • Potential additive hyperbilirubinemia 	<ul style="list-style-type: none"> • No exception
Didanosine + stavudine (EIII)	<ul style="list-style-type: none"> • High incidence of toxicities – peripheral neuropathy, pancreatitis, and hyperlactatemia • Reports of serious, even fatal, cases of lactic acidosis with hepatic steatosis with or without pancreatitis in pregnant women* 	<ul style="list-style-type: none"> • When no other antiretroviral options are available and potential benefits outweigh the risks[†] (DIII)
Didanosine + zalcitabine (EIII)	<ul style="list-style-type: none"> • Additive peripheral neuropathy 	<ul style="list-style-type: none"> • No exception
Efavirenz in first trimester of pregnancy or in women with significant child-bearing potential [†] (EIII)	<ul style="list-style-type: none"> • Teratogenic in nonhuman primates 	<ul style="list-style-type: none"> • When no other antiretroviral options are available and potential benefits outweigh the risks[†] (DIII)
Emtricitabine + lamivudine (EIII)	<ul style="list-style-type: none"> • Similar resistance profile • No potential benefit 	<ul style="list-style-type: none"> • No exception
Lamivudine + Zalcitabine (EIII)	<ul style="list-style-type: none"> • In vitro antagonism 	<ul style="list-style-type: none"> • No exception
Nevirapine initiation in women with CD4 >250 cells/mm ³ or men with CD4 >400 cells/mm ³ (DI)	<ul style="list-style-type: none"> • Higher incidence of symptomatic (including serious and even fatal) hepatic events in these patient groups 	<ul style="list-style-type: none"> • Only if the benefit clearly outweighs the risk
Saquinavir hard gel capsule (Invirase [®]) as single protease inhibitor (EIII)	<ul style="list-style-type: none"> • Poor oral bioavailability (4%) • Inferior antiretroviral activity when compared to other protease inhibitors 	<ul style="list-style-type: none"> • No exception
Stavudine + zalcitabine (EIII)	<ul style="list-style-type: none"> • Additive peripheral neuropathy 	<ul style="list-style-type: none"> • No exception
Stavudine + zidovudine (EII)	<ul style="list-style-type: none"> • Antagonistic effect on HIV-1 	<ul style="list-style-type: none"> • No exception

- * When constructing an antiretroviral regimen for an HIV-infected pregnant woman, please consult "Public Health Service Task Force Recommendations for the Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV-1 Transmission in the United States" in <http://www.aidsinfo.nih.gov/guidelines/>.

Table 16. Strategies to Improve Adherence to Antiretroviral Therapy

- Establish readiness to start therapy
- Provide education on medication dosing
- Review potential side effects
- Anticipate and treat side effects
- Utilize educational aids including pictures, pillboxes, and calendars
- Engage family, friends
- Simplify regimens, dosing, and food requirements
- Utilize team approach with nurses, pharmacists, and peer counselors
- Provide accessible, trusting health care team

Table 17: page 1 of 6

Table 17. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations

17a. Potentially Life-Threatening and Serious Adverse Events

Adverse effects	Causative ARVs	Onset/clinical manifestation	Estimated frequency	Risk Factors	Prevention/monitoring	Management
POTENTIALLY LIFE-THREATENING ADVERSE EFFECTS (Listed in alphabetical order)						
Hepatic Events (nevirapine-associated symptomatic events, including hepatic necrosis)	NVP	<p>Onset: Greatest risk within 1st few weeks of therapy; can occur through 18 weeks</p> <p>Symptoms: Abrupt onset of flu-like symptoms (nausea, vomiting, myalgia, fatigue), abdominal pain, jaundice, or fever with or without skin rash; may progress to fulminant hepatic failure with encephalopathy</p> <p>Approximately 1/2 of the cases have accompanying skin rash</p> <p>Some may present as part of DRESS syndrome (drug rash with eosinophilia and systemic symptoms)</p>	<p>Symptomatic hepatic events:</p> <ul style="list-style-type: none"> • 4% overall (2.5%-11% from different trials) • In women - 11% in those w/ pre-NVP CD4 >250 cells/mm³ vs. 0.9% w/ CD4 <250 cells/mm³. • In men - 6.3% w/ pre-NVP CD4 >400 cells/mm³ vs. 2.3% w/ CD4 <400 cells/mm³ 	<ul style="list-style-type: none"> • Higher CD4 T cell count at initiation (>250 cells/mm³ in women & >400 cells/mm³ in men) • Female gender (including pregnant women) • Elevated ALT or AST at baseline; • HBV and/or HCV co-infection; • Alcoholic liver disease • HIV (-) individuals when NVP is used for post-exposure prophylaxis • High NVP concentration 	<ul style="list-style-type: none"> • Avoid initiation of NVP in women w/ CD4 >250 cells/mm³ or men w/ CD4 >400 cells/mm³ unless the benefit clearly outweighs the risk • Counsel pts re: signs & symptoms of hepatitis; stop NVP & seek medical attention if signs & symptoms of hepatitis, severe skin rash, or hypersensitivity reactions appear • Monitoring of ALT & AST (every 2 weeks x 1st month, then monthly x 3 months, then every 3 months) • Obtain AST & ALT in patients with rash • 2-week dose escalation may reduce incidence of hepatic events 	<ul style="list-style-type: none"> • Discontinue ARV including nevirapine (caution should be taken in discontinuation of 3TC, FTC, or TDF in HBV co-infected patients) • Discontinue all other hepatotoxic agents if possible • Rule out other causes of hepatitis • Aggressive supportive care as indicated <p>Note: Hepatic injury may progress despite treatment discontinuation. Careful monitoring should continue until symptom resolution.</p> <p>Do not rechallenge patient with NVP</p> <p>The safety of other NNRTIs (EFV or DLV) in patients who experienced significant hepatic event from NVP is unknown – use with caution.</p>
Lactic acidosis/hepatic steatosis +/- pancreatitis (severe mitochondrial toxicities)	NRTIs, esp. d4T, ddI, ZDV	<p>Onset: months after initiation of NRTIs</p> <p>Symptoms:</p> <ul style="list-style-type: none"> • Initial onset may be insidious with nonspecific gastrointestinal prodrome (nausea, anorexia, abdominal pain, vomiting), weight loss, and fatigue; • Subsequent symptoms may be rapidly progressive with tachycardia, tachypnea, hyperventilation, jaundice, muscular weakness, mental status changes, or respiratory distress • Some may present with multi-organ failure, such as fulminant hepatic failure, acute pancreatitis, encephalopathy, and respiratory failure <p>Laboratory findings:</p> <ul style="list-style-type: none"> • Increased lactate (often > 5 mmole) • Low arterial pH (some as low as < 7.0) • Low serum bicarbonate • Increased anion gap • Elevated serum transaminases, prothrombin time, bilirubin • Low serum albumin • Increase serum amylase & lipase in patients with pancreatitis • Histologic findings of the liver – microvesicular or macrovesicular steatosis 	<p>Rare</p> <p>One estimate 0.85 cases per 1000 patient-years</p> <p>Mortality up to 50% in some case series, (esp. in patients with serum lactate > 10 mmole)</p>	<ul style="list-style-type: none"> • d4T + ddI • d4T, ZDV, ddI use (d4T most frequently implicated) • Long duration of NRTI use • Female gender • Obesity • Pregnancy (esp. with d4T+ddI) • ddI + hydrosyurea or ribavirin • High baseline body mass index 	<ul style="list-style-type: none"> • Routine monitoring of lactic acid is generally not recommended; • Consider obtaining lactate levels in patients with low serum bicarbonate or high anion gap and with complaints consistent with lactic acidosis; • Appropriate phlebotomy technique for obtaining lactate level should be employed 	<ul style="list-style-type: none"> • Discontinue all ARVs if this syndrome is highly suspected (diagnosis is established by clinical correlations, drug history, and lactate level) • Symptomatic support with fluid hydration • Some patients may require IV bicarbonate infusion, hemodialysis or hemofiltration, parenteral nutrition or mechanical ventilation • IV thiamine and/or riboflavin – resulted in rapid resolution of hyperlactatemia in some case reports <p>Note:</p> <ul style="list-style-type: none"> • Interpretation of high lactate level should be done in the context of clinical findings. • The implication of asymptomatic hyperlactatemia is unknown at this point <p>ARV treatment options:</p> <ul style="list-style-type: none"> • May consider using NRTIs with less propensity of mitochondrial toxicities – (e.g., ABC, TDF, 3TC, FTC) – should not be introduced until lactate returns to normal. • Recommend close monitoring of serum lactate after restarting NRTIs • Some consider using NRTI-sparing regimens with PI + NNRTI +/- FI (e.g., IDV + EFV, LPV/r + EFV, etc) – efficacy and benefit of this type of regimen unknown, but currently under investigation

Table 17: page 2 of 6
 Table 17. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations

17a. Potentially Life-Threatening and Serious Adverse Events (continued)

Adverse effects	Causative ARVs	Onset/clinical manifestation	Estimated frequency	Risk Factors	Prevention/monitoring	Management
POTENTIALLY LIFE-THREATENING ADVERSE EFFECTS (Listed in alphabetical order)						
Lactic acidosis/ Rapidly progressive ascending neuromuscular weakness	Most frequently implicated ARV: d4T	Onset: months after initiation of ARV; then dramatic motor weakness occurring within days to weeks Symptom: very rapidly progressive ascending demyelinating polyneuropathy, may mimic Guillain-Barre Syndrome; some patients may develop respiratory paralysis requiring mechanical ventilation; resulted in deaths in some patients Laboratory findings may include: •Low arterial pH •Increased lactate •Low serum bicarbonate •Increased anion gap •Markedly increased creatine phosphokinase	Rare	Prolonged d4T use [found in 61 of 69 (88%) cases in one report]	Early recognition and discontinuation of ARVs may avoid further progression	<ul style="list-style-type: none"> •Discontinuation of ARVs •Supportive care, including mechanical ventilation if needed (as in cases of lactic acidosis listed previously) •Other measures attempted with variable successes: plasmapheresis, high dose corticosteroid, intravenous immunoglobulin, carnitine, acetylcarnitine •Recovery often takes months – ranging from complete recovery to substantial residual deficits •Symptoms may be irreversible in some patients <p>Do not rechallenge patient with offending agent</p>
Stevens-Johnson Syndrome (SJS)/ Toxic epidermal necrosis (TEN)	NVP > EFV, DLV; Also reported with: APV, f-APV, ABC, ZDV, ddI, IDV, LPV/r, ATV	Onset: first few days to weeks after initiation of therapy Symptoms: <i>Cutaneous involvement:</i> •Skin eruption with mucosal ulcerations (may involve orolingival mucosa, conjunctiva, anogenital area); •Can rapidly evolve with blister or bullae formation; •May eventually evolve to epidermal detachment and/or necrosis <i>Systemic Symptoms:</i> fever, tachycardia, malaise, myalgia, arthralgia <i>Complications:</i> ↓ oral intake → fluid depletion; bacterial or fungal superinfection; multiorgan failure	NVP: 0.3% to 1% DLV & EFV: 0.1% 1-2 case reports for ABC, f-APV, ddI, ZDV, IDV, LPV/r, ATV	NVP – Female, Black, Asian, Hispanic	<ul style="list-style-type: none"> •2-week lead in period with 200mg once daily, then escalate to 200mg twice daily •Educate patients to report symptoms as soon as they appear •Avoid use of corticosteroid during NVP dose escalation – may increase incidence of rash 	<ul style="list-style-type: none"> •Discontinue all ARVs and any other possible agent(s) (e.g., cotrimoxazole) •Aggressive symptomatic support may include: •Intensive care support •Aggressive local wound care (e.g., in a burn unit) •Intravenous hydration •Parenteral nutrition, if necessary •Pain management •Antipyretics •Empiric broad-spectrum antimicrobial therapy if superinfection is suspected <p>Controversial management strategies:</p> <ul style="list-style-type: none"> •Corticosteroid •Intravenous immunoglobulin <p>Do not rechallenge patient with offending agent</p> <ul style="list-style-type: none"> •It is unknown whether patients who experienced SJS while NNRTI are more susceptible to SJS from another NNRTI – most experts would suggest avoiding use of this class unless no other option available
Hypersensitivity reaction (HSR)	ABC	Onset of 1st reaction: median onset – 9 days; approximately 90% within 1 st 6 weeks Onset of rechallenge reactions: within hours of rechallenge dose Symptoms: acute onset of symptoms (in descending frequency): high fever, diffuse skin rash, malaise, nausea, headache, myalgia, chills, diarrhea, vomiting, abdominal pain, dyspnea, arthralgia, respiratory symptoms (pharyngitis, dyspnea/tachypnea) <i>With continuation of ABC, symptoms may worsen to include:</i> hypotension, respiratory distress, vascular collapse Rechallenge reactions: generally greater intensity than 1 st reaction, can mimic anaphylaxis	Approximately 8% in clinical trial (2-9%); 5% in retrospective analysis	<ul style="list-style-type: none"> •HLA-B*5701, HLA-DR7, HLA-DQ3 (from Australian data) •ARV-naïve patients •Higher incidence of grade 3 or 4 HSR with 600mg once daily dose than 300mg twice daily dose in one study (5% vs. 2%) 	<ul style="list-style-type: none"> •Educate patients about potential signs and symptoms of HSR and need for reporting of symptoms promptly •Wallet card with warning information for patients 	<ul style="list-style-type: none"> •Discontinue ABC and other ARVs •Rule out other causes of symptoms (e.g., intercurrent illnesses such as viral syndromes, and other causes of skin rash, etc) •Most signs and symptoms resolve 48 hours after discontinuation of ABC <p><i>More severe cases:</i></p> <ul style="list-style-type: none"> •Symptomatic support – antipyretic, fluid resuscitation, pressure support (if necessary) <p>Do not rechallenge patients with ABC after suspected HSR</p>

Table 17: page 3 of 6

Table 17. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations

17a. Potentially Life-Threatening and Serious Adverse Events (continued)

Adverse effects	Causative ARVs	Onset/clinical manifestation	Estimated frequency	Risk Factors	Prevention/monitoring	Management
POTENTIALLY SERIOUS ADVERSE EFFECTS (listed in alphabetical order)						
Bleeding episodes – increase in hemophilic patients	PIs	Onset: few weeks Symptoms: ↑ spontaneous bleeding tendency – in joints, muscles, soft tissues, and hematuria	Frequency unknown	•PI use in hemophilic patients	•Consider using NNRTI-based regimen •Monitor for spontaneous bleeding	•May require increase use of Factor VIII products
Bone marrow suppression	ZDV	Onset: few weeks to months Laboratory abnormalities: •Anemia •Neutropenia Symptoms: fatigue because of anemia; potential for increase bacterial infections because of neutropenia	Anemia -1.1 to 4% Neutropenia – 1.8-8%	•Advanced HIV •High dose •Pre-existing anemia or neutropenia; •Concomitant use of bone marrow suppressants (such as cotrimoxazole, ribavirin, ganciclovir, etc.)	Avoid use in patients at risk Avoid other bone marrow suppressants if possible Monitor CBC with differential at least every three months (more frequently in patients at risk)	•Switch to another NRTI if there is alternative option; •Discontinue concomitant bone marrow suppressant if there is alternative option; otherwise: For neutropenia: •Identify and treat other causes •Consider treatment with filgrastim For anemia: •Identify and treat other causes of anemia (if present) •Blood transfusion if indicated •Consider erythropoietin therapy
Hepatotoxicity (clinical hepatitis or asymptomatic serum transaminase elevation)	All NNRTIs; All PIs; All NRTIs	Onset: NNRTI – for NVP - 2/3 within 1 st 12 weeks NRTI – over months to years PI – generally after weeks to months Symptoms/Findings: NNRTI – asymptomatic to non-specific symptoms such as anorexia, weight loss, or fatigue. Approximately 1/3 of patients with NVP-associated symptomatic hepatic events present with skin rash. NRTI – •ZDV, ddI, d4T - may cause hepatotoxicity associated with lactic acidosis with microvesicular or macrovesicular hepatic steatosis because of mitochondrial toxicity •3TC, FTC, or tenofovir – HBV co-infected patients may develop severe hepatic flare when these drugs are withdrawn or when resistance develops. PI – •Clinical hepatitis & hepatic decompensation have been reported with TPV/RTV. Underlying liver disease increases risk. •Generally asymptomatic, some with anorexia, weight loss, jaundice, etc.	Varies with the different agents	•Hepatitis B or C co-infection •Alcoholism •Concomitant hepatotoxic drugs •For NVP-associated hepatic events – female w/ pre-NVP CD ₄ >250cells/mm ³ or male w/ pre-NVP CD ₄ >400cells/mm ³	NVP – monitor liver associated enzymes at baseline, 2 & 4 weeks, then monthly for 1 st 3 months; then every 3 months TPV/RTV – contraindicated in patients with moderate to severe hepatic insufficiency; for other patients follow “frequently” during treatment Other agents: monitor liver-associated enzymes at least every 3-4 months or more frequently in patients at risk	•Rule out other causes of hepatotoxicity – alcoholism, viral hepatitis, chronic HBV w/ 3TC, FTC or TDF withdrawal, or HBV resistance, etc. For symptomatic patients: •Discontinue all ARV (with caution in patients with chronic HBV infection treated w/ 3TC, FTC and/or TDF) and other potential hepatotoxic agents •After symptoms subside & serum transaminases returned to normal, construct a new ARV regimen without the potential offending agent(s) For asymptomatic patients: •If ALT > 5-10x ULN, some may consider discontinuing ARVs, others may continue therapy with close monitoring •After serum transaminases returned to normal, construct a new ARV regimen without the potential offending agent(s) Note: Please refer to information regarding NVP-associated symptomatic hepatic events & NRTI-associated lactic acidosis with hepatic steatosis in this table
Nephrolithiasis/ urolithiasis/ crystalluria	IDV – most frequent	Onset: any time after beginning of therapy – especially at times of reduced fluid intake Laboratory abnormalities: pyuria, hematuria, crystalluria; rarely – rise in serum creatinine & acute renal failure Symptoms: flank pain and/or abdominal pain (can be severe), dysuria, frequency	12.4% of nephrolithiasis reported in clinical trials (4.7% -34.4% in different trials)	•History of nephrolithiasis •Patients unable to maintain adequate fluid intake •High peak IDV concentration •↑ duration of exposure	•Drink at least 1.5 to 2 liters of non-caffeinated fluid (preferably water) per day •Increase fluid intake at first sign of darkened urine •Monitor urinalysis and serum creatinine every 3-6 months	•Increase hydration •Pain control •May consider switching to alternative agent or therapeutic drug monitoring if treatment option is limited •Stent placement may be required

Page 73

Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents

Table 17: page 4 of 6
 Table 17. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations

17a. Potentially Life-Threatening and Serious Adverse Events (continued)

Adverse effects	Causative ARVs	Onset/clinical manifestation	Estimated frequency	Risk Factors	Prevention/monitoring	Management
POTENTIALLY SERIOUS ADVERSE EFFECTS (listed in alphabetical order)						
Nephrotoxicity	IDV, potentially TDF	<u>Onset:</u> IDV – months after therapy TDF – weeks to months after therapy <u>Laboratory and other findings:</u> IDV: ↑ serum creatinine, pyuria; hydronephrosis or renal atrophy TDF: ↑ serum creatinine, proteinuria, hypophosphatemia, glycosuria, hypokalemia, non-anion gap metabolic acidosis <u>Symptoms:</u> IDV: asymptomatic; rarely develop to end stage renal disease TDF: asymptomatic to signs of nephrogenic diabetes insipidus, Fanconi Syndrome	Not known	<ul style="list-style-type: none"> History of renal disease Concomitant use of nephrotoxic drugs 	<ul style="list-style-type: none"> Avoid use of other nephrotoxic drugs Adequate hydration if on IDV therapy Monitor serum creatinine, urinalysis, serum potassium and phosphorus in patients at risk 	<ul style="list-style-type: none"> Stop offending agent, generally reversible Supportive care Electrolyte replacement as indicated
Pancreatitis	ddI alone; ddI + d4T; ddI + hydroxyurea (HU) or ribavirin (RBV); 3TC in children	<u>Onset:</u> usually weeks to months <u>Laboratory abnormalities:</u> increased serum amylase and lipase <u>Symptoms:</u> post-prandial abdominal pain, nausea, vomiting	ddI alone – 1-7% ddI with HU – ↑ by 4-5 fold ddI with RBV, d4T or TDF – ↑ frequency 3TC in children – early trials: 14-18%; later trial - <1%	<ul style="list-style-type: none"> High intracellular and/or serum ddI concentrations History of pancreatitis Alcoholism Hypertriglyceridemia Concomitant use of ddI with d4T, HU, or RBV Use of ddI + TDF without ddI dose reduction 	<ul style="list-style-type: none"> ddI should not be used in patients with history of pancreatitis Avoid concomitant use of ddI with d4T, HU or RBV Reduce ddI dose when used with TDF Monitoring of amylase/lipase in asymptomatic patients is generally not recommended 	<ul style="list-style-type: none"> Discontinue offending agent(s) Symptomatic management of pancreatitis – bowel rest, IV hydration, pain control, then gradual resumption of oral intake Parenteral nutrition may be necessary in patients with recurrent symptoms upon resumption of oral intake
Skin rash	NVP > EFV, DLV, ABC, APV, f-APV, ATV, TPV/RTV	<u>Onset:</u> within first few days to weeks after initiation of therapy <u>Symptoms:</u> most rashes are mild to moderate in nature, diffuse maculopapular rash with or without pruritus; severe rash, rash with fever or with mucus membrane involvement warrants immediate discontinuation of ARV TPV-RTV - Rash accompanied by joint pain/ stiffness, throat tightness, or generalized pruritus have been reported. <u>Note:</u> Please also see sections on Stevens-Johnson Syndrome & Systemic Hypersensitivity Reaction	<u>All Grades (severe):</u> <u>NVP:</u> 14.8% (1.5% severe) <u>EFV:</u> 26% (1% grades 3-4) <u>DLV:</u> 35.4% (4.4% grades 3-4) <u>ABC:</u> <5% in pts w/o HSR <u>f-APV:</u> 20-27% (1.0% grades 3-4) <u>ATV:</u> 19% (<1% grades 3-4) <u>TPV/RTV:</u> 21% (<1% severe) TPV/RTV 14% female & 8-10% male in Phase 2/3 trials; 33% in female HIV- subjects in Phase 1 study with ethinyl estradiol	<ul style="list-style-type: none"> NVP – female, Black, Asian, Hispanic f-APV, APV, TPV – sulfonamide derivative – potential for cross hypersensitivity with other sulfa drugs TPV – female gender associated with an increased frequency of skin rash associated with TPV EFV – higher incidence in children 	<ul style="list-style-type: none"> NVP – always use a 2-week low dose lead-in period Avoid use of corticosteroid during NVP dose escalation – may increase incidence of rash Patient education – advise to report first sign of rash Most experts suggest avoidance of EFV or DLV in patients with history of severe rash from NVP, and vice versa 	<ul style="list-style-type: none"> Mild to moderate rash may be managed by symptomatic treatment with antihistamine and continuation of offending agent Discontinue therapy if skin rash progresses to severe in nature (accompanied by blisters, fever, mucous membrane involvement, conjunctivitis, edema, or arthralgias) or in presence of systemic symptoms (including fever) Do not restart offending medication in case of severe rash If rash develops during first 18 weeks of NVP treatment – obtain serum transaminases to rule out symptomatic hepatic event

Table 17: page 5 of 6
 Table 17. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations

17b. Adverse Events With Potential Long-Term Complications (listed in alphabetical order)

Adverse effects	Causative ARVs	Onset/clinical manifestation	Estimated frequency	Risk Factors	Prevention/monitoring	Management
Cardiovascular effects	Possibly all PIs, maybe except for ATV	Onset: months to years after beginning of therapy Presentation: premature coronary artery disease	3-6 per 1000/yr years	Other risk factors for cardiovascular disease such as smoking, age, hyperlipidemia, hypertension, diabetes mellitus, family history of premature coronary artery disease and personal history of coronary artery disease	<ul style="list-style-type: none"> Assess each patient's cardiac risk factors Consider non-PI based regimen Monitor & identify pts w/ hyperlipidemia or hyperglycemia Counseling for life style modification - smoking cessation, diet, and exercise 	<ul style="list-style-type: none"> Early diagnosis, prevention, and pharmacologic management of other cardiovascular risk factors such as hyperlipidemia, hypertension, and insulin-resistance/diabetes mellitus Assess cardiac risk factors Lifestyle modifications: diet, exercise, and/or smoking cessation Switch to agents with less propensity for increasing cardiovascular risk factors, ie NNRTI- or ATV-based regimen & avoid d4T use
Hyperlipidemia	All PIs (except ATV); d4T; EFV (to a lesser extent)	Onset: weeks to months after beginning of therapy Presentation: All PIs except ATV - ↑ in LDL & total cholesterol (TC) & triglyceride (TG), ↓ in HDL LPV/r & RTV - disproportionate ↑ in TG d4T - mostly ↑ in TG; may also have ↑ in LDL & total cholesterol (TC) EFV or NVP: ↑ in HDL, slight ↑ TG	Varies with different agents; 47% -75% of pts receiving PI in some clinics; <u>Swiss Cohort:</u> ↑TC & TG - 1.7-2.3x higher in pts receiving (non-ATV) PI	<ul style="list-style-type: none"> Underlying hyperlipidemia Risk based on ARV therapy EL LPV/r & RTV > NFV & APV > IDV & SQV > ATV; NNRTI: less than PIs; NRTI: d4T > ZDV & TDF 	<ul style="list-style-type: none"> Use non-PI, non-d4T based regimen Use ATV-based regimen Fasting lipid profile at baseline, 3-6 months after starting new regimen, then annually or more frequently if indicated (in high risk patients, or patients with abnormal baseline levels) 	<ul style="list-style-type: none"> Follow ACTG guidelines' s recommendations for management [308] Assess cardiac risk factor Lifestyle modification: diet, exercise, and/or smoking cessation Switching to agents with less propensity for causing hyperlipidemia <p>Pharmacologic Management:</p> <ul style="list-style-type: none"> ↑ total cholesterol, LDL, TG 200-500 mg/dL: "statins" - pravastatin or atorvastatin (See Tables 19 & 20 for Drug Interaction information) TG > 500 mg/dL - gemfibrozil or micronized fenofibrate
Insulin resistance/ Diabetes mellitus	All PIs	Onset: weeks to months after beginning of therapy Presentation: Polyuria, polydipsia, polyphagia, fatigue, weakness; exacerbation of hyperglycemia in patients with underlying diabetes	Up to 3-5% of patients developed diabetes in some series	Underlying hyperglycemia, family history of diabetes mellitus	<ul style="list-style-type: none"> Use PI-sparing regimens Fasting blood glucose 1-3 months after starting new regimen, then at least every 3-6 months 	<ul style="list-style-type: none"> Diet and exercise Consider switching to an NNRTI-based regimen Metformin "glitazones" Sulfonylurea Insulin
Osteonecrosis	All PIs	Clinical Presentation (generally similar to non-HIV population): <ul style="list-style-type: none"> Insidious in onset, with subtle symptoms of mild to moderate periarticular pain 85% of the cases involving one or both femoral heads, but other bones may also be affected Pain may be triggered by weight bearing or movement 	Reported incidence on the rise. <u>Symptomatic osteonecrosis:</u> 0.08% to 1.33%; <u>Asymptomatic osteonecrosis:</u> 4% from MRI reports	<ul style="list-style-type: none"> Diabetes Prior steroid use Old age Alcohol use Hyperlipidemia Role of ARVs and osteonecrosis - still controversial 	<ul style="list-style-type: none"> Risk reduction (e.g., limit steroid and alcohol use) Asymptomatic cases w/ < 15% bony head involvement - follow with MRI every 3-6 months x 1 yr, then every 6 mon x 1 yr, then annually - to assess for disease progression 	<p>Conservative management:</p> <ul style="list-style-type: none"> ↓ weight bearing on affected joint; Remove or reduce risk factors Analgesics as needed <p>Surgical Intervention:</p> <ul style="list-style-type: none"> Core decompression +/- bone grafting - for early stages of disease For more severe and debilitating disease - total joint arthroplasty

Table 17: page 6 of 6
Table 17. Antiretroviral Therapy Associated Adverse Effects and Management Recommendations

17c. Adverse Effects Compromising Quality of Life and/or With Potential Impact on Medication Adherence (listed in alphabetical order)

Adverse effects	Causative ARVs	Onset/clinical manifestation	Estimated frequency	Risk Factors	Prevention/monitoring	Management
Central nervous system effects	EFV	<u>Onset:</u> begin with first few doses <u>Symptoms:</u> may include one or more of the following: drowsiness, somnolence, insomnia, abnormal dreams, dizziness, impaired concentration & attention span, depression, hallucination; exacerbation of psychiatric disorders; psychosis; suicidal ideation Most symptoms subside or diminish after 2-4 weeks	> 50% of patients may have some symptoms	<ul style="list-style-type: none"> Pre-existing or unstable psychiatric illnesses; Use of concomitant drugs with CNS effects 	<ul style="list-style-type: none"> Take at bedtime or 2-3 hours before bedtime; Take on an empty stomach to reduce drug concentration & CNS effects Warn patients regarding restriction of risky activities – such as operating heavy machinery during the 1st 2-4 weeks of therapy 	<ul style="list-style-type: none"> Symptoms usually diminish or disappear after 2-4 weeks May consider discontinuing therapy if symptoms persist and cause significant impairment in daily function or exacerbation of psychiatric illness
Fat maldistribution	PIs, d4T	<u>Onset:</u> gradual - months after initiation of therapy <u>Symptoms:</u> <ul style="list-style-type: none"> Lipoatrophy – peripheral fat loss manifested as facial thinning, thinning of extremities and buttocks (d4T) Increase in abdominal girth, breast size, and dorsocervical fat pad (buffalo hump) 	High – exact frequency uncertain; increases with duration on offending agents	Lipoatrophy – low baseline body mass index	None to date	<ul style="list-style-type: none"> Switching to other agents – may slow or halt progression, however, may not reverse effects Injectable poly-L-lactic acid for treatment of facial lipoatrophy
Gastrointestinal (GI) intolerance	All PIs, ZDV, ddI	<u>Onset:</u> Begin within first doses <u>Symptoms:</u> <ul style="list-style-type: none"> Nausea, vomiting, abdominal pain – all listed agents Diarrhea – commonly seen with NFV, LPV/r, & ddI buffered formulations 	Varies with different agents	All patients	<ul style="list-style-type: none"> Taking with food may reduce symptoms (not recommended for ddI or unboosted IDV) Some patients may require antiemetics or antidiarrheals pre-emptively to reduce symptoms 	<p>May spontaneously resolve or become tolerable with time; if not:</p> <p><u>For nausea & vomiting, consider:</u></p> <ul style="list-style-type: none"> Antiemetic prior to dosing Switch to less emetogenic ARV <p><u>For diarrhea, consider:</u></p> <ul style="list-style-type: none"> Antimotility agents – such as loperamide, diphenoxylate/atropine Calcium tablets Bulk-forming agents, such as psyllium products Pancreatic enzymes <p><u>In case of severe GI loss:</u></p> <ul style="list-style-type: none"> Rehydration & electrolyte replacement as indicated
Injection site reactions	Enfuvirtide	<u>Onset:</u> Within first few doses <u>Symptoms:</u> pain, pruritus, erythema, ecchymosis, warmth, nodules, rarely injection site infection	98%	All patients	Educate patients regarding use of sterile technique, ensure solution at room temperature before injection, rotate injection sites, avoid injection into sites with little subcutaneous fat or sites of existing or previous reactions	<ul style="list-style-type: none"> Massaging area after injection may reduce pain Wear loose clothing – especially around the injection site areas or areas of previous reactions Rarely, warm compact or analgesics may be necessary
Peripheral neuropathy	ddI, d4T, ddC	<u>Onset:</u> weeks to months after initiation of therapy (may be sooner in patients with pre-existing neuropathy) <u>Symptoms:</u> <ul style="list-style-type: none"> Begins with numbness & paresthesia of toes and feet; May progress to painful neuropathy of feet and calf; Upper extremities less frequently involved Can be debilitating for some patients. May be irreversible despite discontinuation of offending agent(s) 	<p>ddI: 12-34% in clinical trials</p> <p>d4T: 52% in monotherapy trial</p> <p>ddC: 22-35% in clinical trials</p> <p>Incidence increases with prolonged exposure</p>	<ul style="list-style-type: none"> Pre-existing peripheral neuropathy; Combined use of these NRTIs or concomitant use of other drugs which may cause neuropathy Advanced HIV disease High dose or concomitant use of drugs which may increase ddI intracellular activities (e.g., HU or RBV) 	<ul style="list-style-type: none"> Avoid using these agents in patients at risk – if possible Avoid combined use of these agents Patient query at each encounter 	<ul style="list-style-type: none"> May consider discontinuing offending agent before pain becomes disabling – may halt further progression, but symptoms may be irreversible <p><u>Pharmacological management (with variable successes):</u></p> <ul style="list-style-type: none"> Gabapentin (most experience), tricyclic antidepressants, lamotrigine, oxycarbamazepine (potential for CYP interactions), topiramate, tramadol Narcotic analgesics Capsaicin cream Topical lidocaine

Table 20. Drugs That Should Not Be Used With PI or NNRTI Antiretrovirals

Drug Category ^a	Calcium channel blocker	Cardiac	Lipid Lowering Agent	Anti-Mycobacterial ^b	Anti-histamine ^c	Gastro-intestinal drug ^d	Neuro-leptic	Psychotropic	Ergot Alkaloid: (vasoconstrictor)	Herbs	Other
Protease Inhibitors											
Amprenavir ^e and Fosamprenavir	bepiridil	(none)	simvastatin lovastatin	rifampin rifapentine	astemizole terfenadine	cisapride	pimozide	midazolam ^f triazolam	dihydroergotamine (D.H.E. 45) ergotamine ^g (various forms) ergonovine methylecgonovine	St. John's wort	delavirdine oral contraceptives
Atazanavir	bepiridil	(none)	simvastatin lovastatin	rifampin rifapentine	astemizole terfenadine	cisapride proton pump inhibitors	pimozide	midazolam ^f triazolam	dihydroergotamine (D.H.E. 45) ergotamine ^g (various forms) ergonovine methylecgonovine	St. John's wort	indinavir irinotecan
Indinavir	(none)	amiodarone	simvastatin lovastatin	rifampin rifapentine	astemizole terfenadine	cisapride	pimozide	midazolam ^f triazolam	dihydroergotamine (D.H.E. 45) ergotamine ^g (various forms) ergonovine methylecgonovine	St. John's wort	atazanavir
Lopinavir + Ritonavir	(none)	flucanide propofenone	simvastatin lovastatin	rifampin/ rifapentine	astemizole terfenadine	cisapride	pimozide	midazolam ^f triazolam	dihydroergotamine (D.H.E. 45) ergotamine ^g (various forms) ergonovine methylecgonovine	St. John's wort	fluticasone ^h
Nelfinavir	(none)	(none)	simvastatin lovastatin	rifampin rifapentine	astemizole terfenadine	cisapride	pimozide	midazolam ^f triazolam	dihydroergotamine (D.H.E. 45) ergotamine ^g (various forms) ergonovine methylecgonovine	St. John's wort	
Ritonavir	bepiridil	amiodarone flucanide propofenone quinidine	simvastatin lovastatin	rifapentine	astemizole terfenadine	cisapride	pimozide	midazolam ^f triazolam	dihydroergotamine (D.H.E. 45) ergotamine ^g (various forms) ergonovine methylecgonovine	St. John's wort	voriconazole (with RTV ≥ 400mg bid) fluticasone ^h alfuzosin
Saquinavir	(none)	(none)	simvastatin lovastatin	rifampin rifabutin ⁱ rifapentine	astemizole terfenadine	cisapride	pimozide	midazolam ^f triazolam	dihydroergotamine (D.H.E. 45) ergotamine ^g (various forms) ergonovine methylecgonovine	St. John's wort garlic supplements	
Tiplranavir	bepiridil	amiodarone flucanide propofenone quinidine	simvastatin lovastatin	rifampin rifapentine	astemizole terfenadine	cisapride	pimozide	midazolam ^f triazolam	dihydroergotamine (D.H.E. 45) ergotamine ^g (various forms) ergonovine methylecgonovine	St. John's wort	fluticasone ^h
Non-nucleoside Reverse Transcriptase Inhibitors											
Delavirdine	(none)	(none)	simvastatin lovastatin	rifampin rifapentine ^j rifabutin	astemizole terfenadine	cisapride H2 blockers proton pump inhibitors	(none)	alprazolam midazolam ^f triazolam	dihydroergotamine (D.H.E. 45) ergotamine ^g (various forms) ergonovine methylecgonovine	St. John's wort	amprenavir fosamprenavir carbamazepine phenobarbital phenytoin
Efavirenz	(none)	(none)	(none)	rifapentine ^j	astemizole terfenadine	cisapride	(none)	midazolam ^f triazolam	dihydroergotamine (D.H.E. 45) ergotamine ^g (various forms) ergonovine methylecgonovine	St. John's wort	voriconazole
Nevirapine	(none)	(none)	(none)	rifampin rifapentine ^j	(none)	(none)	(none)	(none)	(none)	St. John's wort	

Certain listed drugs are contraindicated based on theoretical considerations. Thus, drugs with narrow therapeutic indices and suspected metabolic involvement with P450-3A, 2D6, or unknown pathways are included in this table. Actual interactions may or may not occur among patients.

f HIV patients treated with rifapentine have a higher rate of TB relapse than those treated with other rifamycin-based regimens; an alternative agent is recommended.

Δ Rifabutin may be used with saquinavir only if it is combined with ritonavir.

f In one small study, higher doses of RTV (additional 300 mg BID) or a double dose of LPV/RTV offset rifampin-inducing activity of LPV. Of note, 28% of subjects discontinued because of increases in LFTs. The safety of this combination is still under evaluation. Further studies are needed.

Σ Midazolam can be used with caution as a single dose and given in a monitored situation for procedural sedation.

† This is likely a class effect.

⊘ Astemizole and terfenadine are not marketed in the U.S. The manufacturer of cisapride has a limited-access protocol for patients meeting specific clinical eligibility criteria.

* Each milliliter of amprenavir oral solution has 46 IU of vitamin E. Patients should be cautioned to avoid supplemental doses of vitamin E. Multivitamin products containing minimal amounts of vitamin E are acceptable.

⊙ Concomitant use of fluticasone and ritonavir results in significantly reduced serum cortisol concentrations. Coadministration of fluticasone and ritonavir or any ritonavir-boosted PI regimen is not recommended unless the potential benefit outweighs the risk of systemic corticosteroid side effects. Fluticasone should be used with caution and alternatives considered if given with an unboosted PI regimen.

Suggested Alternatives:

Cerivastatin (no longer marketed in the United States), simvastatin, lovastatin: Pravastatin and fluvastatin have the least potential for drug-drug interactions; atorvastatin should be used with caution, using the lowest possible starting dose and monitor closely; no pharmacokinetic data or safety data are available for coadministration of rosuvastatin with the antiretroviral agents.

Rifabutin: clarithromycin, azithromycin (MAI prophylaxis); clarithromycin, azithromycin, ethambutol (MAI treatment)

Astemizole, terfenadine (no longer marketed in the United States): desloratadine, loratadine, fexofenadine, cetirizine

Midazolam, triazolam: temazepam, lorazepam

Table 22a. Drug Effects on Concentration of PIs

Drug Affected	Fosamprenavir	Atazanavir	Lopinavir/Ritonavir	Nelfinavir	Ritonavir	Saquinavir*	Tipranavir
Protease Inhibitors							
Fosamprenavir (f-APV)	•	Levels: With f-APV/ATV 1,400/400 QD, ATV AUC and Cmin ↓ 33% and 57%, respectively; f-APV AUC and Cmin ↑ 78% and 283%, respectively. With f-APV/r 700/100 mg BID + ATV 300 mg QD, ATV AUC and Cmax ↓ 22% and 24%, respectively; f-APV was unchanged. Dose: Insufficient data for dose recommendation.	Levels: With co-administration of f-APV 700 mg BID and LPV/r capsules 400/100 mg BID, f-APV Cmin ↓ 64% and LPV Cmin ↓ 53%. An increased rate of adverse events was seen with co-administration. Dose: Should not be co-administered, as doses are not established.	•	Levels: f-APV AUC and Cmin ↑ 100% and 400%, respectively, with 200 mg RTV. Dose: f-APV 1,400 mg + RTV 200 mg QD; or f-APV 700 mg + RTV 100 mg BID.	Levels: APV AUC ↓ 32%. Dose: Insufficient data for dose recommendation.	Levels: APV AUC and Cmin ↓ 44% and 55%, respectively, when given as APV/r 600/100 BID with TPV/r. No data with f-APV, but a ↓ in AUC is expected. Dose: Should not be co-administered, as doses are not established.
Indinavir (IDV)	Levels: APV AUC ↑ 33%. Dose: Not established.	Co-administration of these agents is not recommended because of potential for additive hyperbilirubinemia.	Levels: IDV AUC and Cmin ↑. Dose: IDV 600 mg BID.	Levels: IDV ↑ 50%; NFV ↑ 80%. Dose: Limited data for IDV 1,200 mg BID + NFV 1,250 mg BID.	Levels: IDV ↑ 2-5 times. Dose: IDV/RTV 400/400 mg, 800/100 mg, or 800/200 mg BID. Caution: Renal events may ↑ with ↑ IDV concentrations.	Levels: IDV-No effect. SQV ↑ 4-7 times. [†] Dose: Insufficient data.	No data. Should not be co-administered, as doses are not established.
Lopinavir/Ritonavir (LPV/r)	•	Levels: With ATV 300 QD + LPV/r 400/100 BID, ATV Cmin ↑ 45%, ATV AUC and Cmax were unchanged. LPV PK similar to historic data.	•	•	additional ritonavir is generally not recommended.	•	Levels: LPV AUC and Cmin ↓ 55% and 70%, respectively. Dose: Should not be co-administered, as doses are not established.
Nelfinavir (NFV)	Levels: APV AUC ↑ 1.5-fold. Dose: Insufficient data.	•	Levels: With LPV capsules, LPV ↓ 27%; NFV ↑ 25%. Dose: No data with LPV/r tablets. No dosing recommendation.	•	•	•	No data. Should not be co-administered, as doses are not established.
Ritonavir (RTV)	•	Levels: ATV AUC ↑ 238%. Dose: ATV 300 mg QD + RTV 100 mg QD.	Lopinavir is co-formulated with ritonavir as Kaletra®. Additional ritonavir is generally not recommended.	Levels: RTV - No effect. NFV ↑ 1.5 times. Dose: not established.	•	Levels: RTV no effect. SQV ↑ 20 times. ^{††} Dose: 1,000/100 mg SQV sgc or hgc/RTV BID or 400/400 mg BID.	Levels: TPV AUC ↑ 11-fold.
Saquinavir (SQV)	Levels: APV AUC ↓ 32%. Dose: Insufficient data.	Levels: SQV AUC ↑ 60% with SQV/ATV/RTV 1,600/300/100 QD, compared with SQV/RTV 1,600/100 QD. Dose: No dose recommendations can be made.	Levels: SQV [†] AUC and Cmin ↑. Dose: SQV 1,000 mg BID; LPV/r standard.	Levels: SQV ↑ 3-5 times; NFV ↑ 20%. [†] Dose: NFV standard; Fortovase 800 mg TID or 1,200 mg BID.	•	•	Levels: SQV AUC and Cmin ↓ 76% and 82%, respectively, when given as SQV/r 600/100 BID with TPV/r. Dose: Should not be co-administered, as doses are not established.

* Several drug interaction studies have been completed with saquinavir given as Invirase or Fortovase. Results from studies conducted with Invirase may not be applicable to Fortovase.

† Study conducted with Fortovase.

†† Study conducted with Invirase.

Table 22b. Drug Effects on Concentration of NNRTIs

Drug Affected	Delavirdine	Efavirenz	Nevirapine
Fosamprenavir (f-APV)	Levels: Presumably, similar PK effects as APV: APV AUC ↑ 130%, and DLV AUC ↓ 61%. Dose: Co-administration not recommended.	Levels: f-APV C _{min} ↓ 36% (when dosed at 1,400 mg QD with 200 mg RTV). Dose: f-APV 1,400 mg + RTV 300 mg QD; or f-APV 700 mg + RTV 100 mg BID.	No data.
Atazanavir (ATV)	No data.	Levels: With unboosted ATV, ATV AUC ↓ 74%. EFV no change. Dose: ATV 300 + RTV 100 mg QD with food - ATV concentrations similar to unboosted ATV; if desired, ATV concentrations not achieved with ATV/r 300/100 mg, may need to increase the dose of ATV/r - insufficient information for specific recommendation. EFV dose - standard.	No data. A decrease in ATV levels is expected. Co-administration is not recommended. Effect of NVP on ritonavir-boosted ATV combination unknown; if used, consider monitoring ATV level.
Indinavir (IDV)	Levels: IDV ↑ >40%; DLV - No effect. Dose: IDV 600 mg q8h. DLV standard.	Levels: IDV ↓ 31%. Dose: IDV 1,000 mg q8h, or consider IDV/RTV. EFV standard.	Levels: IDV ↓ 28%; NVP no effect. Dose: IDV 1,000 mg q8h, or consider IDV/RTV. NVP standard.
Lopinavir/Ritonavir (LPV/r)	Levels: LPV levels expected to increase. Dose: Insufficient data.	Levels: With LPV/r tablets 600/150 mg BID + EFV 600mg QD, LPV C _{min} and AUC ↑ 35% and 36%, respectively. No formal study of LPV/r tablets 400/100 mg BID + EFV. EFV no change. Dose: LPV/r tablets 600/150 mg BID, when used in with EFV in tx-experienced patients. EFV dose - standard.	Levels: With LPV/r capsules, LPV C _{min} dec. 55%. Dose: LPV/r tablets 600/150 mg BID, when used in combination with NVP in tx-experienced patients. NVP standard.
Nelfinavir (NFV)	Levels: NFV ↑ 2 times. DLV ↓ 50%. Dose: No data.	Levels: NFV ↑ 20%. Dose: Standard.	Levels: NFV ↑ 10%. NVP no effect. Dose: Standard.
Nevirapine (NVP)	No data.	Levels: NVP no effect. EFV: AUC ↓ 22%.	.
Ritonavir (RTV)	Levels: RTV ↑ 70%. DLV no effect. Dose: Appropriate doses not established.	Levels: RTV ↑ 18%. EFV ↑ 21%. Dose: Standard.	Levels: RTV ↓ 11%. NVP no effect. Dose: Standard.
Saquinavir (SQV)	Levels: SQV [†] ↑ 5 times; DLV no effect. Dose: Fortovase 800 mg TID. DLV standard; monitor transaminase levels.	Levels: SQV [†] ↓ 62%. EFV ↓ 12%. SQV is not recommended as sole PI when EFV is used. Dose: Consider SQV/RTV 400/400 mg BID.	Levels: SQV ↓ 25%. NVP no effect. Dose: Consider SQV-5gc/RTV 400/400 mg or 1,000/100 mg BID or SQV-hgc/RTV 1,000/100 mg BID.
Tipranavir	No data.	Levels: With TPV/r 500/100 mg BID, TPV AUC and C _{min} ↓ 31% and 42%, respectively. EFV unchanged. With TPV/r 750/200 mg BID, TPV PK unchanged. Dose: No dose adjustments necessary.	Levels: No data on the effect of NVP on TPV/r PK. NVP PK unchanged. [*]

† Study conducted with Inivirase.

* Study conducted with TPV/r dose(s) other than FDA-approved dose of 500/200 mg BID.

Table 23. Summary of Guidelines for Changing an Antiretroviral Regimen for Suspected Treatment Regimen Failure

<p>Patient Assessment (AIII)</p> <ul style="list-style-type: none"> • Review antiretroviral treatment history. • Assess for evidence of clinical progression (e.g., physical exam, laboratory and/or radiologic tests) • Assess adherence, tolerability, and pharmacokinetic issues. • Distinguish between limited, intermediate, and extensive prior therapy and drug resistance. • Perform resistance testing while patient is taking therapy (or within 4 weeks after regimen discontinuation). • Identify active drugs and drug classes to use in designing the new regimen <p>Patient Management: Specific Clinical Scenarios</p> <ul style="list-style-type: none"> • Limited or intermediate prior treatment with low (but not suppressed) HIV RNA level (e.g., up to 5000 copies/mL): The goal of treatment is to re-suppress HIV RNA to below the level of assay detection. Consider intensifying with one drug (e.g., tenofovir) (BII) or pharmacokinetic enhancement (use of ritonavir boosting of a protease inhibitor) (BII), perform resistance testing if possible, or most aggressively, change two or more drugs in the regimen (CIII). If continuing the same treatment regimen, HIV RNA levels should be followed closely because ongoing viral replication will lead to accumulation of additional resistance mutations. • Limited or intermediate prior treatment with resistance to one drug: Consider changing the one drug (CIII), pharmacokinetic enhancement (few data available) (BII), or, most aggressively, change two or more drugs in the regimen (BII). • Limited or intermediate prior treatment with resistance to more than one drug: The goal of treatment is to suppress viremia to prevent further selection of resistance mutations. Consider optimizing the regimen by changing classes (e.g., PI-based to NNRTI-based and vice versa) and/or adding new active drugs (AII). (See Table 25: Treatment options following virologic failure on initial recommended therapy regimens.) • Prior treatment with no resistance identified: Consider the timing of the drug resistance test (e.g., was the patient off antiretroviral medications?) and/or nonadherence. Consider resuming the same regimen or starting a new regimen and then repeating genotypic testing early (e.g., 2–4 weeks) to determine if a resistant viral strain emerges on treatment (CIII). • Extensive prior treatment and drug resistance: In patients with active antiretroviral agents available (e.g., an active ritonavir-boosted PI and enfuvirtide), the goal of therapy is suppression of viremia. In patients without active antiretroviral agent available and with ongoing viremia, the goal of therapy is preservation of immune responses and delay of clinical progression. It is reasonable to continue the same antiretroviral regimen if there are few or no treatment options (CIII). In general, avoid adding a single active drug because of the risk for the rapid development of resistance to that drug. In advanced HIV disease with a high likelihood of clinical progression (e.g., CD4 cell count <100 cells/mm³), adding a single drug may reduce the risk of immediate clinical progression (CIII). In this complicated scenario, expert advice should be sought. (See Table 24: Novel strategies to consider for treatment-experienced patients with few available active treatment options.) • Immunologic failure (or blunted CD4 response) with virologic suppression: Immunologic failure (or blunted CD4 cell response) may not warrant a change in therapy in the setting of suppressed viremia. Assess for other causes of immunosuppression (e.g., HIV-2, HTLV-1, drug toxicity). The combination of didanosine and tenofovir has been associated with CD4 cell declines or blunted CD4 cell responses. In the setting of immunologic failure (or blunted CD4 response), it would be reasonable to change one of these drugs (BIII). Intensifying with additional antiretroviral drugs or the use of immune-based therapies (e.g., interleukin-2) to improve immunologic responses remain unproven strategies and generally should not be offered (DII).
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Table 28. Preclinical and Clinical Data Relevant to the Use of Antiretrovirals During Pregnancy
(See [Safety and Toxicity of Individual Antiretroviral Drugs in Pregnancy](#) for more detail on drugs.)

Antiretroviral drug	FDA pregnancy category †	Placental passage (newborn: mother drug ratio)	Long-term animal carcinogenicity studies	Animal teratogen studies
Nucleoside and nucleotide analogue reverse transcriptase inhibitors				
Abacavir (Ziagen, ABC)	C	Yes (rats)	Positive (malignant and non-malignant tumors of liver, thyroid in female rats, and preputial and clitoral gland of mice and rats)	Positive (rodent anasarca and skeletal malformations at 1000 mg/kg (35x human exposure) during organogenesis; not seen in rabbits)
Didanosine (Videx, ddI)	B	Yes (human) [0.5]	Negative (no tumors, lifetime rodent study)	Negative
Emtricitabine (Emtriva, FTC)	B	Unknown	Not completed	Negative
Lamivudine (EpiVir, 3TC)	C	Yes (human) [~1.0]	Negative (no tumors, lifetime rodent study)	Negative
Stavudine (Zerit, d4T)	C	Yes (rhesus monkey) [0.76]	Positive (mice and rats, at very high dose exposure, liver and bladder tumors)	Negative (but sternal bone calcium decreases in rodents)
Tenofovir DF (Viread)	B	Yes (rat and monkey)	Positive (hepatic adenomas in female mice at high doses)	Negative (osteomalacia when given to juvenile animals at high doses)
Zalcitabine (HIVID, ddC)	C	Yes (rhesus monkey) [0.30–0.50]	Positive (rodent, thymic lymphomas)	Positive (rodent-hydrocephalus at high dose)
Zidovudine* (Retrovir, AZT, ZDV)	C	Yes (human) [0.85]	Positive (rodent, noninvasive vaginal epithelial tumors)	Positive (rodent-near lethal dose)
Non-nucleoside reverse transcriptase inhibitors				
Delavirdine (Rescriptor)	C	Unknown	Positive (hepatocellular adenomas and carcinomas in male and female mice but not rats, bladder tumors in male mice)	Positive (rodent-ventricular septal defect)
Efavirenz (Sustiva)	D	Yes (cynomolgus monkey, rat, rabbit) [~1.0]	Positive (hepatocellular adenomas and carcinomas and pulmonary alveolar/bronchiolar adenomas in female but not male mice)	Positive (cynomolgus monkey-anencephaly, anophthalmia, microphthalmia)
Nevirapine (Viramune)	C	Yes (human) [~1.0]	Positive (hepatocellular adenomas and carcinomas in mice and rats)	Negative
Protease inhibitors				
Amprenavir (Agenerase)	C	Unknown	Positive (hepatocellular adenomas and carcinomas in male mice and rats)	Negative (but deficient ossification and thymic elongation in rats and rabbits)
Atazanavir	B	Unknown	Positive (hepatocellular adenomas in female mice)	Negative
Fosamprenavir (Lexiva)	C	Unknown	Positive (benign and malignant liver tumors in male rodents)	Negative (deficient ossification with amprenavir but not fosamprenavir)
Indinavir (Crixivan)	C	Minimal (humans)	Positive (thyroid adenomas in male rats at highest dose)	Negative (but extra ribs in rodents)
Lopinavir/Ritonavir (Kaletra)	C	Unknown	Positive (hepatocellular adenomas and carcinomas in mice and rats)	Negative (but delayed skeletal ossification and increase in skeletal variations in rats at maternally toxic doses)
Nelfinavir (Viracept)	B	Minimal (humans)	Positive (thyroid follicular adenomas and carcinomas in rats)	Negative
Ritonavir (Norvir)	B	Minimal (humans)	Positive (liver adenomas and carcinomas in male mice)	Negative (but cryptorchidism in rodents)
Saquinavir (Fortovase)	B	Minimal (humans)	Negative	Negative
Tipranavir (Aptivus)	C	Unknown	In progress.	Negative (decreased ossification and pup weights in rats at maternally toxic doses)
Fusion inhibitors				
Enfuvirtide (Fuzeon)	B	Unknown	Not done	Negative

† Food and Drug Administration Pregnancy Categories:

- A - Adequate and well-controlled studies of pregnant women fail to demonstrate a risk to the fetus during the first trimester of pregnancy (and no evidence exists of risk during later trimesters).
- B - Animal reproduction studies fail to demonstrate a risk to the fetus, and adequate but well-controlled studies of pregnant women have not been conducted.
- C - Safety in human pregnancy has not been determined; animal studies are either positive for fetal risk or have not been conducted, and the drug should not be used unless the potential benefit outweighs the potential risk to the fetus.
- D - Positive evidence of human fetal risk that is based on adverse reaction data from investigational or marketing experiences, but the potential benefits from the use of the drug among pregnant women might be acceptable despite its potential risks.
- X - Studies among animals or reports of adverse reactions have indicated that the risk associated with the use of the drug for pregnant women clearly outweighs any possible benefit.

Table 29, page 1 of 3

Table 29. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy

(See also "[Safety and Toxicity of Individual Antiretroviral Drugs in Pregnancy](#)," Supplement for additional toxicity data and "[Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV-1 Transmission in the United States](#)" for detailed guidelines regarding treatment options.)

Antiretroviral Drug	Pharmacokinetics in Pregnancy	Concerns in Pregnancy	Rationale for Recommended Use in Pregnancy
NRTIs/ NtRTIs		See text for discussion of potential maternal and infant mitochondrial toxicity.	NRTIs are recommended for use as part of combination regimens, usually including two NRTIs with either an NNRTI or one or more PIs. Use of single or dual NRTIs alone is not recommended for treatment of HIV infection (AZT alone may be considered for prophylaxis of perinatal transmission in pregnant women with HIV RNA <1,000 copies/mL).
Recommended agents			
Zidovudine*	Pharmacokinetics not significantly altered in pregnancy; no change in dose indicated [311].	No evidence of human teratogenicity [312]. Well-tolerated, short-term safety demonstrated for mother and infant.	Preferred NRTI for use in combination antiretroviral regimens in pregnancy based on efficacy studies and extensive experience; should be included in regimen unless significant toxicity or stavudine use.
Lamivudine*	Pharmacokinetics not significantly altered in pregnancy; no change in dose indicated [313].	No evidence of human teratogenicity [312]. Well-tolerated, short-term safety demonstrated for mother and infant.	Because of extensive experience with lamivudine in pregnancy in combination with zidovudine, lamivudine plus zidovudine is the recommended dual NRTI backbone for pregnant women.
Alternate agents			
Didanosine	Pharmacokinetics not significantly altered in pregnancy; no change in dose indicated [314].	Cases of lactic acidosis, some fatal, have been reported in pregnant women receiving didanosine and stavudine together [315, 316].	Alternate NRTI for dual nucleoside backbone of combination regimens. Didanosine should be used with stavudine only if no other alternatives are available.
Emtricitabine	No studies in human pregnancy.	No studies in human pregnancy.	Alternate NRTI for dual nucleoside backbone of combination regimens.
Stavudine	Pharmacokinetics not significantly altered in pregnancy; no change in dose indicated [317].	No evidence of human teratogenicity [312]. Cases of lactic acidosis, some fatal, have been reported in pregnant women receiving didanosine and stavudine together [315, 316].	Alternate NRTI for dual nucleoside backbone of combination regimens. Stavudine should be used with didanosine only if no other alternatives are available. Do not use with zidovudine because of potential for antagonism.
Abacavir*	Phase I/II study in progress.	Hypersensitivity reactions occur in ~5-8% of non-pregnant persons; a much smaller percentage are fatal and are usually associated with rechallenge. Rate in pregnancy unknown. Patient should be educated regarding symptoms of hypersensitivity reaction.	Alternate NRTI for dual nucleoside backbone of combination regimens. See footnote regarding use in triple NRTI regimen. [#]
Insufficient data to recommend use			
Tenofovir	No studies in human pregnancy. Phase I study in late pregnancy in progress.	Studies in monkeys show decreased fetal growth and reduction in fetal bone porosity within two months of starting maternal therapy [318]. Clinical studies in humans (particularly children) show bone demineralization with chronic use; clinical significance unknown [191, 319].	Because of lack of data on use in human pregnancy and concern regarding potential fetal bone effects, tenofovir should be used as a component of a maternal combination regimen only after careful consideration of alternatives.
Not recommended			
Zalcitabine	No studies in human pregnancy.	Rodent studies indicate potential for teratogenicity and developmental toxicity (See Table 28).	Given lack of data and concerns regarding teratogenicity in animals, not recommended for use in human pregnancy unless alternatives are not available.

Page 95

Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents

Table 29: page 2 of 3

Table 29. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy

Antiretroviral Drug	Pharmacokinetics in Pregnancy	Concerns in Pregnancy	Rationale for Recommended Use in Pregnancy
NNRTIs			
Recommended agents			
Nevirapine	Pharmacokinetics not significantly altered in pregnancy; no change in dose indicated [320].	No evidence of human teratogenicity [312]. Increased risk of symptomatic, often rash-associated, and potentially fatal liver toxicity among women with CD4 ⁺ counts > 250/mm ³ when first initiating therapy [93, 153]; unclear if pregnancy increases risk.	Nevirapine should be initiated in pregnant women with CD4 ⁺ counts > 250 cells/mm ³ only if benefit clearly outweighs risk, because of the increased risk of potentially life-threatening hepatotoxicity in women with high CD4 ⁺ counts. Women who enter pregnancy on nevirapine regimens and are tolerating them well may continue therapy, regardless of CD4 ⁺ count.
Not recommended			
Efavirenz	No studies in human pregnancy.	FDA Pregnancy Class D; significant malformations (anencephaly, anophthalmia, cleft palate) were observed in 3 (15%) of 20 infants born to cynomolgus monkeys receiving efavirenz during the first trimester at a dose giving plasma levels comparable to systemic human therapeutic exposure; there are three case reports of neural tube defects in humans after first trimester exposure [90, 312, 321]; relative risk unclear. Rodent studies indicate potential for carcinogenicity and teratogenicity (See Table 28).	Use of efavirenz should be avoided in the first trimester, and women of childbearing potential must be counseled regarding risks and avoidance of pregnancy. Because of the known failure rates of contraception, alternate regimens should be strongly considered in women of childbearing potential. Use after the second trimester of pregnancy can be considered if other alternatives are not available and if adequate contraception can be assured postpartum.
Delavirdine	No studies in human pregnancy.	Hyperglycemia, new onset or exacerbation of diabetes mellitus, and diabetic ketoacidosis reported with PI use; unclear if pregnancy increases risk. Conflicting data regarding preterm delivery in women receiving PIs (See text).	Given lack of data and concerns regarding teratogenicity in animals, not recommended for use in human pregnancy unless alternatives are not available.
Protease inhibitors			
Recommended agents			
Nelfinavir	Adequate drug levels are achieved in pregnant women with nelfinavir 1250 mg, given twice daily [109].	No evidence of human teratogenicity [312]. Well-tolerated, short-term safety demonstrated for mother and infant. Nelfinavir dosing at 750 mg three times daily produced variable and generally low levels in pregnant women.	Given pharmacokinetic data and extensive experience with use in pregnancy compared to other PIs, preferred PI for combination regimens in pregnant women, particularly if HAART is being given solely for perinatal prophylaxis. In clinical trials of initial therapy in non-pregnant adults, nelfinavir-based regimens had a lower rate of viral response compared to lopinavir/ritonavir or efavirenz-based regimens, but similar viral response compared with atazanavir or nevirapine-based regimens [97, 98, 102, 299].
Saquinavir-soft gel capsule [SGC] (Fortovase®)/ritonavir	Adequate drug levels are achieved in pregnant women with saquinavir-SGC 800 mg, with ritonavir 100 mg, twice daily [322]. Recommended adult dosing of saquinavir-SGC 1000 mg plus ritonavir 100 mg may be used. No pharmacokinetic data on saquinavir-hard gel capsule [HGC]/ritonavir in pregnancy, but better GI tolerance in non-pregnant adults.	Well-tolerated, short-term safety demonstrated for mother and infant. Inadequate drug levels observed in pregnant women with saquinavir-SGC given alone at 1200 mg three times daily [323].	Given pharmacokinetic data and moderate experience with use in pregnancy, ritonavir-boosted saquinavir-SGC can be considered a preferred PI for combination regimens in pregnancy.

Table 29: page 3 of 3

Table 29. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy

Antiretroviral Drug	Pharmacokinetics in Pregnancy	Concerns in Pregnancy	Rationale for Recommended Use in Pregnancy
Alternate agents			
Indinavir	Two studies including 18 women receiving indinavir 800 mg three times daily showed markedly lower levels during pregnancy compared to postpartum, although suppression of HIV RNA was seen [324, 325].	Theoretical concern re: increased indirect bilirubin levels, which may exacerbate physiologic hyperbilirubinemia in the neonate, but minimal placental passage. Use of unboosted indinavir during pregnancy is not recommended.	Alternate PI to consider if unable to use nelfinavir or saquinavir-SGC/ritonavir, but would need to give indinavir as ritonavir-boosted regimen. Optimal dosing for the combination of indinavir/ritonavir in pregnancy is unknown.
Lopinavir/ritonavir	Phase I/II safety and pharmacokinetic study in progress using twice daily lopinavir 400 mg and ritonavir 100 mg.	Limited experience in human pregnancy.	Preliminary studies suggest increased dose may be required during pregnancy, though specific dosing recommendations not established. If used during pregnancy, monitor response to therapy closely. If expected virologic result is not observed, consult with a specialist with expertise in HIV in pregnancy.
Ritonavir	Phase I/II study in pregnancy showed lower levels during pregnancy compared to postpartum [326].	Minimal experience in human pregnancy.	Given low levels in pregnant women when used alone, recommended for use in combination with second PI as low-dose ritonavir "boost" to increase levels of second PI.
Insufficient data to recommend use			
Ampranavir	No studies in human pregnancy.	Oral solution contraindicated in pregnant women because of high levels of propylene glycol, which may not be adequately metabolized during pregnancy.	Safety and pharmacokinetics in pregnancy data are insufficient to recommend use of capsules during pregnancy.
Fosamprenavir	No studies in human pregnancy.	No experience in human pregnancy.	Safety and pharmacokinetics in pregnancy data are insufficient to recommend use during pregnancy.
Atazanavir	No studies in human pregnancy.	Theoretical concern re: increased indirect bilirubin levels, which may exacerbate physiologic hyperbilirubinemia in the neonate, although transplacental passage of other PIs has been low.	Safety and pharmacokinetics in pregnancy data are insufficient to recommend use during pregnancy.
Tipranavir	No studies in human pregnancy.	No experience in human pregnancy.	Safety and pharmacokinetics in pregnancy data are insufficient to recommend use during pregnancy.
Fusion inhibitors			
Insufficient data to recommend use			
Enfuvirtide	No studies in human pregnancy.	No experience in human pregnancy.	Safety and pharmacokinetics in pregnancy data are insufficient to recommend use during pregnancy.

NRTI = nucleoside reverse transcriptase inhibitor; NtRTI = nucleotide reverse transcriptase inhibitor; NNRTI = non-nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; SGC = soft gel capsule; HGC = hard gel capsule.

* Zidovudine and lamivudine are included as a fixed-dose combination in Combivir®; zidovudine, lamivudine, and abacavir are included as a fixed-dose combination in Trizivir®.

Triple NRTI regimens including abacavir have been less potent virologically compared to PI-based HAART regimens. Triple NRTI regimens should be used only when an NNRTI- or PI-based HAART regimen cannot be used (e.g., because of significant drug interactions). A study evaluating use of zidovudine/lamivudine/abacavir among pregnant women with HIV RNA < 55,000 copies/mL as a class-sparing regimen is in development.

The FDA has a categorization of drug risk to the fetus that runs from “Category A” (safest) to “X” (known danger--don’t use!):

Category A

Controlled studies in women fail to demonstrate a risk to the fetus in the first trimester (and there is no evidence of a risk in later trimesters), and the possibility of fetal harm appears remote.

Category B

Either animal-reproduction studies have not demonstrated a fetal risk but there are no controlled studies in pregnant women, or animal-reproduction studies have shown an adverse effect (other than a decrease in fertility) that was not confirmed in controlled studies in women in the first trimester (and there is no evidence of a risk in later trimesters).

Category C

Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal or other) and there are no controlled studies in women, or studies in women and animals are not available. **Drugs should be given only if the potential benefit justifies the potential risk to the fetus.**

Category D

There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g., if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).

Category X

Studies in animals or human beings have demonstrated fetal abnormalities, or there is evidence of fetal risk based on human experience or both, **and the risk of the use of the drug in pregnant women clearly outweighs any possible benefit.** The drug is contraindicated in women who are or may become pregnant.