

# Treatment of AIDS and HIV-Related Conditions—2002: Antiretroviral Therapy

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Combination antiretroviral therapy against the human immunodeficiency virus (HIV) has been remarkably effective in reducing morbidity, prolonging life, and decreasing deaths from the acquired immunodeficiency syndrome (AIDS). Effective treatment also dramatically reduces the incidence of opportunistic infections and permits discontinuation of opportunistic infection prophylaxis when substantial immune reconstitution occurs.

This Current Report—HIV updates the antiretroviral section of our annual treatment guidelines.<sup>1</sup> These recommendations are based on our experience at San Francisco General Hospital, published guidelines, a review of the medical literature and United States Public Health Service guidelines, and experience gained from answering telephone calls to our National HIV Telephone Consultation Service (Warmline). Table 1 lists the classes and dosages of current antiretroviral drugs, their most common and clinically important adverse effects, and drug interactions.

Clinicians are advised to refer to the excellent federal guidelines on the use of antiretroviral agents,<sup>2</sup> prevention of opportunistic infections,<sup>3</sup> management of tuberculosis,<sup>4</sup> prevention and management of perinatal<sup>5</sup> and pediatric<sup>6</sup> HIV infection, and occupational<sup>7</sup> and nonoccupational<sup>8</sup> exposures. These and other federal guidelines are updated

frequently on the Internet and are available at <http://www.hivatis.org>. Table 2 lists additional Web site resources for clinicians.

## Role of the Primary Care Clinician

Family physicians and general internists can provide most components of comprehensive HIV care. These components include ensuring that HIV-infected persons receive standard health care maintenance; providing risk reduction counseling and education; offering and encouraging HIV counseling and testing; educating, supporting, and counseling HIV-infected persons and their families; maintaining up-to-date immunizations for HIV-infected persons and their family members; monitoring markers of HIV disease progression; initiating antiretroviral therapy; assessing drug side effects, drug interactions, and complications; and instituting prophylaxis against opportunistic infections. Monitoring the effectiveness of antiretroviral therapy and treating most opportunistic infections are also within the scope of generalist care. When antiretroviral therapy failure occurs and interpretation of viral resistance testing is required, the help of HIV experts is generally needed. Managing life-threatening opportunistic infections and other conditions requiring hospitalization also frequently require consultation.

The special skills of primary care specialists can be especially valuable in caring for persons who are unable or unwilling to adhere to medication regimens, managing the psychosocial needs of patients and their families, and, when necessary, providing end-of-life care. Multidisciplinary team collaboration among primary care clinicians, AIDS experts, pharmacists, caseworkers, nurses, social workers, and others can offer the best opportunity to provide comprehensive care for HIV-infected persons and their families.

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**Table 1. Treatment Regimens for HIV Disease.**

System, Problem, and Drug Regimen	Duration	Adverse Effects/Drug Interactions	Comments
<b>GENERAL/SYSTEMIC</b>			
<b>Antiretroviral Therapy</b>			
<p><i>Combination antiretroviral (ARV) therapy is always recommended. Preferred regimens include 2 nucleoside reverse transcriptase inhibitors (NRTIs) along with either 1 or 2 protease inhibitors (PIs) or with the nonnucleoside reverse transcriptase inhibitor (nNRTI) efavirenz. Preferred NRTI combinations are zidovudine plus lamivudine or didanosine, stavudine plus lamivudine or didanosine, and didanosine plus lamivudine. Preferred PI therapy is with nelfinavir or indinavir, or with dual (boosted) PI combination therapy with ritonavir plus indinavir, saquinavir, or lopinavir. An alternative NRTI combination is zidovudine plus zalcitabine. Alternative agents that can be used with 2 NRTIs include abacavir, amprenavir, delavirdine, nevirapine, ritonavir, saquinavir, and nelfinavir plus saquinavir. Cross-resistance among PIs is common, as is cross-resistance among nNRTIs. Zidovudine and stavudine should not be used in combination. Indinavir and saquinavir should not be used in combination. Other drug combinations might be necessary; resistance testing and expert consultation can be helpful. Combinations not recommended are zalcitabine plus didanosine, lamivudine, or stavudine; and zidovudine plus stavudine. See text for further discussion</i></p>			
Nucleoside reverse transcriptase inhibitors (NRTIs)		<p><i>NRTI drug class effects:</i> Nausea, vomiting; aminotransferase elevations (alanine transaminase [ALT], aspartate transaminase [AST]); lactic acidosis with hepatomegaly and hepatic steatosis; mitochondrial toxicity; lipodystrophy; neuromuscular toxicity with progressive weakness resembling Guillain-Barré syndrome</p>	
Zidovudine (AZT, Retrovir) 200 mg po tid or 300 mg po bid; lower dosages (eg, 100 mg 3 times daily) for patients unable to tolerate higher dosages and patients with renal failure or cirrhosis. Available as liquid formulation. Available also as fixed-dose combinations: zidovudine 300 mg plus lamivudine 150 mg (Combivir) given as one tablet po bid; and zidovudine 300 mg plus lamivudine 150 mg plus abacavir 300 mg (Trizivir), given as one tablet po bid. Take with or without food	Until efficacy wanes or toxicity occurs	<p>See NRTI drug class effects, above. Malaise, headache, insomnia, seizures, myalgias. Anemia, granulocytopenia, thrombocytopenia; macrocytosis is an expected effect of zidovudine therapy and requires no intervention. Toxic myopathy (with elevated creatine phosphokinase [CPK]) with long-term use. Blue to black discoloration of nails and skin in pigmented races</p> <p><i>Drug interactions</i> Careful monitoring required when used with other myelosuppressive drugs (ie, trimethoprim-sulfamethoxazole, ganciclovir). Probenecid can increase levels of zidovudine. Acetaminophen (Tylenol) administration does not increase zidovudine toxicity. Avoid concomitant use with ribavirin</p>	<p>Monitor for signs of zidovudine toxicity and reduce dosage if required. Transfusions or erythropoietin (if endogenous erythropoietin level &lt;500 IU/L) therapy can be used if anemia (eg, hemoglobin &lt;8.0 g/dL) occurs in patients who require zidovudine therapy. Decrease dosage or interrupt for absolute neutrophil count (ANC) &lt;500/<math>\mu</math>L; consider granulocyte colony-stimulating factor (G-CSF). Transfusions and erythropoietin and G-CSF therapies are expensive; changing to alternate NRTI preferred</p> <p>Once-daily dosing under investigation</p>

Continued

Table 1. Continued

System, Problem, and Drug Regimen	Duration	Adverse Effects/Drug Interactions	Comments
<b>GENERAL/SYSTEMIC (cont.)</b>			
<b>Antiretroviral Therapy (cont.)</b>			
Didanosine (ddI) as enteric-coated capsules (Videx EC) given as 400-mg capsule po qd (>60 kg) or 250-mg capsule po qd (<60 kg). Also available as buffered tablets (Videx) 400 mg po qhs as two 200-mg buffered tablets, or 200 mg po bid as two 100-mg chewable tablets or 250-mg po bid powder for patients >60 kg; 125 mg (tablets) or 167 mg (powder) po bid for patients <60 kg. Dosage reduction (ie, 200 mg/d) in renal insufficiency. Take on an empty stomach	Until efficacy wanes or toxicity occurs	See NRTI drug class effects, above. Pancreatitis; painful peripheral neuropathy (dosage related, reversible); abdominal cramps, diarrhea related to antacid in formulation; rash; hyperglycemia; hyperuricemia; headache, insomnia, seizures; elevated triglyceride and amylase levels; thrombocytopenia; retinal atrophy  <i>Drug interactions</i> Avoid alcohol and other pancreatic toxins (eg, systemic pentamidine). Avoid concomitant neurotoxic drugs (eg, zalcitabine, vinca alkaloids, oral ganciclovir). Decreases absorption of drugs whose absorption is impaired by buffered products (eg, ketoconazole, itraconazole, indinavir, lopinavir, delavirdine, ritonavir, tetracyclines, quinolone antibiotics). Oral and intravenous ganciclovir might increase didanosine toxicity. Consider increasing chewable didanosine dosage with methadone use. Administer tenofovir (Viread) 2 h before or 1 h after didanosine administration; dosage reduction to 250 mg didanosine to reduce toxicity is under investigation	Monitor for signs of neuropathy  Enteric-coated capsules might cause less diarrhea and fewer drug interactions  Administer buffered didanosine on empty stomach 2 hours apart from antacids, histamine <sub>2</sub> (H <sub>2</sub> ) antagonists, and drugs (eg, ketoconazole, itraconazole, indinavir, lopinavir, ritonavir, tetracyclines, delavirdine, quinolone antibiotics) whose absorption is impaired by buffered products  Two buffered tablets must be given per dose to provide adequate buffer for absorption. Can be difficult to chew; tablets do not dissolve readily in water, can be crushed manually or given with apple juice  Didanosine plus stavudine combination should not be given to pregnant women because of increased risk of fatal lactic acidosis
Zalcitabine (ddC, Hivid) 0.75 mg po tid; 0.375 mg po tid for patients <30 kg. Dosage reduction in renal insufficiency. Take with or without food	Until efficacy wanes or toxicity occurs	See NRTI drug class effects, above. Painful peripheral neuropathy (dosage related, reversible); rash; stomatitis, aphthous ulcers; pancreatitis; esophageal ulceration; seizures; cardiomyopathy  <i>Drug interactions</i> Avoid alcohol and other pancreatic toxins (eg, systemic pentamidine). Avoid concomitant neurotoxic drugs (eg, didanosine, isoniazid, vinca alkaloids, oral ganciclovir)	Zalcitabine is less potent than other NRTIs
Stavudine (d4T, Zerit) 40 mg po bid for patients >60 kg; 15–30 mg po bid for patients 40–60 kg; reduce dosage for patients <40 kg and for patients with renal insufficiency. Take with or without food. Available as liquid formulation	Until efficacy wanes or toxicity occurs	See NRTI drug class effects, above. Painful peripheral neuropathy; anemia, macrocytosis; psychological disturbances, insomnia, anxiety, panic attacks  <i>Drug interactions</i> Avoid concomitant use with zidovudine or drugs that can cause neurotoxicity or pancreatic toxicity  Do not use in combination with zidovudine because of antagonistic antiviral activity	Lower dosages (20 mg po bid) might have a lower incidence of peripheral neuropathy and equivalent efficacy  Sustained-release preparation under investigation  Didanosine plus stavudine combination should not be given to pregnant women because of increased risk of fatal lactic acidosis

Table 1. Continued

System, Problem, and Drug Regimen	Duration	Adverse Effects/Drug Interactions	Comments
<b>GENERAL/SYSTEMIC (cont.)</b>			
<b>Antiretroviral Therapy (cont.)</b>			
Lamivudine (3TC, Epivir) 150 mg po bid; 2 mg/kg po bid for patients <50 kg. Dosage reduction in renal insufficiency. Available as liquid formulation. Available also as fixed-dose combinations: zidovudine 300 mg plus lamivudine 150 mg (Combivir) given as one tablet po bid; and zidovudine 300 mg plus lamivudine 150 mg plus abacavir 300 mg (Trizivir), given as one tablet po bid. Take with or without food	Until efficacy wanes or toxicity occurs	See NRTI drug class effects, above. Headache, fatigue, insomnia; peripheral neuropathy, muscle aches; rash; rare neutropenia, thrombocytopenia; paronychia	Provides some efficacy against hepatitis B. Once-daily dosing (300 mg po qd) under investigation
Abacavir (Ziagen) 300 mg po bid. Available as liquid solution. Available also as fixed-dose combinations: zidovudine 300 mg plus lamivudine 150 mg (Combivir) given as one tablet po bid; and zidovudine 300 mg plus lamivudine 150 mg plus abacavir 300 mg (Trizivir), given as one tablet po bid. Take with or without food	Until efficacy wanes or toxicity occurs	See NRTI drug class effects, above. Headache, malaise; abdominal pain, diarrhea, rash. Hypersensitivity reaction (2%–5%, usually in first 6 weeks): rash, flu-like symptoms, fever, malaise, fatigue, dyspnea, cough, pharyngitis, abdominal cramping, anorexia, nausea, vomiting, diarrhea, elevations in transaminases and creatinine phosphokinase (CPK) levels	Symptoms and signs of hypersensitivity reaction can be progressive; will resolve if drug stopped. Do not rechallenge, as anaphylactic reactions and deaths reported. Genetic predisposition for hypersensitivity reaction  Once-daily dosing under investigation
<i>Nucleotide reverse transcriptase inhibitor</i>			
Tenofovir disoproxil fumarate (Viread) 300 mg po qd with food. Avoid in renal insufficiency (creatinine clearance [CrCl] <60 mL/min)	Until efficacy wanes or toxicity occurs	Nausea, vomiting, diarrhea, flatulence; headache; asthenia; creatine phosphokinase elevation; aminotransferase elevation  Lactic acidosis with hepatic steatosis  <i>Drug interactions</i> Administer tenofovir 2 h before or 1 h after didanosine administration; dosage reduction to 250 mg didanosine to reduce toxicity is under investigation	Might offer benefit in salvage therapy; effectiveness in initial therapy under investigation. Active against hepatitis B virus (HBV)

Continued

Table 1. Continued

System, Problem, and Drug Regimen	Duration	Adverse Effects/Drug Interactions	Comments
<b>GENERAL/SYSTEMIC (cont.)</b>			
<b>Antiretroviral Therapy (cont.)</b>			
<i>Protease inhibitors (PIs)</i>			
		<p><i>PI drug class effects:</i> Nausea, vomiting; aminotransferase elevations, hepatitis; hypertriglyceridemia, hypercholesterolemia, abnormal fat accumulation, hyperglycemia, insulin resistance; osteopenia, osteoporosis, avascular necrosis</p> <p><i>PI drug class interactions:</i> Avoid concomitant use with rifampin (except ritonavir), St. John's wort, garlic supplements, ergotamine, midazolam (Versed), and triazolam (Halcion); can use lorazepam (Ativan) and temazepam (Restoril). Decreased PI levels and increased phenobarbital, phenytoin, and carbamazepine levels when used in combination; dosage adjustments probably required. Avoid simvastatin (Zocor) or lovastatin (Mevacor) because of rhabdomyolysis; can use pravastatin (Pravachol), fluvastatin (Lescol), or low-dose atorvastatin (Lipitor). Limit sildenafil (Viagra) dosage to 25 mg q 48 h</p>	
Nelfinavir (Viracept) 1250 mg po bid or 750 mg po tid. Available as powder for liquid formulation. Take with food. See boosted PI combinations below; note dosage differences	Until efficacy wanes or toxicity occurs	<p>See PI drug class effects, above.</p> <p>Diarrhea</p> <p><i>Drug interactions</i> See PI drug class interactions, above. Moderate P-450 enzyme inhibitor. Decrease rifabutin dosage to 150 mg po qd or 300 mg po 2–3 times weekly and increase nelfinavir dosage to 1 g po tid. Reduces methadone and oral contraceptive (estrogen) levels; might require dosage adjustment</p>	Diarrhea is self-limiting; can be controlled with loperamide, calcium carbonate, oat bran, psyllium, or pancreatic enzymes
Indinavir (Crixivan) 800 mg po q 8 h dosage adjustment to 600 mg po q 8 h in hepatic disease. Take on empty stomach or with skim milk, juice, coffee, tea, toast. See boosted PI combinations below; note dosage differences	Until efficacy wanes or toxicity occurs	<p>See PI drug class effects, above.</p> <p>Nephrolithiasis, crystalluria, interstitial nephritis; diarrhea, abdominal pain; asymptomatic hyperbilirubinemia; rash; insomnia, headache, dizziness, metallic taste; alopecia, dry skin; thrombocytopenia</p> <p><i>Drug interactions</i> See PI drug class interactions, above. Moderate P-450 enzyme inhibitor. Decrease indinavir dosage to 600 mg po q 8 h when given with ketoconazole. Increase indinavir to 1 g po q 8 h when given with efavirenz or nevirapine. Indinavir administration must be at least 1 hour apart from didanosine or antacid administration. Decrease rifabutin dosage to 150 mg po qd or 300 mg po 2–3 times weekly and increase indinavir dosage to 1000 mg po tid</p>	<p>Take with at least 6 glasses of noncaffeinated liquid daily to avoid nephrolithiasis</p> <p>Must be taken every 8 hours, not 3 times daily when used as sole PI</p>

Table 1. Continued

System, Problem, and Drug Regimen	Duration	Adverse Effects/Drug Interactions	Comments
<b>GENERAL/SYSTEMIC (cont.)</b>			
<b>Antiretroviral Therapy (cont.)</b>			
<i>Protease inhibitors (PIs) (cont.)</i>			
Ritonavir (Norvir) 600 mg po bid; can increase from 300 mg po bid to 600 mg po bid over 4–7 days to minimize gastrointestinal symptoms. Take with food. Available as liquid formulation. See boosted PI combinations below; note dosage differences	Until efficacy wanes or toxicity occurs	See PI drug class effects, above. Diarrhea, anorexia in more than 50% of patients; fatigue, weakness; headache, dizziness, circumoral paresthesias; hyperuricemia, increased creatine phosphokinase; taste disturbances  <i>Drug interactions</i> See PI drug class interactions, above. Mixed hepatic P-450 enzyme inhibitor (potent) and inducer. Dosages of antidepressants (except desipramine) might need adjustment. Decrease rifabutin dosage to 150 mg po every other day or three times weekly. Reduces methadone and oral contraceptive levels; dosage adjustment required	Not generally used as sole PI  Capsules must be refrigerated; solution should not be refrigerated  Hepatotoxicity might be greater with ritonavir than with other protease inhibitors  High alcohol content of liquid formulation
Saquinavir soft-gel capsules (Fortovase) 1200 mg po tid. Take with food. See boosted PI combinations below; note dosage differences	Until efficacy wanes or toxicity occurs	See PI drug class effects above. Headache, confusion; fever  <i>Drug interactions</i> See PI drug class interactions, above. Weak hepatic P-450 enzyme inhibitor. Ketoconazole, ritonavir, delavirdine, and grapefruit juice increase saquinavir serum concentration. Avoid concomitant use of saquinavir with indinavir, rifampin, rifabutin, phenytoin, carbamazepine, phenobarbital, efavirenz (when saquinavir is used as the sole PI), dexamethasone, nevirapine, and other enzyme inducers	Hard-gel formulation (Invirase, 600 mg po tid within 2 hours of a high-fat meal to increase absorption) not recommended because of poor bioavailability (4%), even when taken with high-fat meal
Amprenavir (Agenerase) 1200 mg po bid. Take with or without food; avoid high-fat meal. Available as liquid formulation. See boosted PI combinations below; note dosage differences	Until efficacy wanes or toxicity occurs	See PI drug class effects above. Diarrhea; oral paresthesias, headache; rash, Stevens-Johnson syndrome  <i>Drug interactions</i> See PI drug class interactions, above. Mixed P-450 enzyme inhibitor (moderate) and inducer. Might reduce lopinavir levels; increase lopinavir to 4 capsules bid. Decrease rifabutin to 150 mg po qd or 300 mg 2–3 times weekly. Dosages of oral contraceptives might need adjustment	Use with caution in patients with sulfa allergy. Contains vitamin E; avoid concomitant vitamin E coadministration  Increase amprenavir dosage to 1200 mg po tid when used as sole PI with efavirenz  Amprenavir solution contains propylene glycol, which is contraindicated in pregnancy and should be used with caution in hepatic or renal failure or in combination with metronidazole or disulfiram
Atazanavir 400 mg po qd	Until efficacy wanes or toxicity occurs	See PI drug class effects above Nausea, vomiting, diarrhea, abdominal discomfort, hyperbilirubinemia, jaundice; rash  <i>Drug interactions</i> See PI drug class interactions, above. P-450 enzyme inhibitor	Might produce less hyperlipidemia than other PIs  Available by expanded access at 1-877-726-7327

Continued



Table 1. Continued

System, Problem, and Drug Regimen	Duration	Adverse Effects/Drug Interactions	Comments
<b>GENERAL/SYSTEMIC (cont.)</b>			
<b>Antiretroviral Therapy (cont.)</b>			
<i>Protease inhibitor combinations (boosted PIs)</i>			
Ritonavir 200 mg po bid plus Indinavir 800 mg po bid	Until efficacy wanes or toxicity occurs	See PI class effects, drug interactions, and individual agents	Other bid dosing regimens that might be equivalent: ritonavir 100 mg plus indinavir 800 mg; ritonavir 200 mg plus indinavir 600 mg; ritonavir 400 mg plus indinavir 400 mg
Ritonavir 400 mg po bid plus Saquinavir soft-gel capsules 400 mg po bid	Until efficacy wanes or toxicity occurs	See PI drug class effects, drug interactions, and individual agents  <i>Drug interactions</i> Combination can be given with efavirenz without dosage adjustment. Reduce rifabutin dosage to 150 mg po 2–3 times weekly	Generally well tolerated. Combination therapy provides higher saquinavir levels  Ritonavir 100 mg po bid plus saquinavir 1000 mg po bid might be equivalent  Ritonavir 100–200 mg po qd plus saquinavir 1600 mg po qd has been used
Nelfinavir 1250 mg po bid plus Indinavir 1200 mg po bid	Until efficacy wanes or toxicity occurs	See PI drug class effects, drug interactions, and individual agents	Data limited
Ritonavir 400 mg po bid plus Nelfinavir 500–750 mg po bid	Until efficacy wanes or toxicity occurs	See PI drug class effects, drug interactions, and individual agents	Data limited
Saquinavir soft-gel capsules 800 mg po tid plus Nelfinavir 750 mg po tid or 1250 po bid	Until efficacy wanes or toxicity occurs	See PI drug class effects, drug interactions, and individual agents	Data limited
Ritonavir 100 mg po bid plus Amprenavir 600 mg po bid or Ritonavir 200 mg po qd plus Amprenavir 1200 mg po qd	Until efficacy wanes or toxicity occurs	See PI drug class effects, drug interactions, and individual agents  <i>Drug interactions</i> Combination can be given with efavirenz without dosage adjustment	
Lopinavir 400 mg plus ritonavir 100 mg combination (Kaletra); given as 3 fixed-dose capsules po bid with food. Available as liquid formulation. Increase dosage to 4 capsules po bid if administered with efavirenz, nevirapine, or amprenavir 750 mg po bid	Until efficacy wanes or toxicity occurs	See PI drug class effects and individual agents above. Diarrhea; skin rash; edema; headache, weakness  Liquid formulation contains 42 percent alcohol  <i>Drug interactions</i> See PI drug class interactions and ritonavir, above. Increases amprenavir levels; reduce amprenavir dosage to 750 mg po bid. Reduces methadone and oral contraceptive levels; dosage adjustment required. Decrease rifabutin to 150 mg po every other day	Refrigerate capsules; stable at room temperature for 2 months only  Better tolerated than ritonavir alone. Ritonavir-resistant strains can be sensitive to lopinavir-ritonavir combination  Lopinavir-ritonavir 3 capsules po bid plus saquinavir 1000 mg po bid has been used  Once-daily dosing under investigation

Table 1. Continued

System, Problem, and Drug Regimen	Duration	Adverse Effects/Drug Interactions	Comments
<b>GENERAL/SYSTEMIC (cont.)</b>			
<b>Antiretroviral Therapy (cont.)</b>			
<i>Nonnucleoside reverse transcriptase inhibitors (nNRTIs)</i>			
Efavirenz (Sustiva) 600 mg po qhs with or without food; avoid high-fat meal; 200 mg po tid if insomnia or nightmares occur	Until efficacy wanes or toxicity occurs	<p>Dizziness, anxiety, inability to concentrate, lightheadedness, headache, dysphoria, nightmares; nausea; rash (less than other nNRTIs); aminotransferase elevations, hepatitis. Avoid in pregnancy</p> <p><i>Drug interactions</i> Mixed P-450 enzyme inducer and inhibitor. Avoid use with either saquinavir or amprenavir when used as sole PIs. Increase indinavir dosage to 1 g po q 8 h when used as sole PI in combination with efavirenz. Increase rifabutin dosage to 450–600 mg qd or 600 mg 2–3 times weekly. Increase lopinavir-ritonavir to 4 capsules po bid. Reduces methadone and warfarin levels; dosage adjustment necessary</p> <p>Avoid coadministration with St. John's wort and garlic tablets, as they can reduce efavirenz levels</p>	<p>Good central nervous system penetration; central nervous system side effects with increased efavirenz levels</p> <p>Rash from one nNRTI does not predict rash from other nNRTIs</p> <p>Central nervous system side effects with increased efavirenz levels</p>
Nevirapine (Viramune) 200 mg po qd for 14 days; if no rash develops, increase to 200 mg po bid. Once-daily dosing (400 mg po qd) under investigation	Until efficacy wanes or toxicity occurs	<p>Maculopapular rash, Stevens-Johnson syndrome. Black box warning about rare fulminant hepatotoxicity within first 8 weeks; risk increased with concurrent chronic hepatitis and concomitant hepatotoxic drugs. Nausea, vomiting, diarrhea; fatigue, fever, headaches; rare hematologic toxicity</p> <p><i>Drug interactions</i> P-450 enzyme inducer; avoid concomitant use with saquinavir as sole PI, rifampin, and rifabutin. Decreases methadone, warfarin, and estrogen levels; dosage adjustment necessary. Increase lopinavir-ritonavir to 4 capsules po bid. Increase indinavir to 1 g po q 8 h</p>	<p>Discontinue drug at any time if rash is severe. Do not increase dosage if any rash is present during first 14-day lead-in period. Dose escalation can minimize occurrence of rash; prophylactic antihistamines and corticosteroids remain controversial</p> <p>Rash from one nNRTI does not predict rash from other nNRTIs</p>

Continued



Table 1. Continued

System, Problem, and Drug Regimen	Duration	Adverse Effects/Drug Interactions	Comments
<b>GENERAL/SYSTEMIC (cont.)</b>			
<b>Antiretroviral Therapy (cont.)</b>			
Delavirdine (Rescriptor) 400 mg po tid. Can dissolve in 3 oz water as slurry	Until efficacy wanes or toxicity occurs	Maculopapular rash; nausea; headache; aminotransferase elevations, especially when taken with saquinavir; neutropenia when taken with nelfinavir  <i>Drug interactions</i> Moderate P-450 enzyme inhibitor. Avoid concomitant use of rifampin, rifabutin, phenytoin, carbamazepine, simvastatin, lovastatin, alprazolam, midazolam, triazolam, ergotamine, St. John's wort, and garlic supplements; can use lorazepam and temazepam. Ketoconazole, itraconazole, fluconazole, clarithromycin, and fluoxetine can increase delavirdine serum concentrations; dosage reduction might be necessary. Increased warfarin effects. Limit sildenafil to 25 mg q 48 h	Delavirdine increases saquinavir and indinavir levels by 50%. Reduce indinavir dosage to 600 mg po q 8 h and saquinavir dosage to 600 mg po tid when used in combination with delavirdine. Separate didanosine or antacid administration from delavirdine administration by at least 1 hour  Rash from one nNRTI does not predict rash from other nNRTIs
<i>Postexposure prophylaxis for health care workers</i>			
Zidovudine 200 mg po tid or 300 mg po bid plus lamivudine 150 mg po bid, or Combivir one tablet po bid with or without nelfinavir 750 mg po tid (preferred) or 1250 mg po bid or indinavir 800 mg po q 8 h. Stavudine plus lamivudine can substitute for zidovudine plus lamivudine when necessary	4 weeks	Nevirapine should not be used; fulminant hepatic failure has occurred from nevirapine use in occupational postexposure prophylaxis  See above adverse effects and drug interactions. Zidovudine and lamivudine appear safe in pregnancy	Administer within 2 hours or as soon as possible after exposure. Can substitute other antiretroviral agents (except nevirapine) when source patient has received extensive treatment with antiretroviral drugs. Add nelfinavir, indinavir, or other PI for high-risk exposures and when source patient suspected to have antiretroviral resistance. Nevirapine can cause hepatic failure; use only with caution and careful monitoring. Can call the National Clinicians' Post-Exposure Prophylaxis Hotline (PEpline) at 1-888-HIV-4911 for additional assistance 24 h/d
<i>Pregnancy</i>			
Combination antiretroviral therapy recommended according to antiretroviral guidelines. When possible, use zidovudine-containing antiretroviral regimen during pregnancy, plus intrapartum zidovudine until delivery. Consider single-dose nevirapine	Until end of pregnancy	See above adverse effects and drug interactions  Adverse effects on fetus not clear. Anemia, neutropenia; possible mitochondrial toxicity with neurologic abnormalities (infant). Viral resistance to lamivudine is commonly induced in infants; clinical implications unknown	Prenatal and intrapartum therapy with zidovudine or zidovudine plus lamivudine, along with postnatal treatment of infant, decreases HIV transmission  Discussion of risks and benefits is essential. Consider cesarean section  See United States Public Health Service guidelines; consider expert consultation

### Initiating Antiretroviral Therapy

Initiating (and continuing) antiretroviral therapy should always be based on the readiness, willingness, and capability of the HIV-infected person to

adhere to a rigorous and presumably life-long treatment program. All patients with symptomatic HIV disease (regardless of CD4<sup>+</sup> cell count) should be offered and encouraged to take antiretroviral

**Table 2. Sources of Information for Treatment of AIDS and HIV-Related Conditions.***Guidelines*

[www.hivatis.org](http://www.hivatis.org)

Extremely easy to use, AIDS-specific Web site with access to key federal and other guidelines. Has up-to-date revisions of guidelines as they are announced, as well as some documents in draft form

[www.cdc.gov](http://www.cdc.gov)

Guidelines from the Centers for Disease Control and Prevention, including AIDS and Sexually Transmitted Disease

*General information, links to guidelines, and other Web sites*

[www.hivinsite.ucsf.edu](http://www.hivinsite.ucsf.edu)

Comprehensive Web site with access to a wide range of resources. Based in the AIDS Program at San Francisco General Hospital/UCSF

[www.hopkins-aids.edu](http://www.hopkins-aids.edu)

Comprehensive Web site with access to a wide range of resources. Based in the Johns Hopkins University AIDS Service

[www.ama-assn.org/special/hiv](http://www.ama-assn.org/special/hiv)

Provides news, articles, abstracts, and policy information on AIDS from *JAMA* and other AMA sources

[www.ucsf.edu/hivcntr](http://www.ucsf.edu/hivcntr)

National HIV Telephone Consultation Service (Warmline) and National Clinicians' Post-Exposure Prophylaxis Hotline (PEPline) information. Based in the National HIV/AIDS Clinicians' Consultation Center at San Francisco General Hospital

[www.hivpharmacology.com](http://www.hivpharmacology.com)

Clinical pharmacology Web site that maintains current drug profiles, interactions, and adverse effects

*Clinical trials*

[www.actis.org](http://www.actis.org)

Official AIDS Clinical Trials Information Service (ACTIS) Web site for information on clinical trials. Additional information available by calling ACTIS at 1-800-TRIALSA

therapy. The optimal time to begin antiretroviral treatment for asymptomatic persons has not yet been determined, however.<sup>2,9-11</sup> Initiating antiretroviral therapy in asymptomatic persons when their CD4<sup>+</sup> cell count is greater than 350/ $\mu$ L does not appear to offer survival advantages compared with starting antiretroviral therapy at a lower threshold. Treatment at these high CD4<sup>+</sup> cell counts with currently available agents can expose patients to unnecessary drug toxicities and drug resistance without clear benefit. It has also been shown that antiretroviral therapy appears most effective when started before the CD4<sup>+</sup> cell count decreases to fewer than 200/ $\mu$ L. Consequently, persons with a CD4<sup>+</sup> cell count of less than 200/ $\mu$ L should receive antiretroviral therapy whenever possible. For asymptomatic persons with a CD4<sup>+</sup> lymphocyte count between 350/ $\mu$ L and 200/ $\mu$ L, the optimal time to initiate treatment has not been established and is a matter of personal choice, requiring careful discussions and negotiation between the clinician and the patient.

Epidemiologic studies show a substantial rate of progression to AIDS for persons with a high viral load (greater than 55,000 copies/mL). Some experts recommend starting antiretroviral therapy at viral loads greater than 55,000 copies/mL (even

with high CD4<sup>+</sup> cell counts), whereas others defer therapy and monitor CD4<sup>+</sup> cell counts. We generally use the CD4<sup>+</sup> cell count as the key determinant, although repeatedly high viral loads influence the decision to initiate therapy closer to the 350/ $\mu$ L cell count threshold. At high viral load levels, both the branched DNA (bDNA) and the reverse transcriptase polymerase chain reaction (RT-PCR) assays appear accurate. Finally, patients with the acute retroviral syndrome (including fever, myalgias, sore throat, headache, rash, oral or genital ulcers, and lymphadenopathy) can be offered antiretroviral therapy. The strategy of treating acute infection is based on the possibility that decreasing the viral load early in HIV infection to reduce the reservoir of infected cells might result in better long-term outcomes. The results of ongoing clinical trials will establish whether this strategy is beneficial.

Adherence to antiretroviral regimens is difficult even for the most well-intentioned and motivated patient. Simulated medication adherence using placebo pills and other techniques can help the patient develop a realistic sense of ability to adhere to challenging regimens. For persons who cannot maintain strict adherence to antiretroviral regimens, antiretroviral therapy should be postponed,

thus avoiding the risk of developing irreversible drug resistance.

Some reduction in viral load should be apparent within 4 to 6 weeks of initiating therapy. Rapid reduction of viral load within 2 weeks of starting therapy might correlate with a more durable viral suppression. Ideally, the viral load will decrease to undetectable levels (less than 50 copies/mL) within 4 to 6 months. Effective therapy usually shows a viral load (HIV RNA) decrease of at least 1 log. A minimally significant viral load change is a 0.5-log (3-fold) increase or decrease. Patients who obtain substantial decreases in viral loads, but not to undetectable levels, can still obtain clinical benefit from antiretroviral therapy. A sustained rise in CD4<sup>+</sup> cell count of 100/ $\mu$ L or more usually accompanies effective therapy. Divergent results in viral load and CD4<sup>+</sup> cell counts can also occur.

### Recommended Initial Antiretroviral Drug Combinations

Potent antiretroviral drug combinations, also termed highly active antiretroviral therapy (HAART), include two nucleoside reverse transcriptase inhibitors (NRTIs) with the addition of either one or two protease inhibitors or the non-nucleoside reverse transcriptase inhibitor (nNRTI) efavirenz. The preferred NRTI combinations are zidovudine plus lamivudine, zidovudine plus didanosine, stavudine plus lamivudine, stavudine plus didanosine, and didanosine plus lamivudine. The use of tenofovir in an initial NRTI combination also appears promising. The recommended protease inhibitors are nelfinavir, indinavir, or reduced-dose combinations of ritonavir with indinavir, saquinavir, or lopinavir. Ritonavir is extremely effective in raising the blood levels of other protease inhibitors and can be combined (in reduced dosages) in boosted protease inhibitor regimens (see Table 1 for specific regimens). Because of concerns about long-term toxicities and the potential for developing resistance to the protease inhibitor class of drugs, some experts prefer efavirenz (in combination with two NRTIs) to preserve the protease inhibitor class of drugs for subsequent regimens. Alternative drug combinations are available for persons experiencing drug intolerance or toxicity.

### Antiretroviral Therapy Failure and Resistance Testing

Antiretroviral therapy can fail because of poor adherence, acquired drug resistance, poor drug absorption, drug-drug interactions, or lack of drug potency. New opportunistic infections and other clinical illnesses, rising viral load (usually a 3-fold increase or more), or a decreasing CD4<sup>+</sup> cell count usually indicates failed therapy. Virologic failure as indicated by rising viral loads is not always accompanied by either decreasing CD4<sup>+</sup> counts or clinical progression. Many patients retain clinical benefit even after the reemergence of a high viral load.

Antiretroviral drug resistance tests are the best laboratory tests currently available and can be helpful in guiding therapy for persons who have failed multiple antiretroviral regimens. Resistance testing should be obtained while the patient is taking the failing regimen and the viral load is greater than 1,000 copies/mL. These tests include genotypic, phenotypic, and virtual phenotypic tests. Most commonly used are genotypic tests, which are readily available and relatively inexpensive. Genotypic tests results, however, can be difficult to interpret and apply in the clinical setting. The tests are not well standardized, laboratory variability can be substantial, only the predominant viral population (not minor strains) is tested, resistance against boosted (combination protease inhibitor) regimens is not measured, and laboratory reports can at times be confusing or misleading. Despite the imperfections of genotypic resistance testing, better virologic and immunologic outcomes have been shown at 6 months when antiretroviral therapy is guided by genotypic test results. Because knowledge about genotypic testing changes rapidly, Internet-based sites (eg, [http://www.iasusa.org/resistance\\_mutations](http://www.iasusa.org/resistance_mutations) and <http://hivdb.stanford.edu/hiv>) can provide current updates.

Phenotypic testing is more expensive and takes longer to perform but might offer benefits in specific cases. Virtual phenotypic testing requires further investigation. Consultation with an expert to correlate the resistance test results with the clinical history can be extremely helpful and at times essential. Resistance testing should be considered for acute HIV infection if treatment is planned. The recommendations for resistance testing in pregnancy are the same as for nonpregnant women.

## Complications of Antiretroviral Therapy

Antiretroviral treatment is associated with both short-term and long-term toxicities and side effects.<sup>12,13</sup> The major adverse effects and drug-drug interactions<sup>14</sup> for the antiretroviral drugs are listed in Table 1. The NRTI drug class is associated with lipoatrophy, hepatomegaly and hepatic steatosis, neuromuscular toxicity with progressive weakness resembling Guillain-Barré syndrome, and lactic acidosis. The lactic acidosis syndrome, which usually begins with lactic acidemia and nonspecific gastrointestinal symptoms, can progress to severe or fatal lactic acidosis if not recognized. All NRTI drugs should be discontinued; cautious rechallenge using other NRTIs (eg, abacavir) has been successful. Stavudine-containing regimens appear to be associated with lactic acidosis more often than other NRTIs.

Insulin resistance, hyperglycemia, and rarely, diabetes mellitus are strongly associated with protease inhibitor use. The lipodystrophy syndrome, including central obesity, peripheral fat wasting, visceral and dorsocervical (buffalo hump) fat deposition, and sometimes lipid abnormalities, is associated with protease inhibitor and NRTI use but also can occur in the absence of antiretroviral therapy. The clinical consequences of the various lipid abnormalities have not been fully assessed. Other important complications of protease inhibitor therapy include osteopenia, osteoporosis, and avascular necrosis.

Hepatitis B and C coinfection is common in persons with HIV infection. Although most antiretroviral drugs can cause hepatotoxicity, hepatitis coinfection is not an absolute contraindication to the use of antiretroviral drugs. The use of nevirapine, however, should be avoided if possible.

With improvement in the immune system, paradoxical responses can occur as part of an immune reconstitution syndrome. These include flare-ups of latent opportunistic infections, such as tuberculosis, cytomegalovirus (CMV) uveitis or retinitis, viral hepatitis (B or C), herpes zoster, fungal infections, and other mycobacterial diseases. Activation of Kaposi sarcoma, lymphomas, and other malignancies has been reported. These clinical flares should not prompt prompt discontinuation of antiretroviral therapy.

## Sources of Information

The most helpful and up-to-date sources of information can now be found on the Internet. Espe-

cially useful Web sites are listed in Table 2. A selected bibliography highlights some additional articles of clinical interest. Our National HIV Telephone Consultation Service (Warmline) in the University of California, San Francisco, Department of Family and Community Medicine at San Francisco General Hospital (SFGH) provides clinical consultation and education for health care providers; the Warmline is in operation on weekdays at 1-800-933-3413. Our National Clinicians' Post-Exposure Prophylaxis Hotline (PEpline) at 1-888-HIV-4911 provides 24-hour advice and support regarding occupational exposures to blood-borne pathogens. The AIDS Education and Training Centers (AIDS ETCs) of the Health Resources and Services Administration (HRSA) at 1-301-443-6364 offers education, training, and consultation services to health care providers.

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## References

1. Goldschmidt RH, Dong BJ. Treatment of AIDS and HIV-related conditions-2001. *J Am Board Fam Pract* 2001;14:283-309.
2. Guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents. Panel on Clinical Practices for Treatment of HIV Infection. The Living Document, February 4, 2002. Available at <http://www.hivatis.org/trtgdlns.html>. Accessed May 10, 2002.
3. 2001 USPHS/IDSA guidelines for the prevention of opportunistic infections in persons infected with human immunodeficiency virus. US Public Health Service (USPHS) and Infectious Diseases Society of America (IDSA). USPHS/IDSA Prevention of Opportunistic Infections Working Group. November 28, 2001. Available at [http://www.hivatis.org/oi\\_guidelines.html](http://www.hivatis.org/oi_guidelines.html). Accessed May 10, 2002.
4. Prevention and treatment of tuberculosis among patients infected with human immunodeficiency virus: principles of therapy and revised recommendations. Centers for Disease Control and Prevention. *MMWR Recomm Rep* 1998;47(RR-20):1-58. Available at <http://www.hivatis.org>. Accessed May 10, 2002.
5. 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. Perinatal HIV Guidelines Working Group. Public Health Service.

- February 4, 2002. Available at [http://www.hivatis.org/per\\_guidelines.html](http://www.hivatis.org/per_guidelines.html). Accessed May 10, 2002.
6. Guidelines for the use of antiretroviral agents in pediatric HIV infection. Working Group on Antiretroviral Therapy and Medical Management of HIV-Infected Children. December 14, 2001. Available at [http://www.hivatis.org/ped\\_guidelines.html](http://www.hivatis.org/ped_guidelines.html). Accessed May 10, 2002.
7. Public Health Service guidelines for the management of health-care worker exposures to HIV and recommendations for postexposure prophylaxis. Centers for Disease Control and Prevention. MMWR Recomm Rep 1998;47(RR-7):1–33. Available at [http://www.hivatis.org/hcare\\_guidelines.html](http://www.hivatis.org/hcare_guidelines.html). Accessed May 10, 2002.
8. Management of possible sexual, injecting-drug-use, or other nonoccupational exposure to HIV, including considerations related to antiretroviral therapy. Public Health Service statement. Centers for Disease Control and Prevention. MMWR Recomm Rep 1998;47(RR-17):1–14. Available at [http://www.hivatis.org/ne\\_guideline.html](http://www.hivatis.org/ne_guideline.html). Accessed May 10, 2002.
9. Phillips AN, Staszewski S, Weber R, et al, for the Swiss HIV Cohort Study Group, the Frankfurt HIV Clinic Study Group, and the EuroSIDA Study Group. HIV viral load response to antiretroviral therapy according to the baseline CD4 cell count and viral load. JAMA 2001;286:2560–7.
10. Hogg RS, Yip B, Chan KJ, et al. Rates of disease progression by baseline CD4 cell count and viral load after initiating triple-drug therapy. JAMA 2001; 286:2568–77.
11. Pomerantz RJ. Initiating antiretroviral therapy during HIV infection: confusion and clarity. JAMA 2001;286:2597–9.
12. Wanke CA, Falutz JM, Shevitz A, Phair JP, Kotler DP. Clinical evaluation and management of metabolic and morphologic abnormalities associated with human immunodeficiency virus. Clin Infect Dis 2002;34:248–59.
13. Carr A, Cooper DA. Adverse effects of antiretroviral therapy. Lancet 2000; 356:1423–30.
14. Piscitelli SC, Gallicano KD. Interactions among drugs for HIV and opportunistic infections. N Engl J Med 2001;344:984–96.