

Treatment Guidelines

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Drugs for HIV Infection

The approval of new drugs and continuing concerns about drug toxicity and resistance have prompted new antiretroviral treatment guidelines.^{1,2} Resistance testing is now recommended before starting antiretroviral therapy. HIV infection is treated with combinations of antiretroviral drugs while monitoring the patient's HIV RNA levels ("viral load") and CD4 cell count. Increases in viral load while on therapy may indicate development of drug resistance requiring further testing and a change in treatment regimen.

The dosage and cost of drugs for HIV infection are listed in the tables on pages 70 and 71. The regimens of choice are listed on page 72 and drugs that should not be used together on page 73. Antiretroviral drugs interact with each other and with many other drugs. Most of these interactions are not included here. For more information, see *The Medical Letter Adverse Drug Interactions Program*.

NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NRTIs)

Nucleoside analogs inhibit HIV reverse transcriptase and decrease or prevent HIV replication in infected cells. All NRTIs except didanosine generally do not interact with other drugs and can be taken without regard to meals.

Class Adverse Effects – According to the labeling for these drugs, all NRTIs can cause a potentially fatal syndrome of lactic acidosis with hepatic steatosis, probably due to mitochondrial toxicity, and have also been associated with peripheral lipoatrophy, central fat accumulation and hyperlipidemia, but, according to Medical Letter consultants, these adverse effects occur rarely, if at all, with NRTIs other than stavudine and zidovudine.

Abacavir (ABC, Ziagen) – Abacavir is available alone and in fixed-dose combinations with lamivudine (*Epzicom*) and with lamivudine and zidovudine (*Trizivir*). It can be administered once or twice daily. Abacavir should not be used in a three-drug combination with lamivudine (or emtricitabine) and tenofovir because of high rates of virologic failure.³ Treatment with *Trizivir* alone has been associated with higher rates of virologic failure than with *Trizivir*/efavirenz or lamivudine/zidovudine/efavirenz.⁴ Patients with extensive prior NRTI therapy are less likely to respond to abacavir.

Adverse Effects – In 3-9% of patients treated with abacavir, a severe hypersensitivity reaction, usually with rash, fever and malaise, and sometimes with respiratory or gastrointestinal symptoms develops early in treatment (median of 11 days), but can occur at any time. Patients who have a hypersensitivity reaction should not be rechallenged. When rash occurs without systemic symp-

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toms, the drug can sometimes be continued with close monitoring. Whether hypersensitivity reactions can occur when restarting abacavir after a hiatus in patients who previously tolerated the drug is controversial.

Didanosine (ddl, Videx) – Didanosine is available in enteric-coated capsules (*Videx EC*, and others) and as a pediatric powder for oral solution. The chewable buffered tablet formulation has been discontinued. Patients with extensive prior NRTI therapy are less likely to respond to didanosine.

Adverse Effects – Dose-related peripheral neuropathy, pancreatitis and gastrointestinal disturbances are treatment-limiting toxicities of didanosine. Gastrointestinal tolerance is better with the enteric-coated capsules than with earlier formulations. Retinal changes and optic neuritis have been reported.

The combination of didanosine, tenofovir and a non-nucleoside reverse transcriptase inhibitor (NNRTI) is no longer recommended for initial antiretroviral therapy because of a high rate of virologic failure and rapid emergence of resistance.⁵ Paradoxical CD4 cell count decline has been described in patients taking concurrent didanosine and tenofovir, despite virologic suppression.⁶

Drug Interactions – Didanosine buffered tablets (discontinued) and the pediatric powder formulation interfere with absorption of drugs that require gastric acidity, including delavirdine, indinavir, and atazanavir. Use of the enteric-coated preparation appears to eliminate this problem. Tenofovir inhibits metabolism of didanosine; if they are used together, the dose of didanosine should be decreased.

The risk of pancreatitis, neuropathy and lactic acidosis is increased when didanosine is combined with stavudine; the combination of didanosine and stavudine is no longer recommended for initial treatment or for treatment during pregnancy.

Emtricitabine (FTC, Emtriva) – Emtricitabine is the 5-fluorinated derivative of lamivudine.⁷ It is similar to lamivudine in safety and efficacy, and can be given once daily. Emtricitabine is also available in fixed-dose combinations with tenofovir (*Truvada*) and with tenofovir and efavirenz (*Atripla*). Resistance to emtricitabine is conferred by the M184V mutation, which is the main cause of resistance to lamivudine, so cross-resistance is complete.

Adverse Effects – Emtricitabine is among the best tolerated NRTIs. It can cause hyperpigmentation of the palms and soles, particularly in dark-skinned patients. Because emtricitabine is also active against hepatitis B

virus (HBV), HIV-positive patients with chronic HBV infection may experience a flare of hepatitis if emtricitabine is withdrawn or if their HBV strain becomes resistant to the drug.

Lamivudine (3TC, Epivir) – Lamivudine, like emtricitabine, is among the best tolerated of the NRTIs. It can be taken once or twice daily. Lamivudine is also available in fixed-dose combinations with abacavir (*Epzicom*), zidovudine (*Combivir*), and zidovudine and abacavir (*Trizivir*). An increase in viral load during treatment with a lamivudine-containing regimen is often an indication of resistance to lamivudine. Lamivudine-resistant strains are cross-resistant to emtricitabine, and may have a modest decrease in susceptibility to abacavir and didanosine.

A lower-dose lamivudine tablet is approved for treatment of chronic hepatitis B (*Epivir-HBV*).

Adverse Effects – Because lamivudine is also active against hepatitis B virus (HBV), HIV-positive patients with chronic HBV infection may experience a flare of hepatitis if lamivudine is withdrawn or if their HBV strain becomes resistant to the drug. Other adverse effects are uncommon; pancreatitis has been reported rarely in children.

Stavudine (d4T, Zerit) – Stavudine can be given either in initial combination therapy or after failure of regimens containing other NRTIs, but cross-resistance with zidovudine is virtually complete. Concurrent administration of zidovudine causes antagonism.

Adverse Effects – Fatal lactic acidosis may occur more frequently with stavudine than with other NRTIs. Serum aminotransferase activity may increase with stavudine treatment, and pancreatitis has occurred rarely. Lactic acidosis and pancreatitis are more common when stavudine is combined with didanosine; this regimen is no longer recommended for initial treatment or treatment of pregnant women. Stavudine commonly causes peripheral sensory neuropathy, which often disappears when the drug is stopped and may not recur when it is restarted at a lower dose. Stavudine causes lipoatrophy, raises serum lipid concentrations, and has been associated with development of diabetes.

Zalcitabine (ddC, Hivid) – Zalcitabine is less effective, less convenient and more toxic than the other NRTIs; it is used rarely. The manufacturer will discontinue distribution of the drug by December 31, 2006.

Zidovudine (AZT, ZDV, Retrovir, and others) – Zidovudine is available alone and in fixed-dose combinations with lamivudine (*Combivir*) and with

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lamivudine and abacavir (*Trizivir*). It can be given in combination with any other NRTI except stavudine, which causes antagonism. Non-suppressive therapy with a zidovudine-containing regimen results in resistance to zidovudine and cross-resistance to other NRTIs.

Adverse Effects – Adverse effects of zidovudine include anemia, neutropenia, nausea, vomiting, headache, fatigue, confusion, malaise, myopathy, hepatitis, and hyperpigmentation of the oral mucosa and nail beds. It may be better tolerated when taken without food. Zidovudine is less likely than stavudine to cause lipoatrophy, lactic acidosis and hepatic steatosis.

NUCLEOTIDE REVERSE TRANSCRIPTASE INHIBITOR (NRTI)

Nucleotides are phosphorylated nucleosides; nucleoside and nucleotide RTIs have similar mechanisms of action.

Tenofovir disoproxil fumarate (TDF, *Viread*) – Tenofovir DF is the only nucleotide RTI available for treatment of HIV. It is a prodrug of tenofovir, a potent inhibitor of HIV replication. Tenofovir DF is given once daily. It is effective as part of initial HIV therapy and has activity against some HIV strains that are resistant to other NRTIs.

Tenofovir DF is available alone and in fixed-dose combinations with emtricitabine (*Truvada*) and with emtricitabine and efavirenz (*Atripla*).

Tenofovir should not be used in three-drug combinations with abacavir/lamivudine or didanosine/lamivudine because of high rates of virologic failure. The combination of tenofovir with didanosine and an NNRTI has been associated with early virologic failure and is not recommended for initial antiretroviral therapy.⁵

Adverse Effects – Tenofovir is generally well tolerated. Renal toxicity, including a Fanconi-like syndrome and progression to renal failure, has been reported. Tenofovir dosage must be decreased in patients with diminished renal function. Tenofovir is also active against HBV^{8,9}; in patients with chronic HBV infection, a hepatitis flare can occur if it is discontinued.

Drug Interactions – If tenofovir is used in combination with didanosine, the dose of didanosine should be decreased. Tenofovir lowers serum concentrations of atazanavir; ritonavir should be added (100 mg with 300 mg daily of atazanavir) to boost atazanavir levels when given in combination with tenofovir.

FIXED-DOSE NRTI COMBINATIONS

Four different fixed-dose NRTI combinations are available (see table on page 70). They offer the advantage of simplifying dosing schedules and reducing pill burden, but they are less flexible in terms of dosage adjustment. Some patients with hepatic or renal impairment will not be able to take them.

NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NNRTIs)

These drugs are direct, non-nucleoside inhibitors of HIV-1 reverse transcriptase. Combinations of an NNRTI with NRTIs tend to be at least additive in reducing HIV replication *in vitro*.

HIV isolates that are resistant to NRTIs and to protease inhibitors (PI) may remain sensitive to NNRTIs, but cross-resistance is common within the NNRTI class. Resistance to NNRTIs develops rapidly if they are used alone or in combinations that do not completely suppress viral replication. Because of their relatively long plasma half-life, further increased in patients with genetic polymorphisms of CYP450 isoenzymes, discontinuation of NNRTI-based regimens (particularly when efavirenz is the NNRTI) should be approached in a step-wise fashion or by substituting a PI for up to one month to let the NNRTI “wash out”.¹⁰

Class Adverse Effects – All NNRTIs, especially nevirapine, can cause a rash that is sometimes severe. NNRTIs are metabolized by and can affect hepatic CYP450 isozymes; they can interact with PIs and many other drugs.¹¹

Delavirdine (DLV, *Rescriptor*) – Delavirdine is the least potent NNRTI and is given 3 times daily. It is rarely used. Unlike efavirenz and nevirapine, delavirdine inhibits the metabolism and increases serum concentrations of PIs.

Efavirenz (EFV, *Sustiva*) – Efavirenz is the only NNRTI approved for once-daily dosing. In previously untreated patients, the combination of efavirenz with zidovudine/lamivudine has been more effective than indinavir/zidovudine/lamivudine, nelfinavir/zidovudine/lamivudine or abacavir/zidovudine/lamivudine in lowering HIV RNA concentrations, even among patients with high baseline levels (>100,000 copies/mL), and has been better tolerated. Brief studies in treatment-experienced patients or those failing other regimens have shown that efavirenz in combination with at least two other new agents can be effective in suppressing plasma HIV RNA levels and raising CD4 cell counts. Efavirenz is available alone and in a

NRTIs/NNRTIs for HIV Infection

Drug	Usual adult dosage	Total tablets or capsules/day	Cost ¹
NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NRTIs)			
Abacavir (ABC)			
<i>Ziagen</i> – GlaxoSmithKline*	300 mg bid ² or 600 mg once/d ²	2	\$15.50
Didanosine (ddl) enteric-coated capsules			
generic	400 mg once/d ^{3,18}	1	9.95
<i>Videx EC</i> – Bristol-Myers Squibb*			11.15
Emtricitabine (FTC)			
<i>Emtriva</i> – Gilead	200 mg once/d ^{4,18}	1	11.49
Lamivudine (3TC)			
<i>Epivir</i> – GlaxoSmithKline*	150 mg bid ^{5,18} or 300 mg once/d ^{5,18}	2 1	11.52 11.53
Stavudine (d4T)			
<i>Zerit</i> – Bristol-Myers Squibb*	40 mg bid ^{6,18}	2	12.66
Zalcitabine (ddC)			
<i>Hivid</i> – Roche	0.75 mg tid ^{7,18}	3	7.98
Zidovudine (AZT, ZDV)			
generic	300 mg bid ^{8,18}	2	10.70
<i>Retrovir</i> – GlaxoSmithKline*			13.24
NUCLEOTIDE REVERSE TRANSCRIPTASE INHIBITOR (NRTI)			
Tenofovir DF (TDF)			
<i>Viread</i> – Gilead	300 mg once/d ^{9,18}	1	17.43
NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NNRTIs)			
Delavirdine (DLV)			
<i>Rescriptor</i> – Pfizer	400 mg tid ¹⁰	6	9.96
Efavirenz (EFV)			
<i>Sustiva</i> – Bristol-Myers Squibb	600 mg once/d ¹¹	1	16.41
Nevirapine (NVP)			
<i>Viramune</i> – Boehringer Ingelheim*	200 mg bid ¹²	2	14.56
FIXED-DOSE NRTI COMBINATIONS			
Zidovudine/lamivudine			
<i>Combivir</i> – GlaxoSmithKline	300 mg/150 mg bid ¹³	2	25.08
Zidovudine/lamivudine/abacavir			
<i>Trizivir</i> – GlaxoSmithKline	200 mg/150 mg/300 mg bid ¹⁴	2	40.58
Abacavir/lamivudine			
<i>Epzicom</i> – GlaxoSmithKline	600 mg/300 mg once/d ¹⁵	1	26.99
Emtricitabine/tenofovir DF			
<i>Truvada</i> – Gilead	200 mg/300 mg once/d ¹⁶	1	28.98
FIXED-DOSE NNRTI/NRTI COMBINATION			
Efavirenz/emtricitabine/tenofovir DF			
<i>Atripla</i> – Gilead/Bristol-Myers Squibb	600 mg/200 mg/300 mg once/d ¹⁷	1	46.07

* Also available in a liquid or oral powder formulation.

1. Daily cost according to most recent data (July 31, 2006) available from Wolters Kluwer Health.

2. With or without food. Available in 300-mg tablets. Dosage for mild hepatic impairment is 200 mg bid.

3. Doses should be taken on an empty stomach. Available in 125- (only *Videx EC*), 200-, 250- and 400-mg capsules; for patients <60 kg, 250 mg once daily, ≥60 kg, 400 mg once daily. The dose of didanosine should be decreased to 250 mg/d for adults weighing ≥60 kg and to 200 mg/d for those weighing <60 kg when combined with tenofovir, which increases didanosine serum concentrations.

4. With or without food. Available in 200-mg capsules.

5. With or without food. For patients <50 kg, 2 mg/kg bid. Available in 150- and 300-mg tablets.

6. With or without food. For patients <60 kg, 30 mg bid. Available in 15-, 20-, 30- and 40-mg capsules.

7. With or without food. Available in 0.375- and 0.75-mg tablets.

8. With or without food. Available in 100-mg capsules and 300-mg tablets. Can also be given as 200 mg tid. Also available in a parenteral preparation for intrapartum use, the dose during labor is a 2 mg/kg load the first hour, and then 1 mg/kg/hour throughout the duration of labor.

9. May be taken with or without food. Available in 300-mg tablets.

10. With or without food. Available in 100- and 200-mg tablets.

11. At bedtime for at least the first 2 to 4 weeks; taken on an empty stomach. Available in 50-, 100-, and 200-mg capsules and 600-mg tablets.

12. With or without food. 200 mg once/day for the first 2 weeks of treatment to decrease the risk of rash. Available in 200-mg tablets.

13. Each tablet contains 300 mg of zidovudine and 150 mg of lamivudine.

14. Each tablet contains 300 mg of zidovudine, 150 mg of lamivudine and 300 mg of abacavir.

15. Each tablet contains 600 mg of abacavir and 300 mg of lamivudine.

16. Each tablet contains 200 mg of emtricitabine and 300 mg of tenofovir.

17. Each tablet contains 600 mg of efavirenz, 200 mg of emtricitabine, and 300 mg tenofovir. Should be taken without food. Dosing at bedtime may diminish CNS side effects.

18. Dosage adjustment required for renal impairment.

PIs/Fusion Inhibitor for HIV Infection

Drug	Usual adult dosage	Total tablets or capsules/day	Cos ¹
PROTEASE INHIBITORS			
Amprenavir (APV)			
<i>Agenerase</i> – GlaxoSmithKline*	1200 mg bid ^{2,13}	48	26.88
Atazanavir (ATV)			
<i>Reyataz</i> – Bristol-Myers Squibb	300 mg/100 mg RTV once/d ^{3,4,13}	3	39.31
Darunavir (DRV)			
<i>Prezista</i> – Tibotec	600 mg/100 mg RTV bid ^{4,5}	6	49.78
Fosamprenavir (FPV)			
<i>Lexiva</i> – GlaxoSmithKline	1400 mg/200 mg RTV once/d ^{4,6,13}	4	42.24
Indinavir (IDV)			
<i>Crixivan</i> – Merck	800 mg tid or 800 mg/100 mg RTV bid ^{4,7,13}	6 6	18.06 32.34
Lopinavir/ritonavir (LPV/RTV)			
<i>Kaletra</i> – Abbott*	400/100 mg bid ⁸ or 800/200 mg once/d ⁸	4 4	25.16
Nelfinavir (NFV)			
<i>Viracept</i> – Pfizer*	1250 mg bid ⁹ or 750 mg tid ⁹	4 (625-mg tablets) 9 (250-mg tablets)	23.96 21.60
Saquinavir (SQV)			
<i>Invirase</i> – Roche	1000 mg/100 mg RTV bid ^{4,10}	6	46.70
Tipranavir (TPV)			
<i>Aptivus</i> – Boehringer Ingelheim	500 mg/200 mg RTV bid ^{4,11}	8	75.68
FUSION INHIBITOR			
Enfuvirtide (T20)			
<i>Fuzeon</i> – Roche	90 mg SC bid ¹²	—	66.51

* Also available in a liquid or oral powder formulation.

1. Daily cost according to most recent data (July 31, 2006) available from Wolters Kluwer Health.

2. With or without food, but not with a fatty meal. Now available only in 50-mg capsules or as an oral solution. Capsules are also FDA-approved for administration with ritonavir: 1200 mg APV/200 mg RTV once/day or 600 mg APV/100 mg RTV bid. Dose for oral solution is 1400 mg bid.

3. *Reyataz* is taken with food. Available in 100-, 150- and 200-mg capsules. For therapy-experienced patients and when taken with EFV or TDF, the FDA-approved dose is 300 mg ATV/100 mg RTV. For therapy-naïve patients, the FDA-approved dose is 400 mg once/d (300 mg/100 mg RTV once/d is also used).

4. RTV = Ritonavir (*Norvir* – Abbott). Available as a 100-mg soft-gelatin capsule. The liquid formulation has an unpleasant taste; the manufacturer suggests taking it with chocolate milk or a liquid nutritional supplement.

5. *Prezista* is taken with food. Available in 300-mg tablets.

6. *Lexiva* is taken with or without food. Can also be given as 1400 mg bid or 700 mg/100 mg RTV bid in treatment-naïve patients and 700 mg/100 mg RTV bid in PI-experienced patients. When taken once daily with efavirenz, the recommended dosage is 1400 mg/300 mg RTV.

7. RTV-boosted dosage is not FDA-approved. *Crixivan* is taken with water or other liquids, 1 hour before or 2 hours after a meal, or with a light meal. Available in 100-, 200-, 333- and 400-mg capsules. Dosage is 600 mg q8h when taken with DLV. Patients should drink at least 48 ounces (1.5 L) of water daily.

8. Each tablet contains 200 mg of lopinavir and 50 mg of ritonavir. The recommended dose is 600/150 mg bid when taken with EFV, NVP, FPV or NFV in treatment-experienced patients. The higher dose can also be tried if lopinavir resistance is suspected. Once-daily dosing in treatment-naïve patients only. With or without food. No refrigeration.

9. *Viracept* is available in 250- and 625-mg tablets and should be taken with food.

10. *Invirase* should be taken within 2 hours after a full meal. Available in 200-mg capsules and 500-mg tablets. Dosage is 1000 mg bid (without RTV) when taken with LPV/RTV.

11. With food. Available in 250-mg capsules.

12. Available in kits containing a one-month supply of syringes and single-use vials with powder for a 90-mg dose and sterile water for reconstitution.

13. Dosage adjustment required for hepatic impairment.

fixed-dose combination with emtricitabine and tenofovir (*Atripla*).

Adverse Effects – The most common adverse effects of efavirenz have been rash, dizziness, headache, insomnia and inability to concentrate. Vivid dreams and nightmares can occur. Hallucinations, psychosis, depression and suicidal ideation have been reported. CNS effects tend to occur between 1 and 3 hours after each dose. They may stop within a few days or weeks, but can persist for months or years, particularly in patients with

high efavirenz serum concentrations.^{12,13} When the dose is taken at bedtime, CNS effects may still be present in the morning on awakening and may impair driving; this effect generally wanes with time and can be ameliorated by taking the drug earlier in the evening. Hypertriglyceridemia has occurred. Fetal abnormalities have occurred in pregnant monkeys exposed to efavirenz, and neural tube defects have been reported in women who took the drug during the first trimester of pregnancy; the drug should not be given to women who are, or are considering becoming, pregnant.

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Antiretroviral Regimens for Treatment-Naïve Patients

NNRTI-BASED (1 NNRTI + 2 NRTIs)

Regimen of Choice

Efavirenz¹ + (lamivudine or emtricitabine) + (zidovudine or tenofovir)

Substitutes

For the NNRTI: nevirapine

For the NRTIs: (lamivudine or emtricitabine) + (abacavir or didanosine or stavudine)

PI-BASED (1 or 2 PIs + 2 NRTIs)

Regimen of Choice

(Lopinavir/ritonavir or atazanavir/ritonavir) + (lamivudine or emtricitabine) + zidovudine

Substitutes

For the PI(s): fosamprenavir/ritonavir or saquinavir/ritonavir or indinavir/ritonavir or nelfinavir

For the NRTIs: (lamivudine or emtricitabine) + (abacavir or didanosine or stavudine or tenofovir)

TRIPLE NRTI²

Regimen of Choice

Abacavir + lamivudine + zidovudine

1. Except in pregnant women or women who might become pregnant because efavirenz is contraindicated in pregnancy.

2. Should only be considered after NNRTI- and PI-based regimens have been excluded.

Drug Interactions – Efavirenz is an inducer of CYP3A4. Methadone dosage often needs to be increased if efavirenz is used concurrently. Efavirenz decreases serum concentrations of some protease inhibitors. It also decreases serum concentrations of voriconazole (*Vfend*); they should not be taken together.

Nevirapine (NVP, *Viramune*) – Nevirapine appears to be comparable to efavirenz in effectiveness, but must be dosed twice daily and has greater potential for serious adverse effects.

Adverse Effects – Nevirapine can cause severe hepatotoxicity, hepatic failure and death, particularly in patients with previously elevated transaminases or underlying hepatitis B or C. Hepatotoxicity has also occurred when the drug was used for post-exposure prophylaxis in HIV-negative patients. Fever, nausea and headache can occur. Rash is common early in treatment with nevirapine and can be more severe than with other NNRTIs; it may progress to Stevens-Johnson syndrome. To decrease the incidence of rash and hepatic toxicity, the dose of nevirapine should be 200 mg once daily for the first 2 weeks, and then 200 mg twice daily. Women with CD4 counts >250 cells/mm³ and men with a baseline CD4 counts >400 cells/mm³ are at increased risk of nevirapine-associated hepatotoxicity.¹⁴

Drug Interactions – As with efavirenz, the dose of methadone often needs to be increased if nevirapine is used concurrently. Nevirapine decreases serum concentrations of some protease inhibitors.

FIXED-DOSE NNRTI/NRTI COMBINATION

Atripla is the first fixed-dose antiretroviral combination to contain antiretrovirals from two different classes (1 NNRTI/2 NRTIs). Each tablet contains 600 mg of **efavirenz**, 200 mg of **emtricitabine** and 300 mg of **tenofovir DF**. The dose is one tablet once daily.

An open-label, randomized noninferiority study in 517 treatment-naïve patients compared the combination of efavirenz, emtricitabine and tenofovir once daily (separately, not in the combination tablet) with fixed-dose zidovudine and lamivudine (*Combivir*) twice daily plus efavirenz once daily. At week 48, significantly more patients taking emtricitabine/tenofovir/efavirenz achieved and maintained HIV viral loads <400 copies/mL (84% vs. 73%) and <50 copies/mL (80% vs. 70%).¹⁵ At week 96, the percentages of patients with HIV RNA <400 copies/mL were 76% vs. 64%, and with <50 copies/mL were 69% vs. 63%.¹⁶

Adverse Effects – Adverse effects for *Atripla* are generally similar to those with the drugs taken separately. Patients with renal impairment who require dose adjustments and women who are or might become pregnant will not be able to take *Atripla*.

PROTEASE INHIBITORS (PIs)

Protease inhibitors prevent cleavage of protein precursors essential for HIV maturation, infection of new cells and viral replication. Use of a PI in combination with other drugs has led to marked clinical improvement and prolonged survival even in patients with

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Some Antiretroviral Drugs That Should Not Be Used Together

Drugs	Effect	Comments
Abacavir + lamivudine (or emtricitabine) + tenofovir	Early virologic failure	Not recommended
Didanosine + lamivudine (or emtricitabine) + tenofovir	Early virologic failure	Not recommended
Didanosine + stavudine	Increased risk of peripheral neuropathy, pancreatitis and lactic acidosis	Not recommended for initial therapy or in pregnant women
Didanosine + tenofovir + NNRTI	Early virologic failure	Not recommended for initial therapy
Stavudine + zidovudine	Antagonism	Not recommended

advanced HIV infection. Most PIs potently suppress HIV replication *in vivo*. Low-dose ritonavir taken with some other PIs inhibits the metabolism and increases serum concentrations of the other PI (“ritonavir boosting”); this technique is increasingly used.

Class Adverse Effects – Many PIs can cause gastrointestinal distress, increased bleeding in hemophiliacs, hyperglycemia, insulin resistance and hyperlipidemia and have been associated with an increased risk of coronary artery disease. They have also been associated with peripheral lipoatrophy and central fat accumulation. All, especially tipranavir, can cause hepatotoxicity, which may occasionally be severe and is more common in patients who are co-infected with HBV or hepatitis C virus (HCV). All PIs are metabolized by and are inhibitors of hepatic CYP3A4; drug interactions are common and can be severe.¹¹

Amprenavir (APV, Agenerase) – Amprenavir is available in capsules and in an oral solution; full doses taken without ritonavir would require 48 capsules or 187 mL daily. It has largely been replaced by fosamprenavir.

Adverse Effects – The most common adverse effects of amprenavir have been nausea, vomiting (especially in combination with zidovudine), perioral paresthesias and rash. Many patients with rash can continue or restart amprenavir if the rash is mild or moderate, but about 1% of patients have developed severe rash, including Stevens-Johnson syndrome.

Atazanavir (ATV, Reyataz) – Atazanavir is a PI with once-daily dosing.⁷ Most clinicians prefer to use boosted atazanavir whenever possible; atazanavir/ritonavir has been comparable to lopinavir/ritonavir in treatment-experienced patients.

Adverse Effects – Atazanavir causes an asymptomatic indirect hyperbilirubinemia. Unboosted, it has had fewer adverse effects than other PIs on lipid profiles,

fat accumulation or glucose metabolism. It can cause PR prolongation and should be used with caution in patients with cardiac conduction abnormalities.

Darunavir (Prezista) – Darunavir, like tipranavir, has been effective in treatment-experienced patients infected with HIV strains resistant to other protease inhibitors. It must be taken with ritonavir to achieve adequate bioavailability.¹⁷ Patients on darunavir who also received the fusion inhibitor enfuvirtide as part of their regimen have had better response rates.

Adverse Effects – The incidence of adverse effects with darunavir, including diarrhea, nausea, headache, nasopharyngitis and increased aminotransferase activity, has been similar to that with other boosted protease inhibitors. It appears to be better tolerated than tipranavir, but no direct comparison is available. In clinical trials, rash occurred in 7% of patients treated with darunavir and severe rash, including erythema multiforme and Stevens-Johnson syndrome, has been reported. Like tipranavir and fosamprenavir, darunavir contains a sulfonamide moiety; it should be used with caution in patients with sulfonamide allergy.

Fosamprenavir calcium (FPV, Lexiva) – Fosamprenavir calcium, a prodrug of amprenavir, is available in 700-mg tablets equivalent to 600 mg of amprenavir. In patients who have not previously been treated with a PI, fosamprenavir can be taken once daily combined with ritonavir, or twice daily with or without ritonavir. In patients who are treatment-experienced, it should be taken twice daily with ritonavir. Fosamprenavir/ritonavir was as effective and as well tolerated as lopinavir/ritonavir, each in combination with abacavir/lamivudine, in treatment-naïve patients.¹⁸ If fosamprenavir/ritonavir once daily is coadministered with efavirenz, the ritonavir dosage should be increased. Fosamprenavir has largely replaced amprenavir.

Adverse Effects – Adverse effects are similar to those with amprenavir, but in clinical studies the incidence

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of nausea, vomiting and severe rash was lower. Unlike amprenavir, which should not be taken with a fatty meal, fosamprenavir has no food restrictions. Like tipranavir and darunavir, it contains a sulfonamide moiety and should be used with caution in patients with sulfonamide allergy.

Indinavir (IDV, *Crixivan*) – Indinavir has good oral bioavailability and has been effective taken twice daily when combined with low-dose ritonavir, but it is used uncommonly because of its toxicity.

Adverse Effects – In addition to adverse effects similar to those of other protease inhibitors, indinavir causes asymptomatic elevation of indirect bilirubin, indinavir-containing kidney stones and renal insufficiency, dermatologic changes including alopecia, dry skin and mucous membranes, and paronychia and ingrown toenails. Patients should drink at least 1.5-2 liters of water daily to minimize renal adverse effects. Ritonavir boosting increases the risk of nephrolithiasis. Gallstones have also been reported.¹⁹

Lopinavir/ritonavir (LPV/RTV, *Kaletra*) – Lopinavir is available in the US only in a fixed-dose combination with ritonavir.²⁰ A new tablet formulation has replaced the previous capsule formulation; this new formulation has a lower daily pill burden, does not require refrigeration, and can be taken with or without food. Though usually given twice daily, it can be offered once daily to treatment-naïve patients. Lopinavir/ritonavir has been the PI regimen of choice in both treatment-naïve patients and in those with previous HIV treatment and moderate or no PI resistance (<5 resistance mutations); atazanavir/ritonavir appears to be similarly effective in treatment-experienced patients, and in one study in treatment-naïve patients, fosamprenavir/ritonavir was not inferior.¹⁸

Adverse Effects – Lopinavir/ritonavir is generally well tolerated. The most common adverse effects have been diarrhea, nausea, headache and asthenia. As with other PIs, hyperlipidemia, hyperglycemia, increased aminotransferase activity and altered body fat distribution have been reported. Fatal pancreatitis has occurred.

Nelfinavir (NFV, *Viracept*) – Nelfinavir once was a commonly used PI, but it appears to be less potent than lopinavir/ritonavir, and cannot be boosted.

Adverse Effects – Nelfinavir is generally well tolerated. Diarrhea, which is nearly universal but may resolve with continued use, is its main adverse effect.

Ritonavir (RTV, *Norvir*) – Ritonavir is well absorbed from the gastrointestinal tract and at full doses potent-

ly inhibits HIV, but due to poor tolerability it is now used mainly in doses of 100-200 mg once or twice daily to increase the serum concentrations and decrease the dosage frequency of other PIs.

Adverse Effects – Adverse reactions are common with full doses of ritonavir, but less common with the low doses used in PI combinations. Ritonavir can cause hypertriglyceridemia, altered taste, nausea, vomiting and, rarely, circumoral and peripheral paresthesias. It interacts with many other drugs.

Saquinavir (SQV, *Invirase*) – *Invirase*, which is available as a hard-gel capsule or film-coated tablet, is now the only available formulation of saquinavir. Saquinavir is usually well tolerated. Saquinavir/ritonavir appears to be as effective as and better tolerated than indinavir/ritonavir.

Adverse Effects – Saquinavir occasionally causes diarrhea, abdominal discomfort, nausea, glucose intolerance, hyperlipidemia, abnormal fat distribution and increased aminotransferase activity. It can cause increased bleeding in patients with hemophilia, and rarely causes rash and hyperprolactinemia.

Tipranavir (TPV, *Aptivus*) – Tipranavir is available as a capsule and must be taken with low-dose ritonavir.²¹ It can be used in treatment-experienced patients who have ongoing viral replication or in patients with HIV strains known to be resistant to multiple protease inhibitors, but darunavir may be better tolerated for the same indication. In clinical studies of patients with extensive treatment experience and drug resistance, tipranavir-containing regimens were more effective than regimens based on other ritonavir-boosted PIs, such as lopinavir/ritonavir. Patients on tipranavir who also received the fusion inhibitor enfuvirtide as a part of their background regimen had better response rates.²²

Adverse Effects – Severe hepatitis, including some fatalities, has been reported in patients taking tipranavir. Careful monitoring of liver function tests is recommended, especially in patients with chronic HBV or HCV infection. Tipranavir may cause diarrhea, nausea, vomiting and abdominal pain. The drug contains a sulfonamide moiety; caution should be used in patients with sulfonamide allergy. Intracranial hemorrhage has been reported among patients taking tipranavir, prompting a recent safety warning from the manufacturer.

FUSION INHIBITOR — After HIV binds to the host cell surface, a conformational change occurs in the transmembrane glycoprotein subunit (gp41) of the viral envelope, facilitating fusion of the viral and host

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cell membranes, and entry of the virus into the cell. Fusion inhibitors bind to gp41 and prevent the conformational change.

Enfuvirtide (T-20, ENF, Fuzeon) – Enfuvirtide is the first fusion inhibitor approved by the FDA for treatment of HIV infection and is indicated for treatment-experienced patients with ongoing HIV replication despite current antiretroviral use.²³ It is administered twice daily by subcutaneous injection.

Adverse Effects – Almost all patients develop local injection site reactions to enfuvirtide, with mild or moderate pain, erythema, induration, nodules and cysts.²⁴ Other adverse effects include eosinophilia, systemic hypersensitivity reactions, and possibly an increased incidence of bacterial pneumonia.

PREVENTION OF PERINATAL TRANSMISSION

Most perinatal transmission of HIV occurs close to the time of, or during, labor and delivery. **Zidovudine alone**, started at 14-34 weeks of gestation and continued in the infant for the first 6 weeks of life, reduced HIV transmission from 26% to 8%.²⁵

Current guidelines recommend combination therapy with **zidovudine plus another NRTI plus either a PI or nevirapine** throughout pregnancy to prevent transmission of HIV to the offspring.²⁶ Women not already on therapy should consider waiting until after 10-12 weeks gestation to begin. Regardless of the antepartum antiretroviral regimen and the maternal HIV viral load, zidovudine administration is recommended during the intrapartum period and for the newborn for 6 weeks.

Adverse Effects – PI therapy may contribute to development of hyperglycemia in the mother. Some studies suggest that antenatal combination antiretroviral therapy including a PI may be associated with premature birth.²⁷ However, most clinicians believe that the overwhelming benefit of a potent antiretroviral regimen greatly outweighs the risk.

Already in Labor – For women who are already in labor and have had no antiretroviral therapy, **zidovudine** given to the mother and continued in the infant for 6 weeks or given only to the infant for 6 weeks beginning within 8-12 hours after birth, can decrease HIV transmission. A combination of **zidovudine plus lamivudine** given at the onset of labor and to the infant for one week is also effective. **Single-dose nevirapine** given to the mother at the onset of labor and to the infant at 48-72 hours after delivery, either alone or combined with zidovudine, can decrease the risk of

perinatal transmission and may be more effective than zidovudine alone, but single-dose nevirapine has been associated with emergence of nevirapine-resistant strains, which could compromise future treatment of mother and child. For the mother, adding lamivudine/zidovudine and continuing for 3 to 7 days postpartum decreases the risk of nevirapine resistance.²⁸

Drugs Not to be Used – Fatal lactic acidosis from the combination of stavudine and didanosine has occurred in pregnant women; this combination should not be used. Efavirenz should be avoided in pregnancy, especially in the first trimester, because of potential teratogenicity. Initiation of nevirapine in pregnancy should be avoided in women with CD4 counts >250 cells/mm³ because of the increased risk of hepatotoxicity. This restriction does not apply to single-dose nevirapine.

SUMMARY

Depending on the results of resistance testing, reasonable first choices for initial therapy of HIV infection would include either an NNRTI, often efavirenz because it has fewer adverse effects than nevirapine, or a boosted PI combination such as lopinavir/ritonavir (*Kaletra*), either combined with 2 NRTIs. If an NNRTI- or PI-based regimen cannot be used, a final option for initial therapy would be abacavir plus lamivudine and zidovudine. For more advanced disease, combinations should be based on resistance testing and include two or more fully active drugs. Regimens containing darunavir or tipranavir, either combined with enfuvirtide, may be particularly helpful in heavily pretreated patients. For all patients, regular monitoring of viral load and CD4 cell count should be used to guide therapy. NNRTIs and PIs have many adverse interactions with each other and with other drugs.¹¹

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